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High risk percutaneous coronary intervention (chip)

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High risk percutaneous coronary intervention (chip)

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5-Year Clinical Outcomes of Successful Recanalisation for Coronary Chronic Total Occlusions in Patients With or Without Type 2 Diabetes Mellitus

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Background: Despite substantial improvement in chronic total occlusions (CTO) revascularization technique, the long-term clinical outcomes in diabetic patients with revascularized CTO remain controversial. Our study aimed to investigate the 5-year cardiovascular survival for patients with or without type 2 diabetes mellitus (DM) who underwent successful percutaneous coronary intervention (PCI) for CTO.

Methods: Data of the current analysis derived from a large single-center, prospective and observational cohort study, including 10,724 patients who underwent PCI in 2013 at Fuwai Hospital. Baseline, angiographic and follow-up data were collected. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE), which consisted of death, recurrent myocardial infarction (MI), stroke and target vessel revascularization (TVR). The secondary endpoint was all-cause mortality. Cox regression analysis and propensity-score matching was performed to balance the baseline confounders.

Results: A total of 719 consecutive patients with ≥1 successful CTO-PCI were stratified into diabetic (n = 316, 43.9%) and non-diabetic (n = 403, 56.1%) group. During a median follow-up of 5 years, the risk of MACCE (adjusted hazard ratio [HR] 1.47, 95% confidence interval [CI] 1.08–2.00, P = 0.013) was significantly higher in the diabetic group than in the non-diabetic group, whereas the adjusted risk of all-cause mortality (HR 2.37, 95% CI 0.94–5.98, P = 0.068) was similar. In the propensity score matched population, there were no significant differences in the risk of MACCE (HR 1.27, 95% CI 0.92–1.75, P = 0.155) and all-cause mortality (HR 2.56, 95% CI 0.91–7.24, P = 0.076) between groups. Subgroup analysis and stratification analysis revealed consistent effects on 5-year MACCE across various subgroups.

Conclusions: In patients who received successful CTO-PCI, non-diabetic patients were related to better long-term survival benefit in terms of MACCE. The risk of 5-year MACCE appeared to be similar in less-controlled and controlled diabetic patients after successful recanalization of CTO. Further randomized studies are warranted to confirm these findings.

Keywords: chronic total occlusion, percutaneous coronary intervention, diabetes mellitus, prognosis, successful revascularization

INTRODUCTION

Chronic total occlusion (CTO) occurs in ∼15–25% of patients with coronary artery disease (CAD) undergoing diagnostic coronary angiography (1, 2). Due to the development of interventional devices and dedicated techniques, percutaneous coronary intervention (PCI) for CTO has achieved high technical success rates with a low risk for procedural complications, especially in tertiary medical centers. Current guidelines have regarded revascularization for CTO as the IIa B recommendation (3). Considerable evidence suggest that successful CTO-PCI is related to a better improvement of symptoms, quality of life, and ventricular function compared to optimal medical treatment alone and unsuccessful CTO-PCI (4–6), whereas the benefit in terms of improving patient survival was not significant (7). The beneficial effect of CTO-PCI on long-term prognosis is still controversial, especially for the special group of people with diabetes (2, 8).

Type 2 Diabetes mellitus (DM) is a well-established CAD risk equivalent and is associated with a greater atherosclerotic burden, such as multivessel disease, heavily calcified coronary lesions, diffuse and small vessel CAD (9, 10). Previous studies have reported that patients with DM have an elevated incidence of CTO (∼30–40%) (11, 12). In addition, CTO patients with DM are related to longer and more technically challenging occluded lesions, with lower success rates compared with that in non-DM (13). Besides, non-DM patients were more likely to fare better after CTO-PCI for up to 3 years compared to their DM counterparts (14). However, to the best of our knowledge, no previous study has focused on longer term impact of successful recanalisation for CTO lesions in patients with vs. without DM. Therefore, we conducted a prospective, observational and real-world study to investigate 5-year clinical outcomes in type 2 diabetic and non-diabetic patients after successful CTO-PCI.

MATERIALS AND METHODS

Study Population

A total of 10,724 consecutive patients with CAD who underwent PCI were enrolled between January 2013 and December 2013 in Fu Wai Hospital, National Center for Cardiovascular Diseases, Beijing, China. Notably, we included 1,010 (9.42%) patients with at least 1 CTO lesion. CTO lesions were defined as complete obstruction of a native coronary artery for longer than 3 months with thrombolysis in myocardial infarction (TIMI) flow grade of 0 (15). Patients who have undergone a successful CTO-PCI were implanted with second-generation drug-eluting stents (DES) or biodegradable polymer DESs. Patients who received recanalisation treatment for CTO depended on contemporary practice guidelines, judgment from our team's experienced cardiologists and their own preference (16). Exclusion criteria included the following: (1) patients who underwent unsuccessful CTO-PCI ($n = 267$); (2) patients lacking both hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) data ($n = 9$); (3) patients who were diagnosed as acute STEMI within 72 h before admission ($n = 15$). Thus, the remaining 316 (43.9%) patients with type 2 DM and 403 (56.1%) patients without DM were enrolled for the final analysis (**Figure 1**). DM was defined as a FPG of at least 7.0 mmol/L, or glycated HA1c >6.5% or known diabetes, based on previous medical records of the patients and data of the therapeutic status based on the glucose-lowering therapy (17). Less-controlled DM was considered as HbA1c ≥ 7% or non-elevated FPG (18, 19). Left ventricular ejection fraction (LVEF) was measured from two-dimensional echocardiography according to modified Simpson's rule. Estimated glomerular filtration rate (eGFR) was calculated by the modified diet in renal disease equation for Chinese (20). Data of demographic, clinical and angiographic features were collected from the database and medical records retrospectively, whereas clinical endpoints during follow-up were identified prospectively. The study complied with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee at Fu Wai Hospital. All eligible participants gave written informed consent.

PCI Procedures

Coronary interventions were performed according to current standard guidelines at the discretion of the operating physician (16). Before catheterization, unless on chronic P2Y12 inhibitor therapy for > 6 days, selected PCI patients received oral administration of aspirin 300 mg and clopidogrel (loading dose 300 mg) or ticagrelor (loading dose 180 mg) at least 24 h. Patients presenting as acute coronary syndrome (ACS) scheduled for PCI received the same dose of aspirin and ticagrelor or clopidogrel (loading dose 300 or 600 mg) as soon as possible. Thereafter, unfractionated heparin (100 U/kg) was administered before PCI, however, the use of glycoprotein IIb/IIIa inhibitors was at the operator's judgment. CTO-PCI was done using bilateral injections, specialized hydrophilic wires, microcatheters and retrograde approach, when available. If both antegrade and retrograde approaches failed, intravascular ultrasound (IVUS)

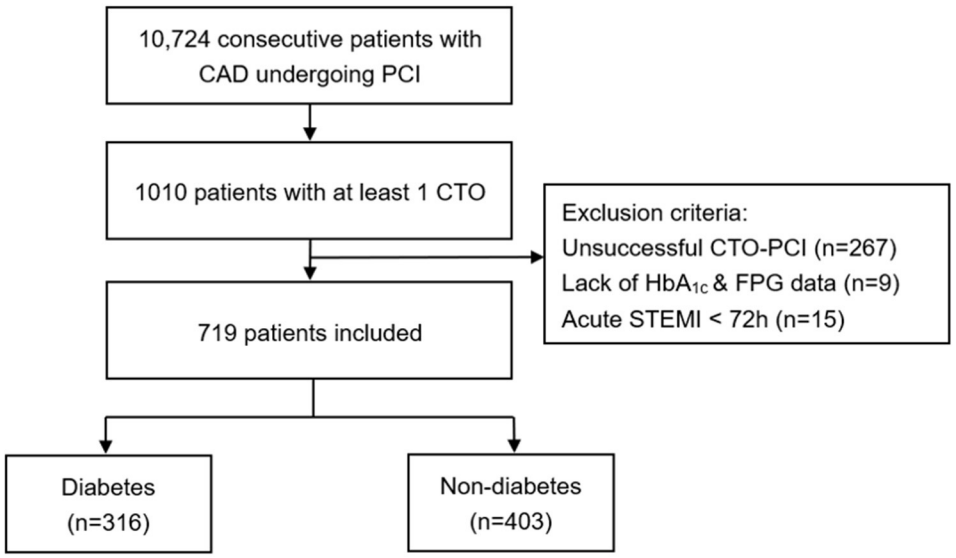

FIGURE 1 | Study flow chart. CAD, coronary artery disease; PCI, percutaneous coronary intervention; CTO, chronic total occlusion; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; STEMI, ST-segment elevation myocardial infarction.

guided wire re-entry technique would be attempted. Standard dual-antiplatelet medication was maintained for at least 12 months after PCI. The PCI procedure was considered successful if residual stenosis <30% with TIMI flow grade 3 at the end of the procedure was obtained according to visual estimation of the angiograms.

Endpoints and Follow-Up

The primary clinical outcome was the occurrence of 5-year major adverse cardiac and cerebrovascular events (MACCE) during follow-up, a composite endpoint of death, recurrent myocardial infarction (MI), stroke and target vessel revascularization (TVR). The secondary endpoint was all-cause mortality. Death that could not be attributed to a non-cardiac etiology was considered cardiac death. MI was defined by the Third Universal Definition (21). TVR was defined as revascularization for a new lesion on the target vessel either by PCI or by surgery (22). Patients were evaluated at 1, 6, and 12 months postoperatively and annually thereafter for up to 5 years. Clinical follow-up was performed through examination of hospital records, telephone follow-up and outpatient clinical visit by research coordinators.

Statistical Analysis

Categorical variables were compared with Chi-square test or Fisher's exact test, where applicable, and data were presented as frequencies and percentages. Continuous variables were tested using Student's *t*-test and were summarized as the mean ± standard deviation. The cumulative incidence of clinical outcomes was calculated by Kaplan–Meier analysis and compared using log-rank test. Covariates that were significant on univariate analysis ($P < 0.10$) or clinically relevant were included in multivariate models. Cox regression was used to compare adjusted hazard ratios based on age, eGFR, LVEF, prior stroke, prior PCI, prior MI, left anterior descending coronary artery (LAD) involvement and peripheral vascular disease (PVD) (Details available in **Supplementary Table 1**). Additionally, propensity score matching (PSM) analysis was constructed to adjust for any potential confounder in baseline characteristics between the two groups based on multivariable logistic regression model. The nearest neighbor matching algorithm was used for PSM via a 1:1 matching protocol. Exploratory subgroup analysis was carried out to assess the effect of glycemic status (DM and Non-DM) on MACCE in specific patient subsets using the same multivariable model. Similarly, stratification analysis was performed to make comparison with different groups (less-controlled DM and controlled DM, and insulin-dependent DM and non-insulin-dependent DM) on major adverse events. Cox regression analysis was also conducted to compare the DM group with non-DM group in the risk of MACCE and all-cause mortality during 2 years of follow-up. Two-tailed *P*-value of <0.05 was considered as statistically significance. The SPSS Version 26.0 (SPSS Inc., Chicago, Illinois, USA) was used for all statistical computations.

RESULTS

Baseline Patient Characteristics

The prevalence of CTO was 9.42% in the total population. Success rate of CTO-PCI was 73.6%. Among a total of 719 selected patients with at least 1 successful CTO-PCI at least in our prospective and observational cohort, 316 (43.9%) patients had DM and 69 (21.8%) were dependent on insulin (**Figure 1**). The baseline demographic and treatment characteristics of the patients with and without DM are shown in **Table 1**. Angiographic and procedural characteristics of the patients are

TABLE 1 | Baseline clinical characteristics in the diabetes and the non-diabetes groups.

Variables	Total population ($n = 719$)		*P*-value	Propensity-matched patients ($n = 578$)		*P*-value
	Diabetes ($n = 316$)	Non-diabetes ($n = 403$)		Diabetes ($n = 289$)	Non-diabetes ($n = 289$)	
Age (years)	57.8 ± 10.2	56.7 ± 10.2	0.141	57.4 ± 10.2	56.6 ± 10.2	0.347
Male	261 (82.6)	342 (84.9)	0.412	240 (83.0)	243 (84.1)	0.736
Current smoking	201 (63.6)	248 (61.5)	0.570	184 (63.7)	185 (64.0)	0.931
Hypertension	209 (66.1)	245 (60.8)	0.140	186 (64.4)	180 (62.3)	0.605
Hyperlipidemia	227 (71.8)	278 (69.0)	0.406	208 (72.0)	199 (68.9)	0.412
LVEF (%), at baseline	60.2 ± 8.6	62.6 ± 6.7	<0.001	61.45 ± 7.2	62.5 ± 6.6	0.066
eGFR (mL/min)	91.3 ± 16.6	93.1 ± 13.7	0.107	92.15 ± 16.2	93.35 ± 13.7	0.340
LDL-C (mmol/L)	2.45 ± 0.9	2.51 ± 1.0	0.399	2.47 ± 0.9	2.49 ± 1.1	0.778
Fasting glucose (mmol/L)	7.11 ± 2.57	5.01 ± 1.05	<0.001	7.24 ± 2.47	5.14 ± 0.58	<0.001
HbA1c (%)	7.51 ± 1.37	5.92 ± 0.33	<0.001	7.50 ± 1.37	5.93 ± 0.34	<0.001
Prior stroke	3 (0.9)	6 (1.5)	0.738	3 (1.0)	2 (0.7)	1.000
Prior PCI	76 (24.1)	89 (22.1)	0.534	65 (22.5)	62 (21.5)	0.763
Prior MI	97 (30.7)	115 (28.5)	0.528	81 (28.0)	79 (27.3)	0.853
Prior CABG	25 (7.9)	28 (6.9)	0.624	21 (7.3)	21 (7.3)	1.000
Familial history of CAD	71 (22.5)	93 (23.1)	0.847	65 (22.5)	72 (24.9)	0.494
COPD	7 (2.2)	12 (3.0)	0.527	7 (2.4)	7 (2.4)	1.000
PVD	8 (2.5)	10 (2.5)	0.966	3 (1.0)	7 (2.4)	0.202
Insulin-dependent DM	69 (21.8)	–	–	60 (20.8)	–	–
Baseline medication						
Aspirin	313 (99.1)	400 (99.3)	1.000	286 (99.0)	287 (99.3)	1.000
Clopidogrel	315 (99.7)	403 (100.0)	0.439	289 (100.0)	289 (100.0)	1.000
Ticagrelor	1(0.3)	–	–	–	–	–
Statin	305 (96.5)	390 (96.8)	0.850	279 (96.5)	279 (96.5)	1.000
β blocker	300 (94.9)	369 (91.6)	0.078	274 (94.8)	269 (93.1)	0.383
CCB	144 (45.6)	188 (46.7)	0.773	137 (47.4)	131 (45.3)	0.617

Values are presented as mean ± standard deviation or number (%). LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; MI, myocardial infarction; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; PVD, peripheral vessel disease; DM, diabetes mellitus; CCB, calcium channel blocker.

shown in **Table 2**. No statistically significant differences were found in the baseline clinical and lesion characteristics between the diabetic and non-diabetic group, except for LVEF. Notably, LVEF in the two groups were all within normal range. After performing propensity score matching for the enrolled patients, 289 matched pairs of patients were created and we did not find considerable differences in the baseline clinical and lesion characteristics between the two matched groups (**Tables 1**, **2**).

Follow-Up Outcomes

Over a median follow-up time was 5 (interquartile range: 2.5–5.1) years, 23 (3.2%) deaths and 175 (24.3%) MACCE occurred. DM group had a higher incidence of MACCE (diabetes vs. non-diabetes: 28.5 vs. 21.1%, unadjusted hazard ratio [HR] 1.40, 95% confidence interval [CI] 1.04–1.88, $P = 0.028$) and all-cause mortality (diabetes vs. non-diabetes: 5.1 vs. 1.7%, adjusted HR 2.97, 95% CI 1.22–7.23, $P = 0.016$). Kaplan-Meier curve analysis showed that similar results (**Figure 2**). Through multivariate analysis, we found that the MACCE risk was significantly higher in the diabetic patients compared to the non-diabetic patients (adjusted HR 1.47, 95% CI 1.08–2.00, $P = 0.013$). However, the occurrence of all-cause mortality (adjusted HR 2.37, 95% CI 0.94–5.98, $P = 0.068$) was not significantly different between the diabetic and non-diabetic groups (**Table 3**).

In propensity score-matched patients, Cox regression analyses showed no significant differences between the two matched groups with regards to the prevalence of MACCE (diabetes vs. non-diabetes: 29.1 vs. 23.2%, unadjusted HR 1.27, 95% CI 0.92–1.76, $P = 0.141$) and all-cause mortality (diabetes vs. non-diabetes: 4.5 vs. 1.7%, unadjusted HR 2.66, 95% CI 0.95–7.47, $P = 0.063$). The results of univariable and multivariable analyses showed that the risk for the primary and secondary clinical outcomes was similar between the two matched group after PSM (**Table 4**).

Additionally, after adjustment of underlying confounding factors using the same method of previous Cox regression analysis, we did not find significant difference between the two groups in the risk of MACCE (adjusted HR 1.37, 95% CI 0.93–2.03, $P = 0.106$) and all-cause mortality (adjusted HR 1.14, 95% CI 0.28–4.63, $P = 0.849$) at 2 years (Details available in **Supplementary Table 2**).

TABLE 2 | Lesion and treatment characteristics in the diabetes and the non-diabetes groups.

Variables	Total population ($n = 719$)		*P*-value	Propensity-matched patients ($n = 578$)		*P*-value
	Diabetes ($n = 316$)	Non-diabetes ($n = 403$)		Diabetes ($n = 289$)	Non-diabetes ($n = 289$)	
Characteristics of CTO lesion						
One CTO lesion	244 (77.2)	301 (74.7)	0.433	220 (76.1)	216 (74.7)	0.699
Two CTO lesions	41 (13.0)	68 (16.9)	0.148	39 (13.5)	48 (16.6)	0.295
Location of CTO lesions						
LAD	131 (41.5)	163 (40.4)	0.785	116 (40.1)	118 (40.8)	0.865
LCX	57 (18.0)	57 (14.1)	0.156	54 (18.7)	41 (14.2)	0.145
RCA	132 (41.8)	186 (46.2)	0.240	123 (42.6)	133 (46.0)	0.402
Multivessel disease	267 (84.5)	331 (82.1)	0.401	245 (84.8)	236 (81.7)	0.316
Proximal or mid	240 (75.9)	324 (80.4)	0.150	219 (75.8)	233 (80.6)	0.158
Severe Calcification	20 (6.3)	23 (5.7)	0.727	19 (6.6)	22 (7.6)	0.627
Length ≥ 20 mm	283 (89.6)	373 (92.6)	0.158	258 (89.3)	268 (92.7)	0.146
Angulation > 45°	59 (18.7)	61 (15.1)	0.207	59 (20.4)	69 (23.9)	0.316
Vessel diameter (mm)	2.97 ± 0.5	2.99 ± 0.5	0.397	2.97 ± 0.5	2.99 ± 0.5	0.621
SYNTAX score	17.30 ± 9.0	17.30 ± 8.6	0.997	17.26 ± 9.1	17.17 ± 9.0	0.909
J-CTO score	1.17 ± 0.6	1.16 ± 0.5	0.877	1.16 ± 0.59	1.24 ± 0.57	0.100
Treatment characteristics						
Number of stents for CTO-PCI						
1	48 (15.2)	75 (18.6)	0.227	43 (14.9)	52 (18.0)	0.312
2	110 (34.9)	144 (35.7)	0.821	100 (34.6)	100 (34.6)	1.000
≥3	109 (34.5)	140 (34.7)	0.945	101 (34.9)	103 (35.6)	0.862
Stent length (mm)	53.42 ± 26.4	54.09 ± 25.5	0.742	52.98 ± 26.3	55.44 ± 26.4	0.283
IVUS use	38 (12.0)	52 (12.9)	0.724	35 (12.1)	38 (13.1)	0.707

Values are presented as mean ± standard deviation or number (%). CTO, chronic total occlusion; LAD, left ascending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; J-CTO, Japanese-chronic total occlusion; PCI, percutaneous coronary intervention; IVUS, intravenous ultrasound.

Post-hoc subgroup analysis showed no significant interactions following MACCE between those covariates (age, sex, hypertension, hyperlipidemia, LVEF and SYNTAX score, all *P* for interaction > 0.05) and patients' glycemic status (**Figure 3**). In diabetic patients with successful CTO-PCI, stratification analysis further showed that patients in the less-controlled DM group were not at higher risk of MACCE, compared with patients in the controlled DM. Similar result was also found between insulin-dependent DM and non-insulin-dependent DM (**Table 5**).

DISCUSSION

We assessed the 5-year cardiovascular survival of successful CTO-PCI patients with or without DM in a prospective and real-world cohort population. Notably, we confirmed the following: (1) Non-diabetic patients were related to better long-term survival benefit in terms of MACCE for the treatment of successful CTO-PCI. (2) The risk of 5-year MACCE appeared to be comparable in less-controlled and controlled diabetic patients after successful recanalization of CTO.

With substantial and significant improvement in interventional devices and techniques, CTO-PCI has emerged as an effective revascularization strategy with high success rates for diabetic patients. Moreover, it is well-established that DM represents an important risk equivalent of CTO and an independent factor for increased MACE after CTO-PCI (23, 24). Sanguineti et al. reported that DM was a significant predictor of cardiac mortality in CTO patients (25). Additionally, Yan et al. found that both successful CTO-PCI and CTO-CABG of right coronary artery in diabetic patients showed significant reduction of all-cause death (HR 0.445, 95% CI 0.278–0.714) during long-term follow-up (26). Recently, Guo et.al also reported that in DM group, successful CTO-PCI reduced MACE risk (HR 0.61, 95% CI 0.42–0.87, $P = 0.005$) compared to optimal medical therapy alone (27). Likewise, Tsai et al. also found that DM was associated with poor prognosis in patients with CTO lesions compared with non-DM (14). Moreover, this study also showed that successful CTO-PCI was independently associated with reduced risks of all-cause death and adverse cardiovascular events only in DM population, but not in non-DM patients, which was consistent with the finding of Guo and co-workers (27). These evidences highlighted the unfavorable role of DM in CTO patients and the importance of complete recanalization of CTO patients with DM. Contrary to the results of previous findings, subgroup analysis of the randomized COURAGE trial demonstrated that there was no obvious difference in the incidence of adverse events between the medical therapy group and the PCI group in DM patients with stable coronary disease (28).

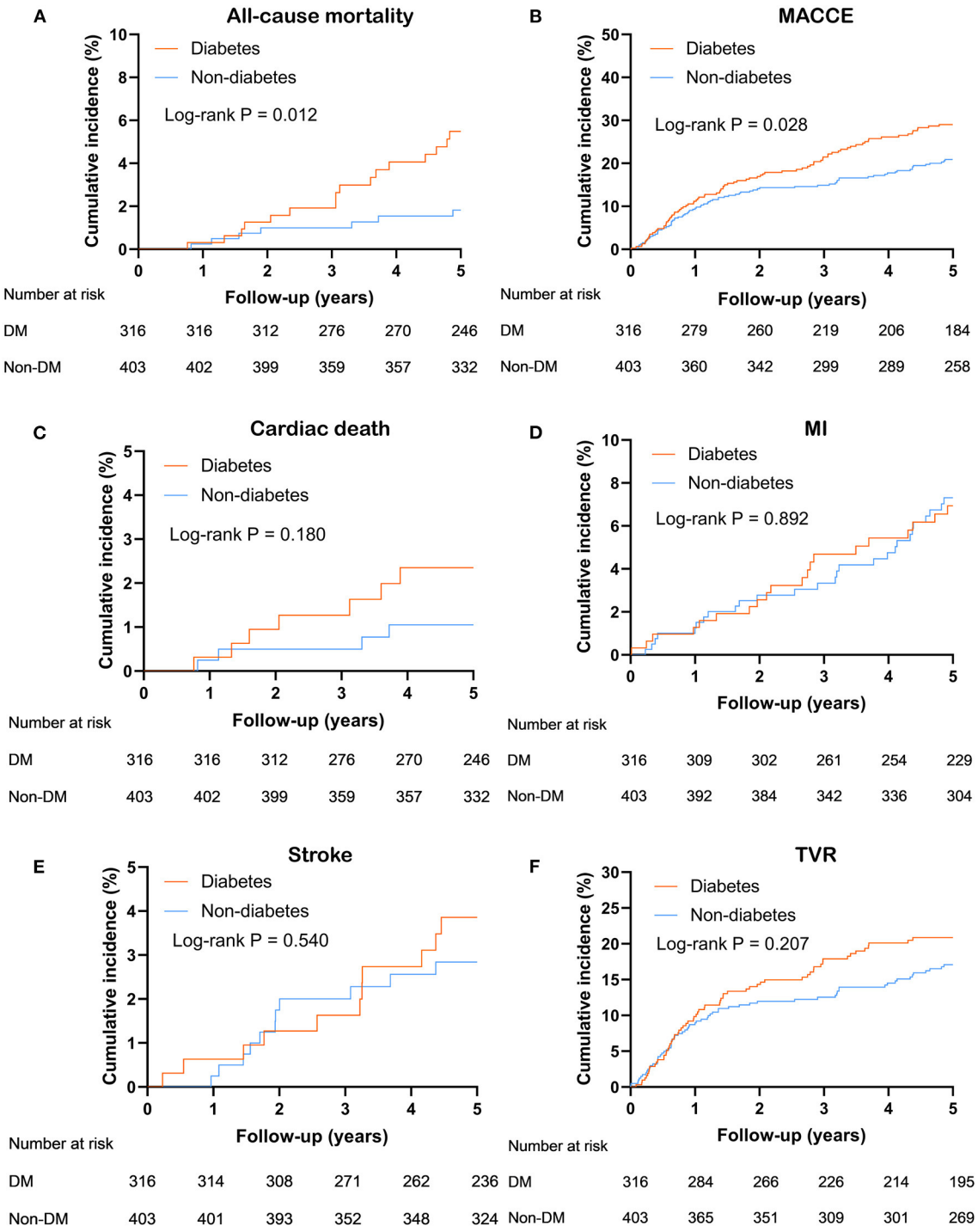

FIGURE 2 | Kaplan Meier survival curves for 5 years **(A)** all-cause mortality; **(B)** MACCE; **(C)** cardiac death; **(D)** MI; **(E)** stroke; **(F)** TVR in entire population. MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; TVR, target-vessel revascularization.

This difference may be explained by the high rate (∼30%) of crossover from medication to revascularization during the follow-up period, which may underestimate the actual effect of successful CTO-PCI.

Considerable evidence has demonstrated that the existence of DM has a detrimental effect on glucose and lipid metabolism, endothelial function and angiogenesis, leading to premature development and progression of coronary artery atherosclerosis,

TABLE 3 | Risk of various clinical outcomes up to 5 years in all patients.

Outcomes	Incidence of event at 5 years [*n* (%)]		Crude HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
	Diabetes (*n* = 316)	Non-diabetes (*n* = 403)				
All-cause mortality	16 (5.1)	7 (1.7)	2.97 (1.22–7.23)	0.016	2.37 (0.94–5.98)	0.068
Cardiac death	7 (2.2)	4 (1.0)	2.26 (0.66–7.73)	0.192	1.17 (0.30–4.60)	0.822
MI	23 (7.3)	32 (7.9)	0.93 (0.54–1.59)	0.790	0.91 (0.52–1.59)	0.744
Stroke	11 (3.5)	11 (2.7)	1.30 (0.56–2.99)	0.541	1.00 (0.43–2.35)	1.000
TVR	64 (20.3)	67 (16.6)	1.25 (0.89–1.76)	0.204	1.28 (0.90–1.81)	0.169
MACCE	90 (28.5)	85 (21.1)	1.40 (1.04–1.88)	0.028	1.47 (1.08–2.00)	0.013

MI, myocardial infarction; TVR, target-vessel revascularization; MACCE, major adverse cardiac and cerebrovascular events.

TABLE 4 | Risk of various clinical outcomes up to 5 years in propensity-matched patients.

Outcomes	Incidence of event at 5 years [*n* (%)]		Crude HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
	Diabetes (*n* = 316)	Non-diabetes (*n* = 403)				
All-cause mortality	13 (4.5)	5 (1.7)	2.66 (0.95–7.47)	0.063	2.56 (0.91–7.24)	0.076
Cardiac death	4 (1.4)	3 (1.0)	1.36 (0.30–6.06)	0.690	1.18 (0.25–5.50)	0.835
MI	22 (7.6)	24 (8.3)	0.93 (0.52–1.66)	0.807	0.94 (0.53–1.68)	0.835
Stroke	11 (3.8)	6 (2.1)	1.88 (0.69–5.07)	0.216	1.00 (0.39–2.60)	1.000
TVR	61 (21.1)	54 (18.7)	1.13 (0.79–1.64)	0.502	1.13 (0.78–1.64)	0.509
MACCE	84 (29.1)	67 (23.2)	1.27 (0.92–1.76)	0.141	1.27 (0.92–1.75)	0.155

MI, myocardial infarction; TVR, target-vessel revascularization; MACCE, major adverse cardiac and cerebrovascular events.

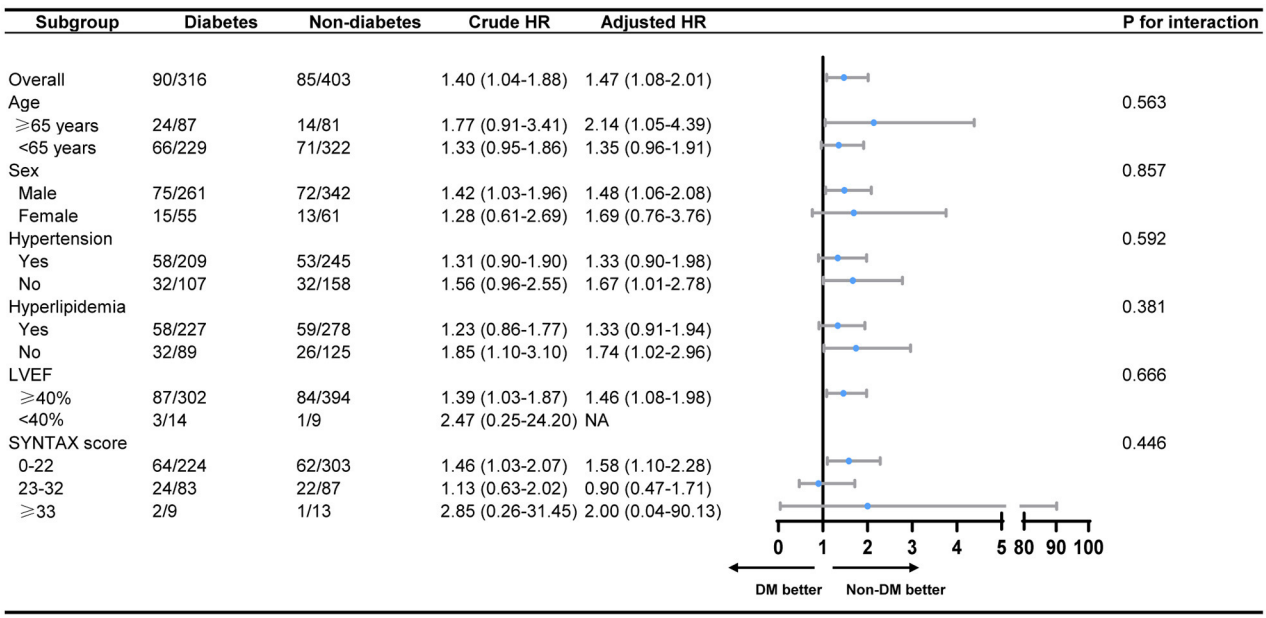

FIGURE 3 | Subgroup analysis on MACCE between the diabetes group and the non-diabetes group. MACCE, major adverse cardiac and cerebrovascular events; LVEF, left ventricular ejection fraction; LAD, left ascending coronary artery; NA, not applicable.

inadequate collateral development and harmful clinical outcomes (29–31). Previous studies have showed that well-established collateral circulation after CTO is crucial to supply the downstream perfusion area, alleviate myocardial damage, reduce infarct size, improve LVEF and eventually decrease adverse events (32, 33). This may explain the worse prognosis on diabetic

TABLE 5 | Stratification analysis on 5-year MACCE in the diabetes group.

Stratification	Adjusted HR (95% CI)	*P*-value
Less-controlled DM ($n = 169$)	1.05 (0.68–1.62)	0.822
Controlled DM ($n = 147$)		
Insulin-dependent DM ($n = 69$)	1.34 (0.82–2.20)	0.241
Non-insulin-dependent DM ($n = 247$)		

patients with successful CTO-PCI. However, recently, Yang et al. reported that after successful recanalization of CTO, there was no significant distinction between diabetic and non-diabetic effects of coronary collaterals on MACCE and repeat revascularization during a median follow-up of 13.5 months (34). Yang and co-workers speculated that well-developed coronary collaterals may not adequately substitute normal blood supply and thus good collateral circulation is insufficient.

Recently, with regard to the long-term clinical outcomes of successful CTO-PCI in patients with vs. without DM, a meta-analysis by Zhu et al. which included 9,847 patients after successful CTO-PCI (4,238 diabetic patients and 5,069 non-diabetic patients) revealed that the prevalence of MACEs (RR 1.26, 95% CI 1.02–1.56, $P = 0.03$) was significantly higher, compared with patients without DM (35). Likewise, consistent with Guo and co-workers (27), our study also reported that the rates of MACCE after successful CTO-PCI were higher in diabetic patients than in non-diabetic patients. In contrast, Ruiz Garcia et al. reported that in patients who underwent successful revascularization of CTO comparable rate of MACE was observed between the diabetic and non-diabetic patients in the drug-eluting stent era (36). Although this was a prospective randomized clinical study, the atypical definition of CTO (occlusion longer than 2 weeks), the small sample size of its enrolled patients (75 diabetic and 132 non-diabetic patients) and the modest follow-up period of 1 year restricted the accuracy of the results. In our study, we also found that the prevalence of 2-year (shorter term) clinical outcomes was comparable between the diabetic patients and non-diabetic patients, which was consistent with the findings of Ruiz Garcia and co-workers. Thus, it is necessary to evaluate longer term prognosis for diabetic patients undergoing successful CTO-PCI.

Besides, we found that diabetic patients with less-controlled DM were not at a higher risk of 5-year MACCE, compared with those with controlled DM, which was consistent with the findings of the randomized VADT trial (37). It demonstrated that intensive glucose control had shown no evidence of cardiovascular or overall survival benefit during the median follow-up of 5.6 years. However, Holman et al. reported that after longer-term (about 10 years) observational follow-up, both in the sulfonylurea-insulin group and the metformin group, diabetic patients with glycemic control had significant reductions in MI and all-cause mortality (38). We speculated that the reasons for the inconsistent findings of previous studies may be the different population characteristics and therapeutic approaches. Further randomized controlled trials with longer term follow-up are warranted to validate our results.

Our study had some inevitable limitations. First, it was a single-center, prospective and observational study. Although we performed propensity score matching to reduce potential selection bias and minimize the confounding factors, unadjusted confounders still existed. Second, our real-world study is a *post-hoc* analysis of a consecutively enrolled cohort of CAD patients undergoing PCI. Since this was not a dedicated CTO cohort, we expected the sample size of CTO patients to be modest when designing the study. Third, there was a lack of specific information in our database, such as coronary collateral scoring and the glycemic control during the long follow up, which may impair the precise evaluation of future risk of adverse events in CTO patients. Fourth, our center was a tertiary medical hospital which performed high volume of CTO-PCI and had many experienced cardiologists. Generalizability might be limited in less experienced center with lower number of CTO-PCI cases. In fact, previous studies have indicated that patients in DM group were more likely to have complex clinical characteristics (9, 13). However, in our study, baseline clinical and lesion characteristics were comparable between the diabetic and non-diabetic groups, which may be partially interpreted by these limitations above.

CONCLUSIONS

The present study suggests that diabetic patients with successful CTO-PCI encountered more long-term adverse clinical outcomes, based on their complex lesions and co-morbidities. After a successful CTO-PCI, non-diabetic patients were associated with better long-term survival benefit in terms of MACCE. The risk of 5-year MACCE appeared to be comparable in less-controlled and controlled diabetic patients. These findings may provide clinical insight into treatment option for unselected patients with diabetes. Further randomized controlled trials with longer term follow-up are required to validate our results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Ethics Committee at Fu Wai Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

PW, DY, SJ, RG, and JY contributed to the study design and interpretation of the results. PZ, LJ, YS, JX, XT, CZ, SJ, YL, DY,

and TL contributed to the collection, analysis, or interpretation of data. PW prepared the manuscript. JY, RG, BX, YY, XZ, SJ, and DY critically revised the manuscript. All authors read and approved the final submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.691641/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Cardiovascular Medicine

CASE REPORT
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Case Report: Key Role of the Impella Device to Achieve Complete Revascularization in a Patient With Complex Multivessel Disease and Severely Depressed Left Ventricular Function

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Background: Left ventricle (LV) assist devices may be required to stabilize hemodynamic status during complex, high-risk, and indicated procedures (CHIP). We present a case in which elective hemodynamic support with the Impella CP device was essential to achieve complete revascularization with PCI in a patient with complex multivessel disease and severely depressed LV function.

Case Summary: A 45-year-old male with no previous history of cardiovascular disease presented to the emergency department for new onset exertional dyspnoea. Echocardiography showed severely depressed LV function (EF 27%) that was confirmed with cardiac magnetic resonance. Two chronic total occlusions (CTOs) of the proximal right coronary artery (RCA) and left circumflex coronary artery (LCx) were found at coronary angiography. After Heart Team evaluation, PCI with Impella hemodynamic support was planned. After crossing and predilating the CTO of the LCx, ventricular fibrillation (VF) occurred. No direct current (DC) shock was performed because the patient was conscious thanks to the support provided by the Impella pump. About 1 min later, spontaneous termination of VF occurred. Afterwards, the two CTOs were successfully treated with good result and no complications. Recovery of LV function was observed at discharge. At 9 months, the patient had no symptoms and echocardiography showed an EF of 60%.

Discussion: In this complex high-risk patient, hemodynamic support was essential to allow successful PCI. It is remarkable that the patient remained conscious and hemodynamically stable during VF that spontaneously terminated after 1 min, likely because the Impella pump provided preserved coronary perfusion and LV unloading. This case confirms the pivotal role of Impella in supporting CHIP, particularly in patients with multivessel disease and depressed LV function.

Keywords: coronary intervention, PCI, Impella, LV assistance, ventricular fibrillation

INTRODUCTION

A percutaneous coronary intervention (PCI) performed in complex coronary anatomy, such as multivessel disease, left main involvement, chronic total occlusions (CTOs) and last remaining vessel, particularly in patients with poor left ventricle (LV) function is dubbed "CHIP" (complex, high-risk, and indicated procedure) (1). To deal with CHIP, mechanical circulatory support may be necessary to increase procedural safety and success (2). Several studies have demonstrated that the Impella pump (Abiomed, Danvers, MA, USA), a catheter-based miniaturized ventricular assist device, is safe, easy to implant and provides excellent hemodynamic support during high-risk PCI (3–6). The efficacy of this device has been proven superior to intra-aortic balloon pump (IABP) in this scenario (7). We present a case in which elective hemodynamic support with the Impella pump was essential for allowing complete revascularization in a young patient with complex multivessel coronary disease and severely depressed LV function.

CASE PRESENTATION

A 45-year-old male, smoker, with no previous history of cardiovascular disease presented to our emergency department for new onset of exertional dyspnoea. Echocardiography showed LV dilatation (EDV/ESV 245/180 ml) with diffuse hypokinesia, inferior wall akinesia and reduced ejection fraction (27%). Cardiac magnetic resonance (MRI) confirmed severely depressed LV function with viable myocardium and a limited subendocardial scar suggesting hibernating myocardium, potentially reversible by revascularization. Coronary angiography showed chronic total occlusions (CTOs) of the proximal right coronary artery (RCA) and mid left circumflex (LCx) coronary artery (**Figure 1**). The case was discussed with the heart team that decided to treat the patient with Impella-supported PCI because of the high surgical risk related to the depressed LV function and patient's preference. The right femoral access was used to introduce the Impella CP device through a 14-Fr introducer with preclosure by two suture-mediated closure devices (ProGlide, Abbott Vascular Devices, Redwood City, CA, USA). A detailed description of percutaneous catheter-based left ventricular support using the Impella CP device has been previously reported (8). A dual access (left common femoral artery with a 7-Fr introducer and right radial artery with a 6-Fr introducer) was obtained for visualization of the occluded vessels and contra-lateral coronary injection. The CTO of the LCx was successfully crossed using a Fielder XT guidewire (Asahi Intecc Co., Ltd, Japan) supported by a microcatheter (Finecross, Terumo Medical, Corp., Japan) and predilatation of the obtuse marginal branch was performed. At this point, ventricular fibrillation (VF) occurred but the patient remained conscious and hemodynamically stable. We asked the nurse to prepare the sedation before direct current (DC) shock. However, about 1 min later, spontaneous termination of the tachyarrhythmia occurred. The Impella CP parameters during the procedure and the hemodynamic support provided by the device during VF are shown in **Figure 2**. PCI of the LCx and obtuse marginal branch was successfully performed with implantation of two drug-eluting stents (DES) using a T-stent

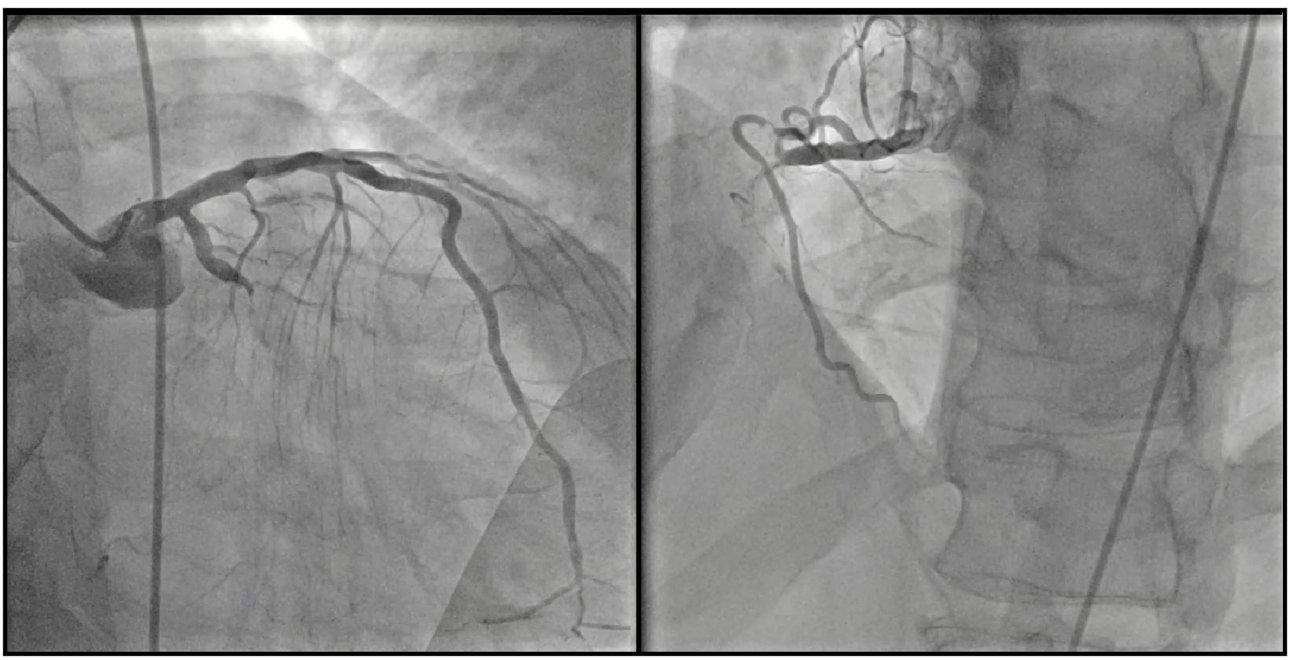

FIGURE 1 | Coronary angiography. *Left panel*: chronic total occlusion of the mid left circumflex coronary artery. *Right panel*: chronic total occlusion of the proximal right coronary artery.

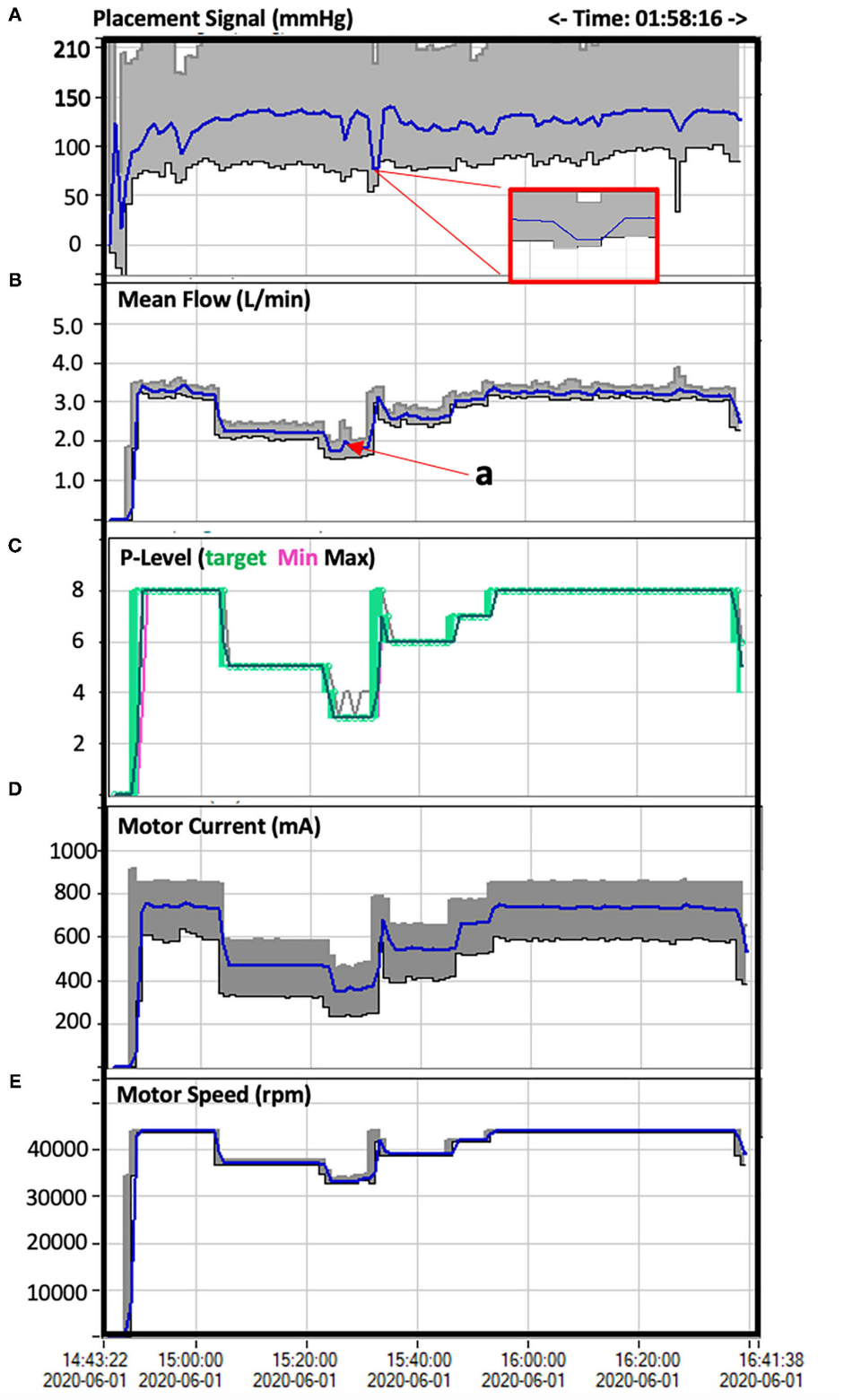

FIGURE 2 | Impella CP parameters during the procedure. **(A)** the Placement Signal is an approximation of the central aortic pressure (mmHg) with the gray area representing the systolic and diastolic pressures and the blue line the mean aortic pressure. The red box highlights in magnified form the 1-min pressure drop and

(Continued)

FIGURE 2 | reduced pulsatility during the VF episode and the immediate increase of pressure and pulsatility after spontaneous termination of the tachyarrhythmia. **(B)** This curve represents the mean Impella flow (L/min) during the procedure. A short flow peak (**a**) is visible at maximal compromised cardiac function during VF due to proportional reversed response to compensate for the reduced cardiac flow. Impella flow is managed based on the Performance (P-Level) **(C)**, which corresponds to Motor Current (mA) **(D)** and motor speed (rpm) **(E)** and can be manually adjusted. High flow requires high Motor Current and Motor Speed (8). During the VF episode, Impella Performance and Flow were manually and gradually reduced (from P8 down to P3) in anticipation to DC shock and were increased again as soon as the patient stabilized after VF termination.

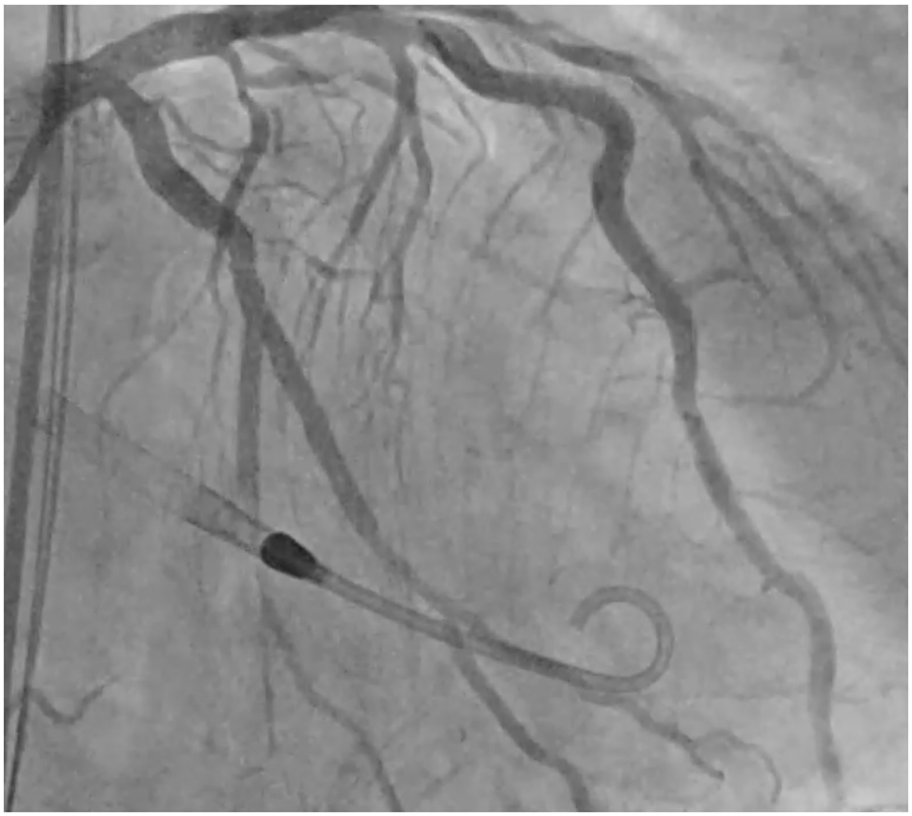

FIGURE 3 | Left circumflex coronary artery after PCI. Final result after implantation of two drug-eluting stents using the T-stent technique.

technique (**Figure 3**). Afterwards, we attempted PCI of the RCA occlusion using a dual-lumen microcatheter (Crusade, Kaneka Medical Products, Japan) to perform a parallel-wire technique. After crossing the CTO with a 0.014" Gaia Third guidewire (Asahi Intecc Co., Ltd, Japan) and predilation with a 2.0-mm semi-compliant balloon, coronary angiography showed a dominant RCA with a bifurcation lesion involving a large marginal branch. A Supercross 120° microcatheter (Teleflex Inc., Morrisville, NC, USA) was used to wire the branch and PCI was performed deploying a dedicated stent for bifurcation lesions (Tryton side branch stent, Cardinal Health Inc., Dublin, Ohio, USA) in the marginal branch and multiple DES in the main vessel with a good angiographic result (**Figure 4**). Of note, after the short VF episode, a stable hemodynamic status was maintained by the Impella CP support during this complex procedure. After withdrawal of the Impella and removal of the 14-Fr sheath, haemostasis was successfully obtained by tightening the two ProGlide sutures. Afterwards, the patient was treated with i.v. levosimendan. Three days later, the echocardiogram showed reduction of LV volume (EDV/ESV from 245/180 to 130/53 ml), persistent inferior akinesia and normalization of LV function (EF 59%), confirming the hypothesis of hibernating myocardium suggested by MRI. The patient was discharged 5 days after PCI. At 30-day follow-up, he was asymptomatic and resumed moderate physical activity. At 9 months, he resumed full physical activity and the echocardiogram showed an EF of 60%.

DISCUSSION

Patients with multivessel or left main coronary artery disease (CAD) and severely depressed LV function are generally considered for revascularization by coronary artery bypass graft surgery (CABG). Such patients may also be deemed potential candidates for high-risk PCI. In our case, due to patient's preference for PCI over CABG, the heart team decision was to proceed with a percutaneous intervention.

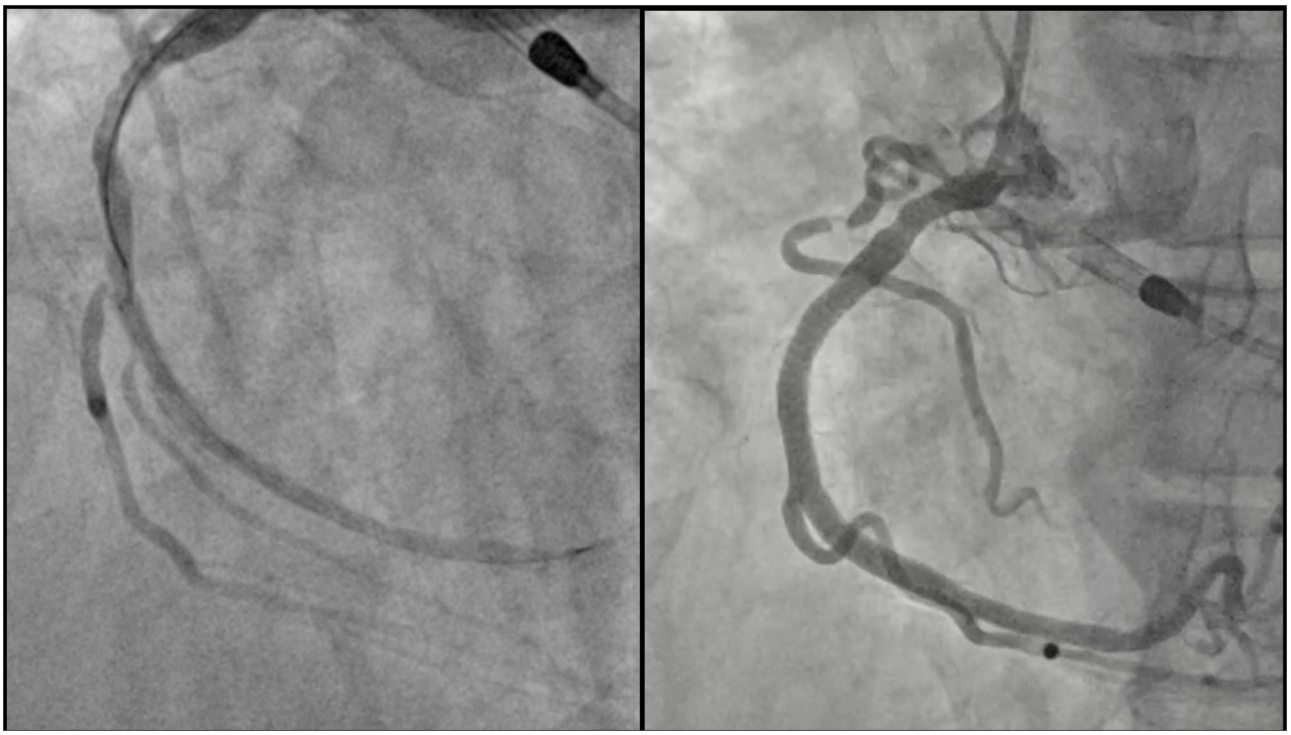

FIGURE 4 | Right coronary artery after PCI. *Left panel*: result after predilatation. A severe stenosis of the marginal branch ostium is shown. Note the Supercross 120° microcatheter that was used to wire the branch. *Right panel*: final result after deployment of the Tryton side branch stent in the marginal branch and multiple drug-eluting stent implantation in the right coronary artery.

This option, is potentially hazardous as transient ischemia caused by coronary balloon inflation and stent deployment may result in hemodynamic collapse or lethal arrhythmias. Thus, we used circulatory support with the Impella CP device, initiated prior to the intervention that allowed successful PCI of the two CTOs without abrupt cardiovascular deterioration during the procedure. Beside procedural safety, the possibility of complete revascularization during Impella-protected PCI has demonstrated a reduction of re-hospitalization (9). It is remarkable that the patient remained conscious and hemodynamically stable during VF that lasted about 1 min and spontaneously terminated, likely because Impella support maintained coronary perfusion and LV unloading. Indeed, effective LV unloading provided by the Impella pump has a clear benefit in patients with severely impaired LV function because it can effectively support the failing circulation. A growing body of registries and observational data suggests an important role for the Impella system in the treatment of selected high-risk PCI. In a systematic review of 20 studies (4 randomized controlled trials [RCTs], 2 controlled observational studies, and 14 uncontrolled observational studies) in 1,287 patients, the Impella device was found to improve procedural and hemodynamic parameters (10, 11). However, large RCTs will be needed to conclusively provide the level of clinical evidence needed to achieve a Class I guideline/recommendation for Impella support for high-risk PCI. The PROTECT IV (ClinicalTrials.gov Identifier: NCT04763200), a large, prospective, multi-center RCT is ongoing for assessing the effectiveness and safety of Impella-supported PCI compared with IABP to achieve complete revascularization and improve outcome in high-risk patients with complex CAD and reduced LV function. The trial is also supposed to clarify which patients benefit most from this approach.

CONCLUSION

This case confirms the Impella pivotal role in supporting complex high-risk PCI, particularly in patients with multivessel CAD and depressed LV function even in presence of malignant tachyarrhythmias such as ventricular fibrillation.

AUTHOR'S NOTE

This paper was the original work of the authors who have all seen and approved of the paper and authorship. The article has not been published elsewhere and is not under consideration in any other journals.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the individual's legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

GM have collected data for the paper writing and edited the figures. GM, LG, and AB performed the procedure. PO and AB contributed in the writing of the manuscript and the final revision of the manuscript.

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Effect of Drug-Coated Balloon in Side Branch Protection for *de novo* Coronary Bifurcation Lesions: A Systematic Review and Meta-Analysis

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Background: At present, there are a variety of treatment strategies for percutaneous coronary intervention. The role of drug-coated balloon (DCB) in the treatment of side branch for *de novo* coronary bifurcated lesions (CBL) is unclear.

Objective: To examine the effect of DCB in side branch protection for *de novo* CBL.

Methods: Electronic databases, including Pubmed, Embase, the Web of science, Cochrance library, CNKI, CBM, WanFang Data and VIP were searched for studies that compared DCB with non-drug-coated balloon (NDCB) in side branch protection for *de novo* CBL from inception through July 7th, 2021. The primary outcome was target lesion revascularization (TLR). Secondary clinical outcomes included myocardial infarction (MI), cardiac death (CD). The angiographic outcomes included side branch late lumen loss (LLL), minimum lumen diameter (MLD), diameter stenosis (DS) and binary restenosis (BR). The target lesion failure (TLF) was also analyzed.

Results: A total of 10 studies, including 5 randomized controlled trials and 5 non-randomized observational studies, with 934 patients were included. Meta-analysis results of angiographic outcomes suggested that DCB group had the less LLL, DS and BR and the higher MLD compared with NDCB group at follow-up ($P < 0.05$). Meta-analysis results of clinical outcomes suggested that the significant difference in the TLR, MI and CD between DCB group and NDCB group has not been found yet ($P > 0.05$). However, the MACE of DCB group was significantly less than that of NDCB group at 9-month follow-up [OR = 0.21, 95%CI (0.05, 0.84), $P = 0.03$] and 12-month follow-up [OR = 0.45, 95%CI (0.22, 0.90), $P = 0.02$]. In addition, there was no significant difference in TLF between DCB group and NDCB group ($P > 0.05$).

Conclusions: DCB had great effect in side branch protection for *de novo* CBL at short and medium-term follow-up with no reduction in the procedural success rate.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=267426, PROSPERO [Identifier: CRD42021267426].

Keywords: DCB, CBL, side branch, TLR, TLF, systematic review, meta-analysis

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HIGHLIGHTS

- DCB did not reduce the procedural success rate.
- DCB had great effect in side branch protection.
- DCB reduced the major adverse cardiac events.

INTRODUCTION

Coronary bifurcation lesions (CBL) account for 15–20% of all percutaneous coronary intervention (PCI) and remain one of the most challenging lesions in interventional cardiology (1). Compared with coronary artery disease without bifurcation lesions, interventional treatment of CBL is not only more difficult in technology and more complicated in operation, but also poor in prognosis (2, 3). The optimal management, which can improve the procedural success rate and reduce long-term cardiac events, is still the subject of considerable debate. The provisional stenting strategy is currently considered the standard approach for the treatment of the majority of CBL (3, 4). The side branch may (or may not) be treated after the main vessel stent implantation according to the side branch flow and angiographic results. The advantage of the provisional stenting strategy is that the side branch treatment remains an open choice throughout the procedure. Early definite stent thrombosis is reduced when a single-stent strategy is used in CBL compared with the double-stent strategy (5). PCI using a provisional stenting strategy in CBL is associated with a reduction in all-cause mortality at long-term follow-up (6). Nevertheless, the side branch which has obvious functional value to patients cannot be lost during PCI. Long-term clinical outcomes are not only determined by the main vessel status after stent implantation, but also related to the side branch treatment. Therefore, it is a valuable problem that how to deal with the side branch. Drug-Coated Balloon (DCB), a combination of common balloon angioplasty and drug-eluting technology, releases antiproliferative drugs to the coronary artery wall locally, so as to inhibit intimal hyperplasia. In *de novo* CBL, DCB use in the side branch is an attractive approach (7). A study including 349 patients compared the side branch result using DCB vs. common balloon angioplasty indicates that DCB can reduce the side branch late lumen loss, but cannot reduce the side branch binary restenosis significantly at 9 months (8). However, the results are inconclusive, with many unanswered questions including actual impact on meaningful clinical endpoints. We performed a systematic review and meta-analysis to examine the effect of DCB in side branch protection for *de novo* CBL.

METHODS

The study protocol was registered with PROSPERO (CRD42021267426) and performed based on the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines (9).

Eligibility Criteria

Clinical studies comparing DCB with non-drug-coated balloon (NDCB) for the treatment of the side branch in *de novo* CBL were included. The side branch was treated with DCB in the treatment group, while in the control group, the side branch was treated with NDCB. In both groups, the side branch did not consider stent implantation. The type of study design included randomized controlled trial (RCT) and non-randomized observational study (nROS). Studies with incomplete data and no access to key data were excluded.

Outcomes and Definitions

The primary outcome was target lesion revascularization (TLR). Secondary clinical outcomes included myocardial infarction (MI), cardiac death (CD). The major adverse cardiac events (MACE) which was defined as the sum of TLR, MI and CD was also analyzed. The angiographic outcomes included the side branch late lumen loss (LLL), minimum lumen diameter (MLD), diameter stenosis (DS) and binary restenosis (BR). The LLL was defined as the difference between the MLD measured post-procedure and the MLD measured at angiographic follow-up. The BR was defined as a diameter stenosis of at least 50%. The target lesion failure (TLF) was also concerned. The TLF was defined as the failure of side branch protection during operation, including complications such as dissection and thrombosis, and thrombolysis in myocardial infarction (TIMI) less than grade 3, or even salvage stent implantation.

Search Strategy

Electronic databases, including Pubmed, Embase, the Web of science, Cochrance library, China National Knowledge Infrastructure (CNKI), China Biomedical database (CBM), Wanfang Data knowledge service platform (WanFang Data), and VIP information resource integration service platform (VIP) were searched without language restriction from inception through July 7th, 2021. The searched strategy was as follows: ("coronary bifurcation lesions" OR "bifurcation lesions" OR "CBL") AND ("drug eluting balloon" OR "drug coated balloon" OR "drug balloon" OR "DEB" OR "DCB").

Study Screening and Data Extraction

Two researchers combined the eligibility criteria, independently screened the articles, extracted the data and cross-checked, and the differences were decided through discussion or arbitrated by the third researcher. Firstly, duplicate records were excluded through document management software. Then, the titles and abstracts of the remaining articles were read and the articles that obviously did not meet the eligibility criteria were excluded. Finally, after reading the full text of the remaining articles, the articles that meet the eligibility criteria were retained. Data were extracted from the included articles, including general information, methodological information, research object information, intervention information, and treatment outcome.

Quality Assessment

The quality of each study was assessed by evaluating specific elements of each study design, with Jadad scales (10) and Newcastle-Ottawa Scales (NOS) (11) for RCTs and nROSs, respectively. In addition, the risk of bias for RCTs was assessed according to the Risk of

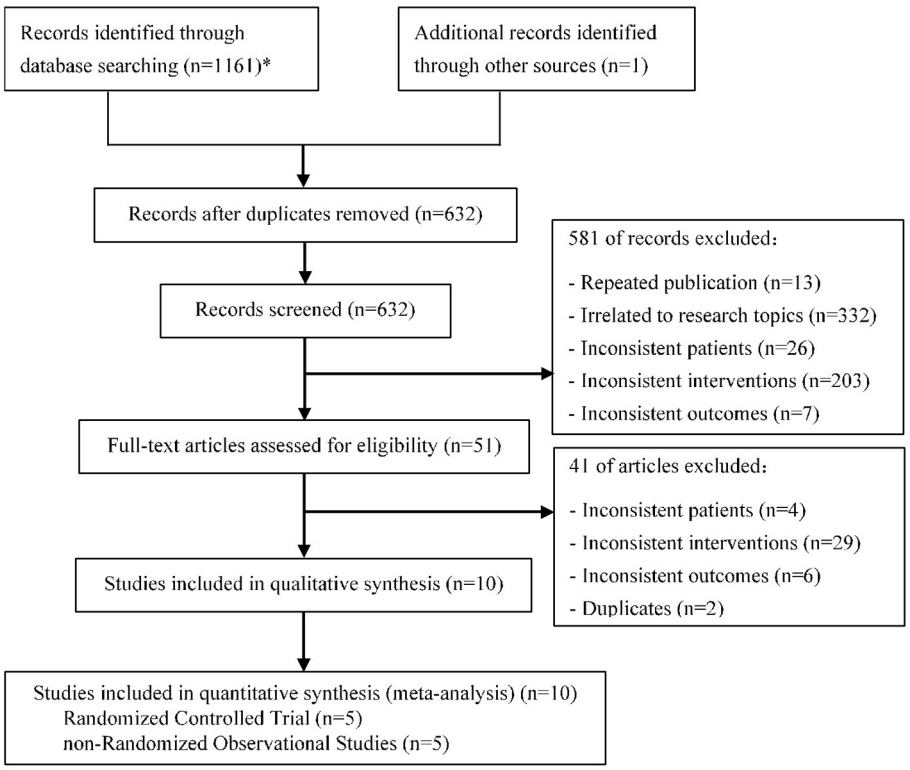


FIGURE 1 | Flow chart for literature screening (PRISMA Flow Diagram). *PubMed (178); Embase (123); Web of science (313); Cochrane library (164); CNKI (174); CBM (61); WanFang (86); VIP (62).

Bias assessment Tool that was recommended by the Cochrane Collaboration (12).

Statistical Analysis

Statistical analysis was performed using RevMan 5.3 and Stata 14 software. Continuous variables were expressed as mean difference (MD) expressed by 95% confidence intervals (CI). Binary variables were expressed as odds ratio (OR) expressed by 95%CI. First, clinical heterogeneity and methodological heterogeneity was assessed. Then, statistical heterogeneity was assessed using the Cochrane Q and I^2 statistics (13). A $P < 0.05$ or $I^2 \geq 50\%$ suggested a high degree of statistical heterogeneity. The fixed-effect model was used when the heterogeneity was not significant, otherwise, the random-effect model was used (14). Inverse Variance pooling model was adopted in both the fixed-effects model and random-effects model. The trial sequential analysis was carried out to evaluate the reliability of the primary outcome results. Funnel plots were drawn to evaluate the possibility of publication bias when the number of studies was ≥10. The funnel plot of asymmetric distribution indicated that there was a high possibility of publication bias. In addition, the possibility of publication bias was analyzed by Egger's test. A $P \geq 0.05$ indicated that the possibility of publication bias was less. Finally, in order to evaluate the stability of the results, we carried out sensitivity analysis by eliminating included studies item by item.

RESULTS

Search Results and Study Characteristics

After screening 1,162 initial articles using the electronic databases, 10 clinical studies (15–24) were finally identified, including 5 RCTs and 5 nROSs. The flow chart for literature screening was shown in **Figure 1**. Two of the 10 studies were multi-center studies (17, 18). The lesion location of 7 studies included the left main coronary artery (15, 16, 19, 20, 22–24), while the other 3 studies did not (17, 18, 21). There was no significant difference in age, gender, and risk factor (such as hypertension, diabetes mellitus, smoking status, et al.) between the treatment group and the control group in each study. In 9 studies, the main vessel was treated with stenting (15–17, 19–24), among which 2 studies did not specify the types of stents (19, 20). In all studies, the side branch was treated with DCB in the treatment group, while in the control group, the side branch was treated with NDCB. Eight of the 10 studies used the DCB of paclitaxel (16–18, 20–24), while the other two studies did not describe the specific type of DCB (15, 19). One study did not mention the presence or absence of pre-dilation (16), and the others used pre-dilation technology. In addition, all patients

TABLE 1 | The baseline characteristics of included studies.

References	Year	Design	Multi-center	Lesion location	CBL type	Pre-dilation	Gender (M/F)		Age (year)		Main vessel	Side branch		DCB type	Outcomes and follow-up		TLF report	Jadad/ NOS
							T	*C*	*T*	*C*		*T*	*C*		Angiographic	Clinical		
Bu et al. (15)	2021	RCT	N	Ang type	Lefevre I	Y	23/7	21/9	61.5 ± 7.3	59.1 ± 10.7	DES	DCB	NDCB	NA	TLR; MI; CD (12-months)	MLD; DS (6-months)	N	3*
Herrador et al. (16)	2013	nROS	N	Ang type	Ang type	NA	43/7	40/10	63.1 ± 11	61.9 ± 10.8	DES	DCB	NDCB	SeQuent Please	TLR; MI; CD (12-months)	LLL; MLD; DS; BR (12-months)	Y	8$^{\Delta}$
Jing et al. (17)	2020	RCT	Y	Non-LM	Medina (1,1,1); (0,1,1); (1,0,1)	Y	90/23	71/38	59.9 ± 10.1	61.8 ± 9.4	DES	DCB	NDCB	Bingo	TLR; MI; CD (1/6/9-months)	LLL; MLD; DS (9-months)	Y	6*
Kleber et al. (18)	2016	RCT	Y	LAD; LCX; RCA	Medina (0,0,1); (0,1,0); (0,1,1)	Y	24/8	23/9	66 ± 12	69 ± 10	no-stenting	DCB	NDCB	SeQuent Please	TLR; MI; CD (9-months)	LLL; MLD; DS; BR (9-months)	Y	6*
Li et al. (19)	2019	nROS	N	LM	Medina (1,1,1)	Y	27/17	37/29	58.8 ± 10.2	58.3 ± 9.5	any stent	DCB	NDCB	NA	TLR; MI; CD (12-months)	DS (12-months)	N	8$^{\Delta}$
Xia et al. (20)	2019	nROS	N	LM; LAD; LCX	Medina (1,1,1); (0,1,1); (1,0,1)	Y	40/9	42/24	61.14 ± 10.74	58.46 ± 11.87	any stent	DCB	NDCB	SeQuent Please	MI; CD (6/9/12-months)	—	Y	9$^{\Delta}$
Zhang (21)	2019	nROS	N	LAD; LCX; RCA	Ang type	Y	25/21	27/28	64.46 ± 4.14	65.02 ± 5.08	DES	DCB	NDCB	SeQuent Please	MI; CD (3/6/12-months)	—	Y	8$^{\Delta}$
Zhang et al. (22)	2019	nROS	N	Ang type	Medina (1,1,1); (0,1,1); (1,0,1)	Y	21/7	22/10	62.0 ± 8.3	58.5 ± 10.8	DES	DCB	NDCB	SeQuent Please	TLR; MI; CD (9-months)	LLL; MLD (9-months)	Y	7$^{\Delta}$
Zhao (23)	2017	RCT	N	Ang type	Medina (1,1,1); (0,1,1); (1,0,1)	Y	23/6	25/6	57.5 ± 11.6	61.2 ± 9.2	DES	DCB	NDCB	SeQuent Please	TLR; MI; CD (12-months)	LLL; MLD; BR (9-months)	Y	3*
Zong et al. (24)	2018	RCT	N	Ang type	Medina (1,1,1); (0,1,1); (1,0,1)	Y	13/8	11/10	57.5 ± 7.4	55.2 ± 7.3	DES	DCB	NDCB	SeQuent Please	TLR; MI; CD (6-months)	LLL; MLD (6-months)	N	4*

**Jadad.*

$^{\Delta}$NOS.

CBL, coronary bifurcation lesions; M, male; F, female; T, treatment group; C, control group; NOS, Newcastle-Ottawa Scales; RCT, randomized controlled trial; nROS, non-randomized observational study; LM, Left main coronary artery; LAD, Left anterior descending artery; LCX, Left circumflex artery; RCA, Right coronary artery; DES, drug-eluting stent; DCB, drug-coated balloon; NDCB, non-drug-coated balloon; TLF, Target lesion failure; TLR, Target lesion revascularization; MI, Myocardial infarction; CD, Cardiac death; LLL, Late lumen loss; MLD, Minimum lumen diameter; DS, Diameter stenosis; BR, Binary restenosis; NA, unavailable.

were treated with dual antiplatelet therapy. The longest follow-up time was 12 months. Characteristics of included studies were shown in **Table 1**.

Risk of Bias in the Included Studies

The quality of each study was assessed by evaluating specific elements of each study design, with Jadad or NOS for RCTs and nROSs, respectively. The studies included were of relatively high quality (**Table 1**). In addition, we assessed the risk of bias for RCTs according to the Cochrane Collaboration Tool. The risk of bias in the included studies was relatively low (**Figure 2**). Only two studies were multicenter design (17, 18). Three studies explained the specific method of random allocation (17, 18, 24), and two studies only mentioned "randomization" (15, 23).

Target Lesion Revascularization

A total of 8 studies (15–19, 22–24) reported the TLR in patients with CBL (**Figures 3A–C**). Meta-analysis results suggested that there was no significant difference in the TLR between DCB group and NDCB group at 6-month follow-up [OR = 0.21, 95%CI (0.02, 2.09), $P = 0.18$], 9-month follow-up [OR = 0.33, 95%CI (0.06, 1.70), $P = 0.18$] and 12-month follow-up [OR = 0.56, 95%CI (0.25, 1.22), $P = 0.14$] (**Supplementary Figure S1**). We applied Egger's test to evaluate publication bias. Although the difference was not statistically significant, we found a trend of DCB group with significant advantages. Trial sequential analysis was performed to evaluate the reliability of the results (**Figures 4A–C**). The statistical power was only 4, 5, and 7%, respectively, which indicated that the results of TLR lacked reliability due to insufficient sample size. A p ($P = 0.949$) value more than 0.05 was considered to be unlikely to exist publication bias.

Secondary Clinical Outcomes

A total of 10 studies (15–24) reported the MI and CD in patients (**Figure 5**). Meta-analysis results suggested that there was no significant difference in the MI and CD between DCB group and NDCB group at follow-up ($P > 0.05$) (**Supplementary Figures S2, S3**). Egger's test results suggested that there was great possibility of publication bias in MI at 9-month follow-up ($P = 0.049$) and CD at 12-month follow-up ($P = 0.025$). The MACE was defined as the sum of TLR, MI and CD. A total of 8 studies (15–19, 22–24) reported the TLR, MI and CD at the same time (**Figure 5**). Meta-analysis results suggested that the MACE of DCB group was significantly less than that of NDCB group at 9-month follow-up [OR = 0.21, 95%CI (0.05, 0.84), $P = 0.03$] and 12-month follow-up [OR = 0.45, 95%CI (0.22, 0.90), $P = 0.02$] (**Supplementary Figure S4**). However, there was no significant difference in the MACE between DCB group and NDCB group at 1-month follow-up and 6-month follow-up ($P > 0.05$). Egger's test results suggested that there was less possibility of publication bias ($P > 0.05$).

Angiographic Outcomes

A total of 8 studies (15–18, 21–24) and 5 studies (15–19) reported the MLD and DS measured post-procedure in patients with CBL, respectively (**Figure 6**). Meta-analysis results suggested that there was no significant difference in the MLD and DS measured post-procedure between DCB group and NDCB group ($P > 0.05$) (**Supplementary Figures S5, S6**). A total of 6 studies (16–18, 22–24), 7 studies (15–18, 22–24), and 5 studies (15–19) reported the LLL, MLD, and DS measured at follow-up, respectively (**Figure 6**). The LLL of DCB group was significantly less than that of NDCB group at 6-month follow-up [MD = -0.47, 95%CI (-0.55, -0.39), $P < 0.00001$], 9-month follow-up [MD = -0.24, 95%CI (-0.32, -0.16), $P < 0.00001$] and 12-month follow-up [MD = -0.31, 95%CI (-0.50, -0.12), $P = 0.002$] (**Supplementary Figure S7**). The MLD of DCB group was significantly more than that of NDCB group at 6-month follow-up [MD = 0.33, 95%CI (0.16, 0.51), $P = 0.0002$], 9-month follow-up [MD = 0.31, 95%CI (0.21, 0.41), $P < 0.00001$] and 12-month follow-up [MD = 0.30, 95%CI (0.08, 0.52), $P = 0.006$] (**Supplementary Figure S5**). The DS of DCB group was significantly less than that of NDCB group at 6-month follow-up [MD = -15.06, 95%CI (-24.79, -5.33), $P = 0.002$], 9-month follow-up [MD = -11.96, 95%CI (-17.05, -6.88), $P < 0.00001$] and 12-month follow-up [MD = -13.17, 95%CI (-18.58, -7.75), $P < 0.00001$] (**Supplementary Figure S6**). Egger's test results suggest that there was less possibility of publication bias ($P > 0.05$).

A total of 3 studies (16, 18, 23) reported the BR measured at follow-up (**Figure 7**). The BR of DCB group was significantly less than that of NDCB group at 9-month follow-up [OR = 0.14, 95%CI (0.03, 0.72), $P = 0.02$] and 12-month follow-up [OR = 0.25, 95%CI (0.09, 0.75), $P = 0.01$] (**Supplementary Figure S8**). The number of studies was too small to apply Egger's test.

Target Lesion Failure

A total of 7 studies (16–18, 20–23) reported the TLF (**Figure 8**). Meta-analysis results suggested that there was no significant difference in the TLF between DCB group and NDCB group [OR = 0.93, 95%CI (0.39, 2.21), $P = 0.86$] (**Supplementary Figure S9**). Egger's test results suggest that there was less possibility of publication bias ($P = 0.614$).

Sensitivity Analysis

Sensitivity analysis was carried out though seriatim excluding one trial each time and re-performing meta-analysis of the remaining trials. When Kleber FX's or Zhang WL's article was eliminated, the difference of MACE between DCB group and NDCB group at 9-month follow-up became no significant ($P = 0.07$ or $P = 0.14$). When Bu JZ's or Herrador JA's article was eliminated, the difference of MACE between DCB group and NDCB group at 12-month follow-up became no significant ($P = 0.11$ or $P = 0.10$). When Herrador JA's or Zhao Y's article was eliminated, the difference of BR between DCB group and NDCB group at 12-month follow-up became no significant ($P = 0.06$ or $P = 0.09$). These changes were thought to be caused by the decrease of sample size. When Zong XM's article was eliminated, the difference of MLD measured post-procedure between DCB group and NDCB group became significant [MD = 0.08, 95%CI (0.02, 0.14), $P = 0.009$] (**Figure 9**). However, this difference lacked clinical value. The other results and statistical heterogeneity did not change significantly when eliminating

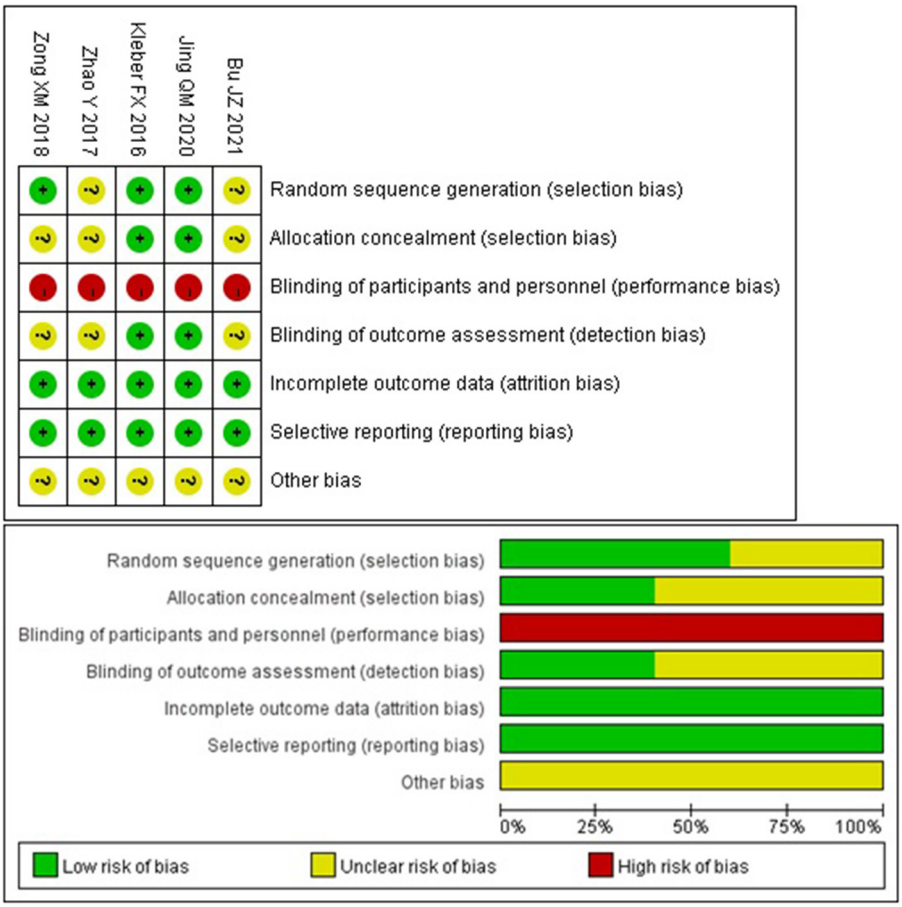


FIGURE 2 | Risk of bias for RCTs (Cochrane risk tool).

included studies item by item, which indicated that the results were stable.

DISCUSSION

A CBL was a lesion occurring at, or adjacent to, a significant division of a major coronary artery (25). The long-term clinical outcomes of CBL patients mainly depended on the state of the main vessel after stent implantation. At the same time, the significant side branch that the operators do not want to lose after PCI should not be ignored. Bifurcation treatment techniques should be considered when the opening of the side branch may affect the prognosis or the stenosis of the side branch may cause symptoms. The provisional stenting strategy was currently considered the standard approach for the treatment of the majority of CBL. The advantage of balloon angioplasty instead of stent implantation in the side branch treatment was that it was associated with a reduction in definite stent thrombosis, all-cause mortality while restoring anatomy (5, 6, 26). However, the risk of binary restenosis in the long term was still high after the application of traditional balloon angioplasty in the side branch. With the continuous combination of drug-coated technology and traditional balloon angioplasty, DCB came into being. DCB was to carry the anti-intimal hyperplasia drug on the balloon surface by matrix coating or nano-microporous technology. When the DCB expanded, the drug it carried was released to the blood vessel wall, thus inhibiting intimal hyperplasia and reduce vascular endothelial inflammation and thrombosis (27).

DCB combined the advantages of common balloon angioplasty and drug-eluting stent implantation. Several single-arm trials suggested that the DCB angioplasty for the side branch with main vessel stenting seemed to improve the clinical outcome at short and medium-term follow-up (28–31). DCB had the advantage of the lack of foreign material in the artery and got rid of the high incidence of restenosis after stent implantation. In the 15th consensus document from the European Bifurcation Club, DCB technology was considered to as pivotal to enhance clinical outcomes (7). This study systematically evaluated the procedural success, cardiovascular events and side branch protection of DCB for *de novo* CBL. Besides, angiographic and clinical outcomes according to different follow-up nodes was considered.

In this systematic review and meta-analysis of 10 studies, including 5 RCTs and 5 nROSs of 934 patients

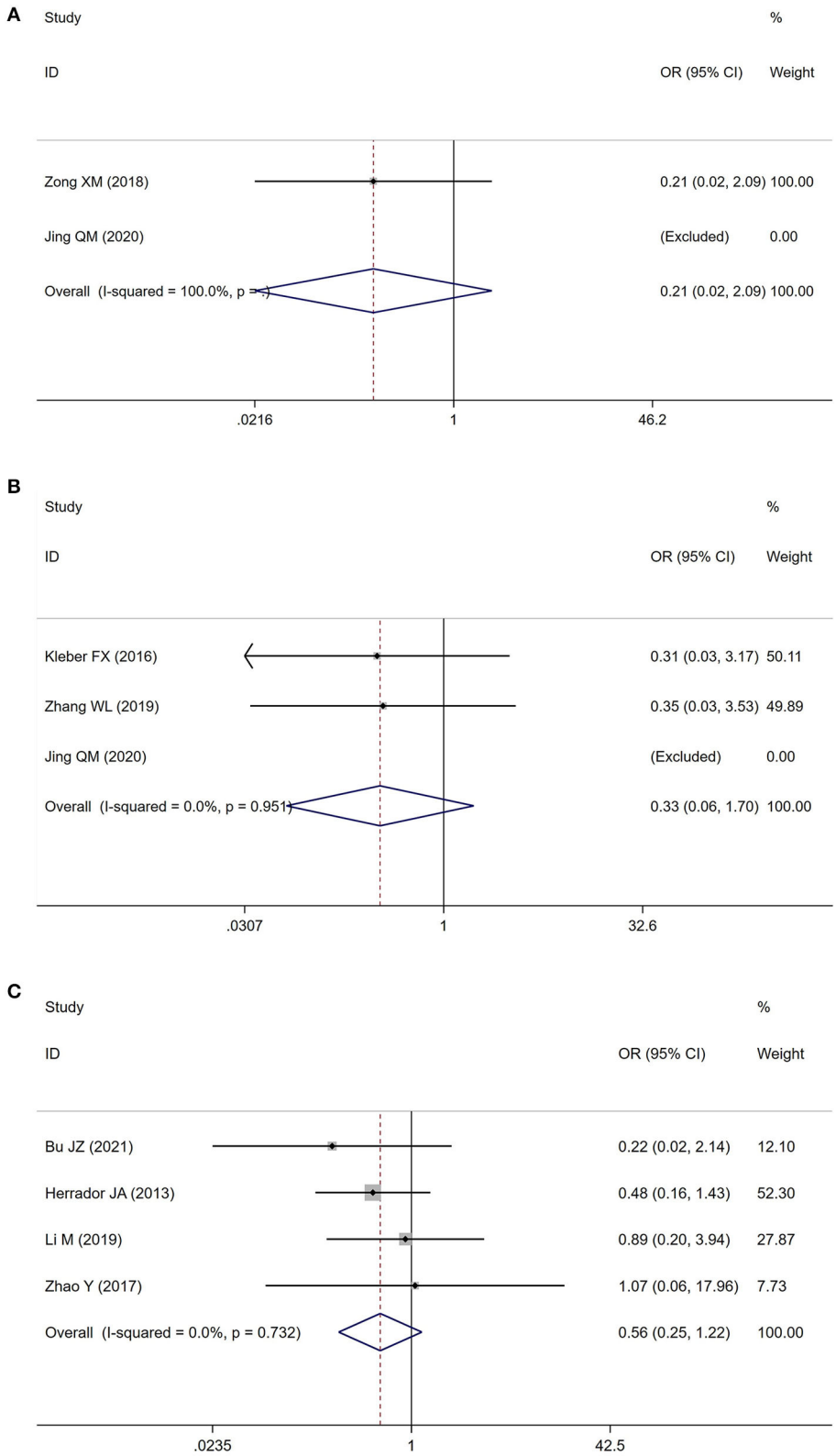


FIGURE 3 | Meta analysis for the target lesion revascularization (**A**: at 6-month follow-up; **B**: at 9-month follow-up; **C**: at 12-month follow-up).

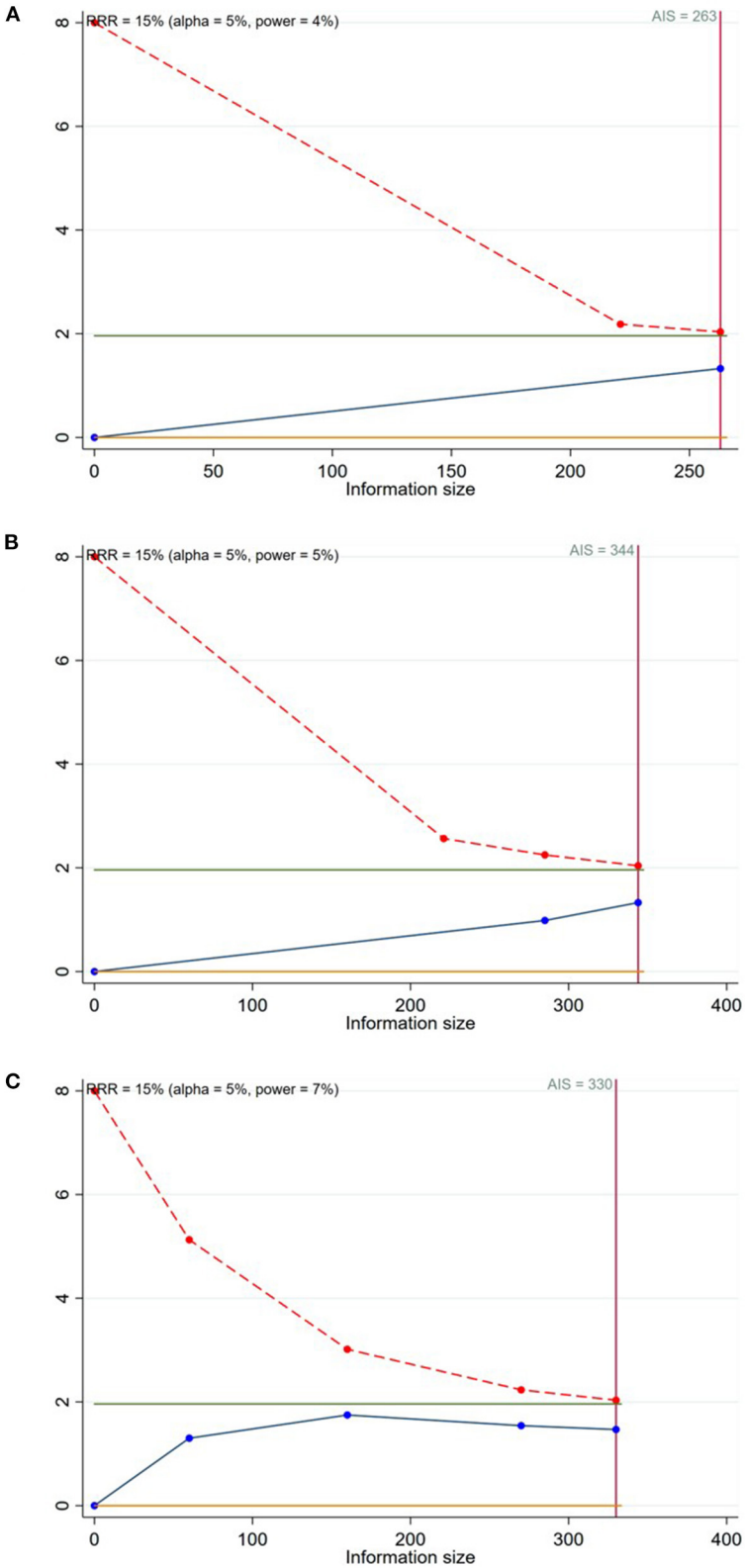


FIGURE 4 | Trial sequential analysis for the target lesion revascularization (**A**: at 6-month follow-up; **B**: at 9-month follow-up; **C**: at 12-month follow-up).

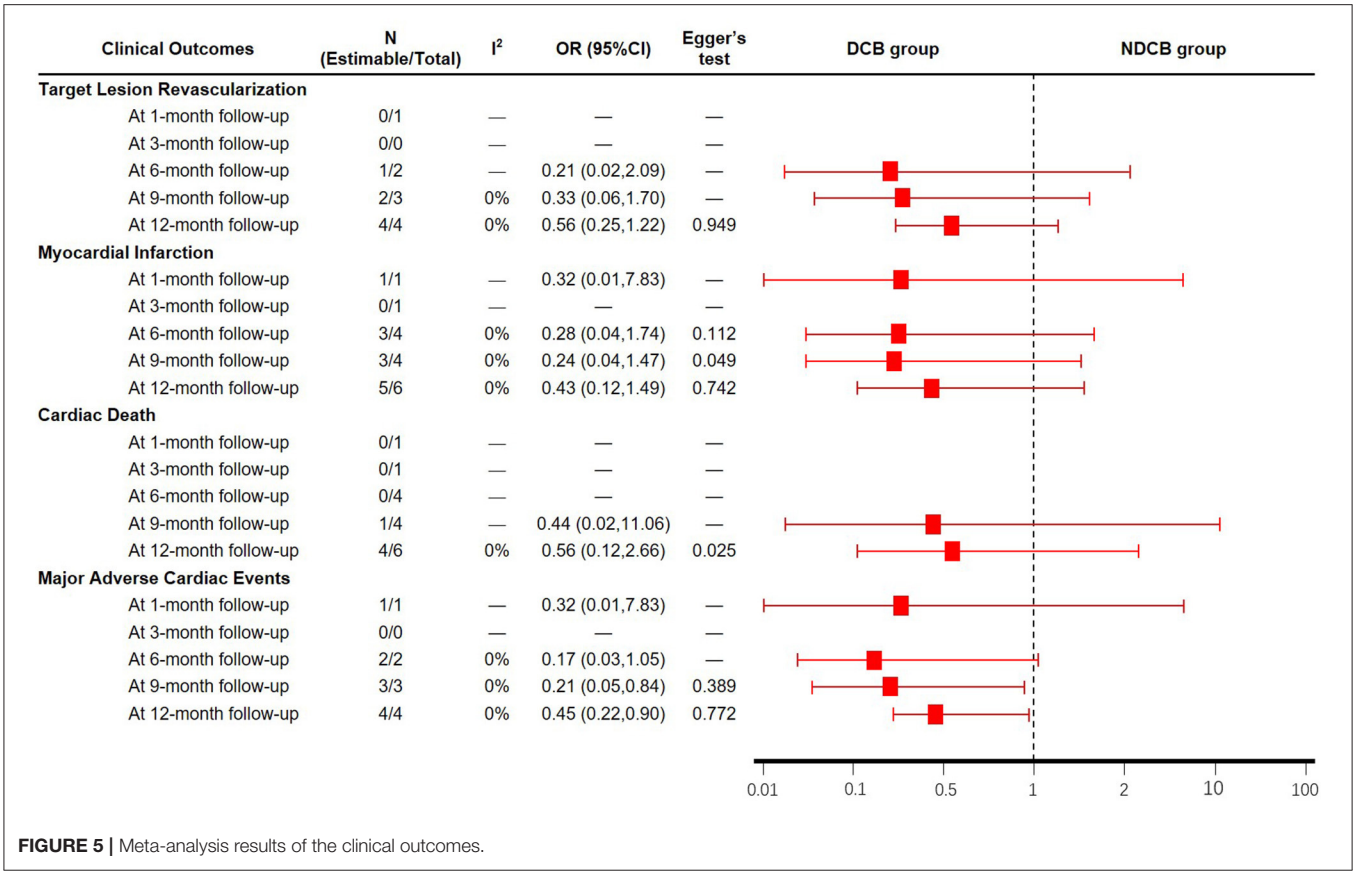


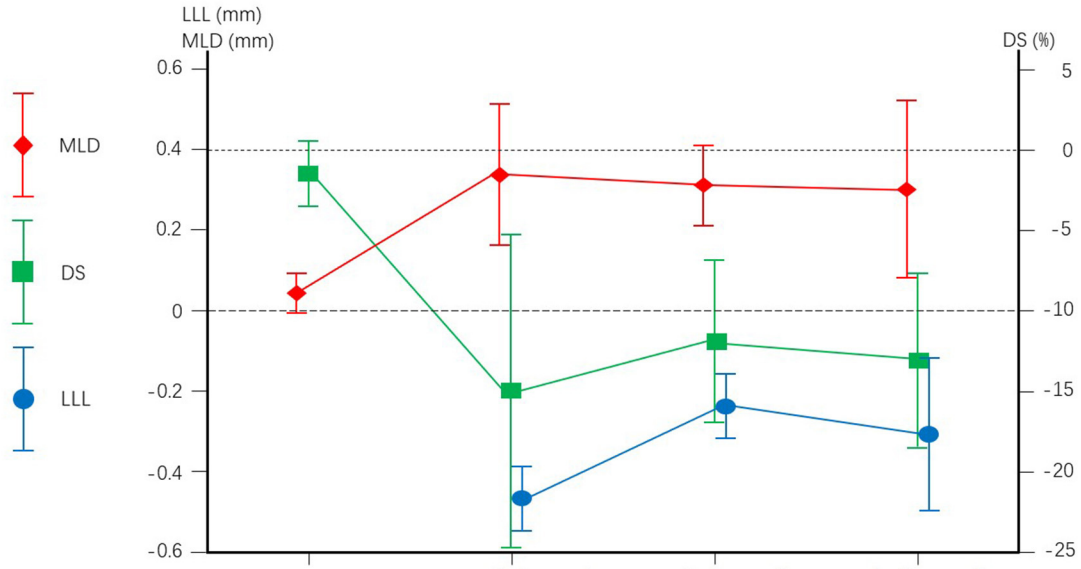
FIGURE 5 | Meta-analysis results of the clinical outcomes.

with *de novo* CBL, we documented that DCB not only had great effect in reducing LLL, DS and BR, and increasing MLD of side branch for *de novo* CBL with no reduction in the procedural success rate, but also reduced the MACE.

In term of angiographic outcomes, meta-analysis results suggested that there was no significant difference in the MLD and DS measured post-procedure between DCB group and NDCB group. However, DCB group had lower LLL, DS and BR measured at follow-up and higher MLD measured at follow-up compared with NCB group. The biggest benefit occurred at 6-month follow-up. The results showed that the immediate effect of the DCB and NDCB in side branch protection was similar, but over time, the DCB gradually showed its advantages of the side branch protection. The side branch protection benefited from drug release.

In term of clinical outcomes, meta-analysis results suggested that the MACE of DCB group was significantly less than that of NDCB group at 9-month follow-up and 12-month follow-up. This result proved that the application of DCB in the side branch can improve the clinical outcomes of patients with CBL. However, due to the limitation of sample size, there was no significant difference in the MACE between the two groups at 1-month follow-up and 6-month follow-up. The difference in the TLR, MI and CD between DCB group and NDCB group was not significant in this study. As shown by trial sequential analysis results, the low incidence of TLR lead to the need for a larger sample size with enough statistical power to find the significant difference between groups. For MI and CD, the negative results may be caused by the same reason. Therefore, it may be not that there was no significant difference in TLR, MI and CD between the two groups, but that significant difference had not been found yet. More large-sample and high-quality RCTs need to be implemented to draw such a conclusion. According to current evidence, the reduction of MACE was not transparent enough to prove that the side branch protective effect of DCB was successfully transformed into the improvement of clinical outcomes.

In addition, there was no significant difference in TLF between DCB group and NDCB group. The procedural success rate of DCB and NDCB was similar. It was safe and reliable to apply DCB angioplasty to the side branch in the treatment of patients with CBL. In European Society of Cardiology guidelines, DCB was recommended for the treatment of in-stent restenosis within bare-metal stent or drug eluting stent while there were no convincing data to support the use of DCB angioplasty for *de novo* disease (3). This study systematically examined the effect of DCB in side branch protection for *de novo* CBL. However, there were still many unanswered questions including the appropriate lesion location selection (non-left main coronary artery or left main coronary artery), appropriate side branch selection (vessel



	Post-procedure	At 6-month follow-up	At 9-month follow-up	At 12-month follow-up
Late lumen loss (mm)				
N	—	1	4	1
I^2	—	—	0%	—
MD (95%CI)	—	-0.47(-0.55,-0.39)	-0.24 (-0.32,-0.16)	-0.31 (-0.50,-0.12)
Egger's test	—	—	0.701	—
Minimum lumen diameter (mm)				
N	8	2	4	1
I^2	40%	59%	0%	—
MD (95%CI)	0.04 (-0.01,0.09)	0.33 (0.16,0.51)	0.31 (0.21,0.41)	0.30 (0.08,0.52)
Egger's test	0.262	—	0.066	—
Diameter stenosis (%)				
N	5	1	2	2
I^2	1%	—	0%	0%
MD (95%CI)	-1.54 (-3.51,0.43)	-15.06 (-24.79,-5.33)	-11.96 (-17.05,-6.88)	-13.17 (-18.58,-7.75)
Egger's test	0.302	—	—	—

FIGURE 6 | Meta-analysis results of the late lumen loss, minimum lumen diameter and diameter stenosis.

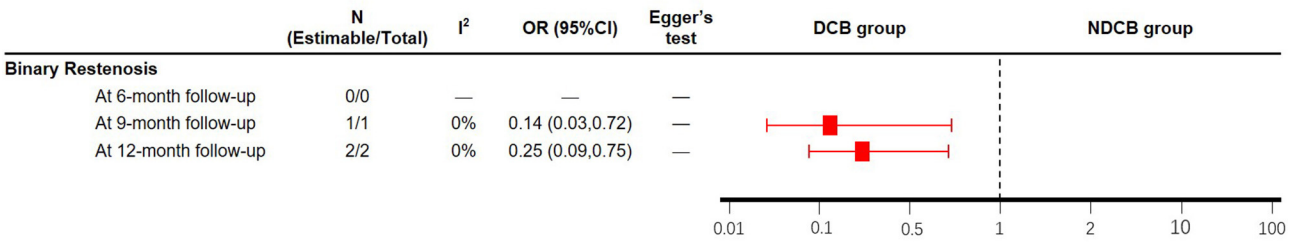


FIGURE 7 | Meta-analysis results of the binary restenosis.

diameter less or more than 2.8 mm), coating drugs selection (Paclitaxel, Zotarolimus or Sirolimus), and balloon angioplasty technique (DCB with or without final kissing ballooning or repeat POT).

LIMITATION

However, there were several limitations in our study. First, only articles published in English and Chinese were incorporated,

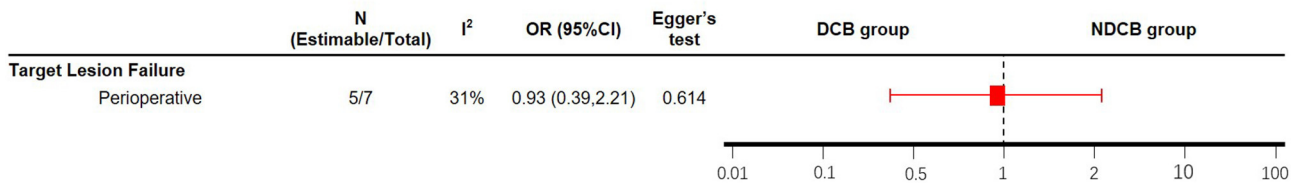


FIGURE 8 | Meta-analysis results of the target lesion failure.

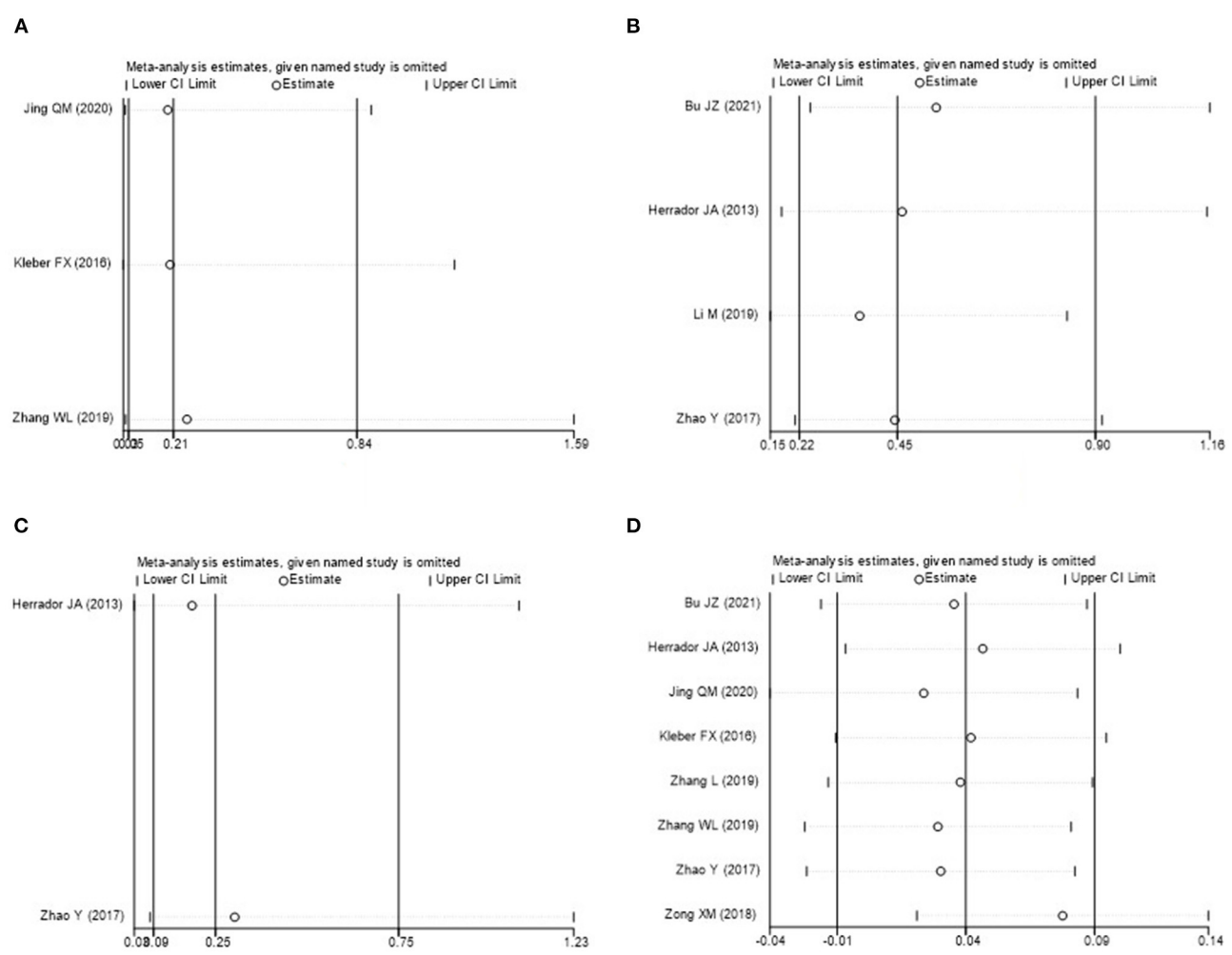


FIGURE 9 | Sensitivity analysis (**A**: MACE at 9-month follow-up; **B**: MACE at 12-month follow-up; **C**: BR at 12-month follow-up; **D**: MLD measured post-procedure).

which led to a potential selection bias. Second, because of the lack of background data for studies in meta-analyses, the data were not further stratified by other factors that may affect outcomes. Third, there was no significant difference in the TLR between groups accompanied by poor statistical power. This result was not reliable due to the limitation of sample size. It's the same reason for MI and CD. At present, several trials are under study, which is expected to clarify this problem. Forth, sensitivity analysis suggested that several results of this study were not stable because the number of trials for each indicator was small, accompanied by a small sample size. Fifth, the follow-up time of the included trials was between 1 and 12 months, so as to obtain the conclusion of short and medium-term follow-up, while no long-term follow-up outcome could be evaluated.

CONCLUSION

Current evidence indicated that DCB had great effect in side branch protection for *de novo* CBL at short and medium-term follow-up with no reduction in the procedural success rate. Due to the limitation of the quantity and quality of the included studies, the conclusions of this study still need to be confirmed by more high-quality, multi-center and large-sample size RCTs. The relevant systematic review should be updated in time when new trials are published.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

YZ and JC conceived and designed the experiments and revised the manuscript. YZ, JL, and LWa performed the experiments. YZ, JL, and LWu and analyzed the data. YZ, JL, PY, and HS wrote the manuscript. All authors reviewed and approved the manuscript prior to submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.758560/full#supplementary-material

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The Procedural and Clinical Outcomes of Rotational Atherectomy in Patients Presenting With Acute Myocardial Infarction

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Background: Rotational atherectomy (RA) is an indispensable tool used for calcified lesion preparation in percutaneous coronary intervention (PCI). However, use of RA in the setting of acute myocardial infarction (AMI) is challenged with limited clinical data.

Objectives: This study aims to retrospectively investigate the procedural results, periprocedural complications, and clinical outcomes of RA in patients with AMI.

Methods: All possible consecutive patients who received RA in AMI from January 2009 to March 2018 in a single tertiary center were analyzed retrospectively. Patients without AMI during the study period were also enrolled for comparison.

Results: A total of 121 patients with AMI (76.0 ± 10.8 years, 63.6% males) and 290 patients without AMI were recruited. Among the AMI group, 81% of patients had non-ST-elevation myocardial infarction (NSTEMI) and 14% presented with cardiogenic shock. RA could be completed in 98.8% of patients in the AMI group and 98.3% in the non-AMI group ($p = 1.00$). The periprocedural complication rates were comparable between the AMI and non-AMI groups. The risks of in-hospital, 30-day, 90-day, and 1-year cardiovascular major adverse cardiac events (CV MACE) were significantly higher in the AMI group compared with the non-AMI group (in-hospital 13.2 vs. 2.8%, $p < 0.001$; 30-day 14.2 vs. 4.5%, $p < 0.001$; 90-day 20.8 vs. 6.9%, $p < 0.001$; 1-year 30.8 vs. 19.1%, $p = 0.01$). AMI at initial presentation and cardiogenic shock were predictors for both in-hospital CV MACE and 1-year CV MACE in multivariable binary logistic regression analysis. Other predictors for 1-year CV MACE included serum creatinine level and triple vessel disease.

Conclusion: RA in patients with AMI is feasible with a high procedural completion rate and acceptable periprocedural complications. Given unstable hemodynamics and complex coronary anatomy, the in-hospital and 1-year MACE rates remained higher in patients with AMI compared with patients without AMI.

Keywords: percutaneous coronary intervention, rotational atherectomy, acute coronary syndrome, acute myocardial infarction, coronary artery disease

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INTRODUCTION

Rotational atherectomy (RA) is an indispensable tool used for calcified lesion preparation in percutaneous coronary intervention (PCI) (1, 2). In the era of bare-metal stents, RA was once used for aggressive plaque debulking. In the era of drug-eluting stents (DES), stent underexpansion has been shown to associate with worse clinical outcomes and higher risks of stent failure at follow-up (3). The purpose of RA has paradigm-shifted from the merely successful delivery of the stent to adequate modification of plaque, leading to better stent expansion with large minimal stent area (4, 5). RA is widely adopted nowadays for optimal lesion preparation in diverse clinical scenarios, including undilatable or uncrossable lesions (6, 7), non-protected left main lesions (8, 9), side-branch lesions (10), chronic total occlusions (11), complex and high-risk coronary procedures (12), and even in PCI under mechanical circulatory support (13).

In the setting of acute myocardial infarction (AMI), RA has been underused due to several reasons. First, the main mechanism of AMI is plaque rupture with thrombus formation and possible coronary vasospasm. RA was not recommended for treatment with thrombotic lesions (4). Second, RA generates more platelet activation and aggregation, resulting in high-platelet reactivity, which is undesirable in AMI with a prothrombotic state (14, 15). Lastly, the incidence of slow flow or no-reflow phenomenon is higher in RA (4, 16) and could lead to hemodynamic instability or collapse in patients with AMI who already have poor or unstable epicardial coronary flows before RA.

In this study, we aim to evaluate the success rate of RA among patients with AMI, as well as periprocedural complications and major adverse cardiovascular events in a tertiary center.

METHODS

Patient Population

From January 2009 to March 2018, we enrolled consecutive patients undergoing PCI with RA in our Taichung Veterans General Hospital, a tertiary medical center in Taiwan. Their data were analyzed retrospectively. Patients who met the criteria of current universal definitions of myocardial infarction at the time of PCI (17, 18) were allocated to the AMI group.

Two researchers independently reviewed the computerized electronic medical chart records. Clinical characteristics and biochemical results at the time of hospitalization and during follow-ups were retrieved and recorded in a standardized case record form. Patients who had missed clinical follow-up for more than 3 months were arranged with telephone interviews. For those who died during the study period, we recorded their etiology of death from their death certificates.

The study design and protocol were approved by the Institutional Review Board for Human Research of our institute.

Angiographic Characterization and Measurements

All angiographies were retrieved from the database in our institute. The lesion characteristics were analyzed using the Rubo DICOM Viewer (version 2.0, build 170828, Rubo Medical Imaging, Aerdenhout, The Netherlands), and the Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) scores were calculated for each lesion with at least 50% stenosis of lumen diameter in vessels $\geq$1.5 mm by an official online calculator at the website. In our study, any significant stenosis of at least 70% stenosis in luminal diameter at non-left main major coronary arteries and at least 50% stenosis at left main coronary artery was defined as coronary artery disease (CAD) and indicated for revascularization anatomically. The other indications of PCI, such as severe ischemia at myocardial perfusion imaging, positive physiological evaluation with fractional flow reserve, or instantaneous wave-free ratio, were at the discretion of interventional cardiologists. In the setting of AMI, the culprit lesions were ascertained by surface ECG, echocardiography, or left ventricular angiogram. Lesions identified by angiography and intracoronary imaging with features suggestive of plaque rupture, plaque erosion, or calcium nodule with or without epicardial coronary flow limitation were also considered as culprit lesions warranting revascularization.

Procedure Details for RA

Only qualified interventional cardiologists performed RA in our institute. Details of the procedure were reported earlier (10, 13) and were in line with the latest expert consensus regarding RA (4, 5). All patients were pretreated with a standard dose of dual antiplatelet therapy before PCI, as well as calcium channel blocker and nitrate to prevent coronary artery spasm. Indications for RA were either primary (for heavy and circular/rotating intimal calcification or severe fibrotic lesions) or secondary as bailout method (for undilatable or uncrossable lesions).

Rotational atherectomy was executed using Rotablator RA system (Boston Scientific, Marlborough, MA, USA). A 0.014-inch workhorse wire was advanced to the lesion and then exchanged to floppy or extra support RotaWire via a microcatheter. In some lesions uncrossable by microcatheter, bare wiring technique with RoraWire was applied gently and meticulously. A flushing cocktail comprising normal saline, heparin, and isosorbide dinitrate was continuously infused during RA and another bolus of 1,200–1,600 μg of isosorbide dinitrate was given intracoronarily before the activation of RA and stepped burr strategy beginning with an initial 1.25 or 1.5 mm burr at a rotational speed of 170,000–180,000 rpm in most cases. In selective lesions in which burr could not cross easily, a higher speed up to 200,000 rpm was applied. The maximal burr size was determined by the vessel diameter and the effect of adequate debulking, based on either the angiography or intracoronary imaging. After plaque modification by RA, the RotaWire was replaced by a workhorse wire using the same wire-exchange technique. The procedure proceeded with balloon angioplasty with or without stent implantation to achieve optimal angiographic results with minimal residual stenosis. Completion of RA was defined as full debulking of the target lesion without premature termination of RA before proceeding to subsequent treatment.

After stent implantation, dual antiplatelet therapy with aspirin (100 mg/day) and one P2Y12 inhibitor, namely clopidogrel,

ticagrelor or prasugrel, were continued for at least 12 months after DES implantation in patients with AMI. In the non-AMI subgroup, the default 6-month duration of DAPT was further adjusted during the follow-up period after weighing the ischemic and bleeding risks.

Clinical Outcomes

The major adverse cardiac events (MACE) at follow-ups were defined as all-cause death, stroke, non-fatal myocardial infarction, or target vessel revascularization; the cardiovascular major adverse cardiac events (CV MACE) were defined as cardiovascular death, stroke, non-fatal myocardial infarction, or target vessel revascularization. Regular follow-up with invasive angiography was only encouraged and applied to those patients with high anatomical and clinical risks of target vessel failure. Hence, most events of target lesion revascularization in this study were clinically driven.

Statistical Analysis

Data of continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as numbers and frequency. Intergroup differences in continuous variables were assessed with unpaired Student's *t*-test, and differences in categorical variables with chi-square test or Fisher's exact tests. Multivariable Cox regression analysis was performed to identify any independent predictors for in-hospital and 1-year CV MACE, respectively. Variables with p-values < 0.10 in univariable analysis were assessed using the multivariable model. All statistical analyses were performed using the IBM SPSS statistical packages software for Windows, version 26.0.0.0 (IBM Corp., New York, USA). Two-tailed p-values < 0.05 were considered statistically significant.

RESULTS

Baseline Characteristics of Patients

During the study period, a total of 411 consecutive patients treated with RA were enrolled in this study (**Table 1**). In the AMI group, 81% of patients had NSTEMI and 14% presented with cardiogenic shock. Compared with the non-AMI group, patients with AMI were significantly older (76.0 ± 10.8 vs. 72.9 ± 11.4, $p = 0.011$) and had lower level of hemoglobin (10.8 ± 2.4 vs. 11.5 ± 2.0, $p = 0.001$) and lower left ventricular ejection fraction (LVEF) (42.0 ± 11.0 vs. 47.5 ± 13.0, $p < 0.001$). Multivessel disease accounted for 88.4% in the AMI group but only 71.4% in the non-AMI group. Most demographic findings, including sex, hypertension, diabetes, peripheral artery disease, and serum creatinine levels, did not differ between these two groups.

Percutaneous Coronary Intervention Procedural Characteristics

Rotational atherectomy was completed in 98.6% of patients with AMI and 98.3% of patients without AMI ($p = 1.00$; **Table 2**). In both groups, most patients underwent rotablation *via* femoral approach using 7 Fr. sheath, 1.5 mm burr, and were treated with DES. Both groups had similar percentages of heavy calcification, tortuosity, ostial and bifurcation lesions, chronic total occlusion lesions, and ACC/AHA B2/C lesions, whereas stent size was smaller (2.8 ± 0.3 vs. 3.1 ± 2.4, $p = 0.017$) and total lesion length was longer (49.3 ± 25.7 vs. 43.0 ± 23.9, $p = 0.019$) in patients with AMI.

The baseline (35.3 ± 14.0 vs. 29.1 ± 14.1, $p < 0.001$), post-PCI (11.1 ± 11.3 vs. 7.5 ± 9.8, $p = 0.001$), and net gain (24.2 ± 11.9 vs. 21.6 ± 11.2, $p = 0.036$) of SYNTAX scores were higher in the AMI group compared with the non-AMI group, implicating more complex coronary anatomy in the AMI group. In addition, the use of hemodynamic support was more frequent in the AMI group (28.9% vs. 9.7%, $p < 0.001$).

A total of 411 patients were selected, of which 405 underwent successful RA. Among them, 372 patients were treated with stenting after rotablation (91.9%) and 33 were left unstented. The reasons why we did not perform stenting were rotablation for side branches (12 patients, 36.4%), diffuse and small lesions without adequate stent landing zone (7 patients, 27.3%), and in-stent restenosis (5 patients, 15.2%; most of them were treated with drug-eluting balloon), chronic total occlusions with negative vessel remodeling in the distal vessel that was too small to be stented with confidence (5 patients, 15.2%), and patient factors (2 patients, 6.1%; one was supposed to undergo urgent non-cardiac surgery right after PCI, another patient could not cooperate with the procedure after successful rotablation and plain old balloon angioplasty (POBA)), operator discretion (2 patients, 6.1%; one patient had slow-flow phenomenon after rotablation and POBA, another one was treated with cutting balloon at the discretion of the operator).

Procedure Outcomes

Overall, no difference was observed in the incidence of acute no-flow phenomenon, vessel perforation, wire fracture, and profound in-procedure shock between the AMI and non-AMI groups (**Table 3**). No patient died or needed emergent CABG during the procedure. Nevertheless, the AMI group had a higher incidence of ventricular arrhythmia (5.8% vs. 0.7%, $p = 0.003$).

In-hospital and Clinical Outcomes up to 1 Year

The in-hospital and clinical outcomes at different time points are presented in **Table 4**. For all patients who underwent RA in the setting of AMI, the in-hospital, 30-day, 90-day, and 1-year CV MACE rates were significantly higher than those in the non-AMI group (in-hospital 13.2 vs. 2.8%, $p < 0.001$; 30-day 14.2 vs. 4.5%, $p < 0.001$; 90-day 20.8 % vs. 6.9%, $p < 0.001$; 1-year 30.8%, 19.1%, $p = 0.01$). Patients in the AMI group also had significantly higher MACE, death, and CV death up to 1 year. No difference was found between the two groups regarding in non-fatal myocardial infarction, target vessel revascularization, stroke, or stent thrombosis rates.

Multivariable Logistic Regression Analysis for In-hospital and 1-Year CV MACE

The multivariable analysis identified independent predictors for in-hospital CV MACE as follows: age, female sex, peripheral

TABLE 1 | Demographic data of rotational atherectomy in acute myocardial infarction (AMI) vs. non-AMI cases in the study period.

Variables	AMI *N* = 121	Non-AMI *N* = 290	*p*-value*
Sex (M/F)	77/44	192/98	0.617
Age (years)	76.0 ± 10.8	72.9 ± 11.4	**0.011**
Clinical diagnosis (*N*, %)			**<0.001**
Stable angina	0	83 (28.6%)	
Unstable angina	0	147 (50.7%)	
NSTEMI	90 (74.4%)	0	
STEMI	14 (11.6%)	0	
Ischemic CM	0	56 (19.3%)	
Unstable angina + shock	0	2 (0.7%)	
NSTEMI + shock	8 (6.6%)	0	
STEMI + shock	9 (7.4%)	0	
Ischemic CM + shock	0	2 (0.7%)	
Hypertension (*N*, %)	219 (75.5%)	83 (68.6%)	0.147
Diabetes (*N*, %)	77 (63.6%)	164 (56.6%)	0.184
PAD (*N*, %)	10 (8.3%)	34 (11.7%)	0.301
LVEF (%)	42.0 ± 11.0	47.5 ± 13.0	**<0.001**
Lab data			
Hemoglobin (g/dl)	10.8 ± 2.4	11.5 ± 2.0	**0.001**
BUN (mg/dl)	53.2 ± 113.1	31.8 ± 21.8	0.060
Cr (mg/dl)	2.9 ± 2.7	2.7 ± 3.0	0.488
Cholesterol (mg/dl)	145.4 ± 30.2	149.8 ± 32.9	0.266
HDL-chol (mg/dl)	42.9 ± 15.1	45.3 ± 13.1	0.185
LDL-chol (mg/dl)	83.4 ± 26.4	85.8 ± 29.1	0.524
HbA1c (mg/dl)	6.9 ± 1.8	6.6 ± 1.2	0.166
Total CK (U/L)	339.4 ± 507.1	129.9 ± 143.3	**<0.001**
CK-MB (U/L)	16.3 ± 18.6	8.8 ± 9.1	**<0.001**
Troponin (ng/ml)	8.7 ± 15.9	1.2 ± 4.2	**<0.001**
CAD vessels			**0.021**
SVD (*N*, %)	14 (11.6%)	83 (28.6%)	
DVD (*N*, %)	35 (28.9%)	91 (31.4%)	
TVD (*N*, %)	72 (59.5%)	116 (40.0%)	
Plus LM (*N*, %)	19 (15.7%)	37 (12.8%)	
Prior CABG (*N*, %)	8 (6.6%)	12 (4.1 %)	

**RA in AMI vs. RA in non-AMI.*

CM, ischemic cardiomyopathy; DVD, double vessel disease; FBS, fasting blood sugar; LVEF, left ventricular ejection fraction; LM, left main coronary artery; PAD, peripheral artery disease; SVD, single vessel disease; TVD, triple vessel disease. Bold values meant Statistically significant ($p < 0.05$).

artery disease, AMI at presentation, cardiogenic shock, and post-PCI SYNTAX score (**Table 5**). In the multivariable analysis for 1-year CV MACE, AMI at presentation [odds ratio (OR) 1.79; 95% CI 1.02–3.15; $p = 0.042$) and cardiogenic shock (OR 2.41; 95% CI 1.29–4.53; $p = 0.006$) remained as independent predictors. Serum creatinine level (OR 1.12; 95% CI1.03–1.22; $p = 0.009$) and triple vessel disease (compared to single-vessel disease; OR 2.75; 95% CI 1.16–6.52; $p = 0.022$) were the other predictors for 1-year CV MACE (**Table 5**).

DISCUSSION

In summary, our retrospective study revealed several important findings regarding RA among patients with AMI in the modern era: (1) RA in the setting of AMI is safe and feasible, associated with high procedural success and acceptable periprocedural complications; (2) the in-hospital, 30-day, 90-day, and 1-year CV MACE rates in the AMI group were significantly higher than non-AMI group; (3) AMI at initial presentation, cardiogenic shock, age, female sex, peripheral artery disease, and post-PCI SYNTAX score were independent predictors for in-hospital CV MACE; whereas, AMI at initial presentation and cardiogenic shock remained as predictors of 1-year CV MACE, as well as serum creatinine level and triple vessel disease.

According to a national cohort study on US Veterans, the proportion of patients undergoing PCI for calcification lesions has been on the rise recently (19). Patients with severe

TABLE 2 | Demographic and PCI findings of rotational atherectomy in acute myocardial infarction (AMI) vs. non-AMI cases in the study period.

Variables	AMI *N* = 121	Non-AMI *N* = 290	*p*-value*
Rotablation vessels			0.237
LM (*N*, %)	1 (0.8%)	0	
LAD (*N*, %)	70 (57.9%)	155 (19.0%)	
LCX (*N*, %)	9 (7.4%)	27 (9.3%)	
RCA (*N*, %)	18 (14.9%)	59 (20.3%)	
LM + LAD (*N*, %)	3 (2.5%)	15 (5.2%)	
LM + LCX (*N*, %)	3 (2.5%)	5 (1.7%)	
LM + RCA (*N*, %)	0	1 (0.3%)	
LAD + LCX (*N*, %)	10 (8.3%)	13 (4.5%)	
LAD + RCA (*N*, %)	2 (1.7%)	11 (3.8%)	
LCX + RCA (*N*, %)	1 (0.8%)	0	
LM + LAD + LCX (*N*, %)	2 (1.7%)	2 (0.7%)	
LM + LAD + RCA (*N*, %)	2 (1.7%)	2 (0.7%)	
Access site			0.060
Radial (*N*, %)	28 (23.1%)	95 (32.8%)	
Femoral (*N*, %)	91 (75.2%)	184 (63.4%)	
Brachial (*N*, %)	2 (1.7%)	11 (3.8%)	
Guide size			0.624
6F (*N*, %)	40 (33.1%)	89 (30.7%)	
7F (*N*, %)	80 (66.1%)	195 (67.2%)	
8F (*N*, %)	1 (0.8%)	6 (2.1%)	
SYNTAX score[#]	35.3 ± 14.0	29.1 ± 14.1	**<0.001**
SYNTAX score post-PCI[#]	11.1 ± 11.3	7.5 ± 9.8	**0.001**
SYNTAX score gain[#]	24.2 ± 11.9	21.6 ± 11.2	**0.036**
Rotablation completed	119 (98.6%)	286 (98.3%)	1.000
Largest burr size			0.403
1.25 mm (*N*, %)	25 (20.7%)	46 (15.9%)	
1.5 mm (*N*, %)	73 (60.4%)	166 (57.2%)	
1.75 mm (*N*, %)	21 (17.4%)	73 (25.2%)	
2.0 mm (*N*, %)	2 (1.7%)	4 (1.4%)	
2.25 mm (*N*, %)	0	1 (0.3%)	
Stenting (*N*, %)	110 (90.9%)	262 (90.3%)	0.862
BMS (*N*, %)	35 (31.8%)	55 (21.0%)	0.131
DES (*N*, %)	75 (68.2%)	205 (78.2%)	
BVS (*N*, %) ?	0	1 (0.4%)	
BMS + DES (*N*, %)	0	1 (0.4%)	
Stent number	2.0 ± 0.9	1.9 ± 0.9	0.339
Stent size (mm)	2.8 ± 0.3	3.1 ± 2.4	**0.017**
Total stent length (mm)	55.6 ± 28.3	51.2 ± 26.8	0.161
Rotablation vessel characteristics			
Total lesion length (mm)	49.3 ± 25.7	43.0 ± 23.9	**0.019**
Heavy calcification	117 (98.3%)	281 (96.9%)	0.521
Tortuosity (*N*, %)	54 (44.6%)	143 (49.3%)	0.386
Ostial lesion (*N*, %)	48 (39.7%)	101 (34.8%)	0.351
Bifurcation (*N*, %)	37 (30.6%)	97 (33.5%)	0.571
Chronic total occlusion	18 (14.9%)	37 (12.8%)	0.566
ACC/AHA lesion B2/C	121 (100%)	286 (98.6%)	0.325
Total contrast dose (ml)	196.8 ± 83.8	194.1 ± 66.6	0.759
Hemodynamic support	35 (28.9%)	38 (9.7%)	**<0.001**

**RA in AMI vs. RA in non-AMI.*

[#]Residual SYNTAX score in patients with prior CABG.

BMS, bare metal stent; BVS, bioresorbable vascular scaffold; DES, drug-eluting stent; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main coronary artery; RCA, right coronary artery. Bold values meant Statistically significant (p < 0.05).

TABLE 3 | Procedure outcomes of rotational atherectomy in acute myocardial infarction (AMI) vs. non-AMI cases in the study period.

Variables	AMI *N* = 121	Non-AMI *N* = 290	*p*-value*
Acute no flow (*N*, %)	10 (8.3%)	25 (8.6%)	0.906
Perforation (*N*, %)	2 (1.7%)	3 (1.0%)	0.634
Wire transection (*N*, %)	1 (0.8%)	0	N/A
Profound/ refractory shock	19 (15.7%)	31 (10.7%)	0.156
Ventricular arrhythmia (*N*, %)	7 (5.8%)	2 (0.7%)	**0.003**
Emergent CABG (*N*, %)	0	0	N/A
Die on table (*N*, %)	0	0	N/A

**RA in AMI vs. RA in non-AMI.*

CABG, coronary artery bypass graft. Bold values meant Statistically significant ($p < 0.05$).

calcification had significantly more major adverse cardiac events after PCI compared with those without (20). Hence, how to deal with a calcified plaque by different tools to get good lesion preparation in PCI has attracted more attention lately (21, 22). Clinical use of RA for heavy calcified or severe fibrotic lesions accounted for 0.8–3.1% among patients undergoing PCI in European countries (5). Among patients undergoing RA, the percentage of acute coronary syndrome (ACS) ranged from 20 to 37% in several studies focused on RA in ACS (23–26). In this study, we enrolled patients with AMI with a stricter definition and only patients with elevated high-sensitivity cardiac troponins were included. Patients with AMI were near 30% of patients undergoing RA in our cohort, a proportion that is comparable with previous studies (23–26). The previous studies reported that RA in patients with ACS had a high procedure completion rate, comparable with patients without ACS. To our knowledge, our cohort had the largest number of patients with AMI undergoing RA in a single center. Patients in our cohort also carried more high-risk clinical features with a mean age of 76 years old, 63.6% with diabetes, as well as more high-risk anatomical features with 88.4% multivessel disease and extremely high syntax score with a mean of 35.3 compared with previous studies. Nevertheless, our results still demonstrated a similar procedure success rate, reassuring the feasibility of RA in these high-risk patients.

In a single-center cohort in Germany, including 8 STEMI and 100 NSTE-ACS patients treated with RA, the 2-year MACE rate was higher in patients with ACS compared with 433 patients with stable CAD (39.9 vs. 22.4%, log-rank $p = 0.002$; hazard ratio (HR) 1.39; 95% CI: 1.12–1.73; $p = 0.003$) (23). In our study, despite the comparable procedural success rates of RA in the AMI and non-AMI groups, we still found higher in-hospital and 1-year CV MACE rates in the AMI group. The poor outcome in the AMI group could be attributed to unstable hemodynamic and vulnerable plaques in the setting of AMI, as well as high clinical and anatomical risks in the AMI group. In our study, patients in the AMI group were older and had smaller stent size, longer total lesion length, higher baseline and residual SYNTAX scores, as well as more frequent use of hemodynamic support compared with the non-AMI group. All the above characteristics were known unfavorable factors for MACE after PCI. From an analysis in patients with ACS undergoing RA derived from the ROTational AThErectomy (ROTATE) registry, MACE after a median of 27.9 months was significantly higher in the NSTE-ACS group compared with the stable angina group (32.4 vs. 24.2%, log-rank $p < 0.001$), but this difference no longer persisted after propensity score matching (25), implicating that higher risk profiles other than ACS *per se* in the NSTE-ACS group contributed to the poor clinical outcomes.

Recently, a prospective European multicentral registry (Euro4C registry) demonstrated a high clinical success in 91.9% of rotablation. Factors independently associated with 1-year MACE were female gender, renal failure, ACS at admission, depressed LVEF, and left main lesion (26). In our study, the AMI at initial presentation and serum creatinine level were found to be independent predictors for 1-year CV MACE, in line with the recent Euro4C registry. Of note, the Euro4C registry indicated that women had worse clinical outcomes following RA during hospitalization and at 1-year follow-up. However, the procedural complications did not significantly differ between genders, and the reasons for poor clinical outcomes in women following RA remained unknown (27). In our study, female gender was a predictor for in-hospital CV MACE but not for 1-year CV MACE. Further studies focusing on gender difference of patients undergoing RA are warranted to clarify the relationship of gender and clinical outcomes of RA.

Of interest, 98.3% of patients had heavily calcified lesions and 44.6% had torturous lesions in our AMI group. Nevertheless, the perforation rate of RA was only 1.7%, comparable with other RA studies (4). In addition to meticulous skills and experienced hands, another crucial point is that we learned from mistakes. The mechanism of perforation was sought and discussed case by case in a formal conference in our institute (28). Knowing why perforation occurs in RA could help operators avert such disasters and maintain lower complication rates.

On the other hand, the incidence of slow flow or no-reflow phenomenon in our AMI group was 8.3%, higher than the

TABLE 4 | Clinical outcomes of rotational atherectomy in acute myocardial infarction (AMI) vs. non-AMI cases in the study period.

Variables	AMI $N = 121$	Non-AMI $N = 290$	*p*-value*
In-hospital			
MACE[#] (*N*, %)	22 (18.2%)	9 (3.1%)	**<0.001**
CV MACE[†] (*N*, %)	16 (13.2%)	6 (2.8%)	**<0.001**
Death (*N*, %)	21 (17.4%)	6 (2.1%)	**<0.001**
CV death (*N*, %)	14 (11.6%)	3 (1.0%)	**<0.001**
Non-fatal MI (*N*, %)	2 (1.7%)	1 (0.3%)	0.208
Stent thrombosis	1 (0.8%)	0	0.294
Stroke (*N*, %)	0	1 (0.3%)	1.000
TLR (*N*, %)	0	0	N/A
TVR (*N*, %)	1 (0.8%)	2 (0.7%)	1.000
30-day			
MACE (*N*, %)	25 (20.8%)	16 (5.5%)	**<0.001**
CV MACE (*N*, %)	17 (14.2%)	13 (4.5%)	**0.001**
Death (*N*, %)	23 (19.2%)	10 (3.4%)	**<0.001**
CV death (*N*, %)	14 (11.7%)	7 (2.4%)	**<0.001**
Non-fatal MI (*N*, %)	2 (1.7%)	1 (0.3%)	0.206
stent thrombosis	2 (1.7%)	1 (0.3%)	0.206
Stroke (*N*, %)	0	2 (0.7%)	1.000
TLR (*N*, %)	1 (0.8%)	2 (0.7%)	1.000
TVR (*N*, %)	2 (1.7%)	4 (1.4 %)	1.000
90-day			
MACE (*N*, %)[§]	36 (30.0%)	27 (9.3%)	**<0.001**
CV MACE	25 (20.8%)	20 (6.9%)	**<0.001**
Death (*N*, %)	27 (22.5%)	15 (5.2%)	**<0.001**
CV death (*N*, %)	15 (12.5%)	8 (2.8%)	**<0.001**
Nonfatal MI (*N*, %)	4 (3.3%)	2 (0.7%)	0.064
Stent thrombosis	2 (1.7%)	1 (0.3%)	0.207
Stroke (*N*, %)	0	2 (0.7%)	1.000
TLR (*N*, %)	6 (5.0%)	7 (2.4%)	0.215
TVR (*N*, %)	8 (6.7%)	10 (3.5 %)	0.150
1-year			
MACE (*N*, %)[§]	57 (47.5%)	74 (25.7%)	**<0.001**
CV MACE	37 (30.8%)	55 (19.1%)	**0.01**
Death (*N*, %)	41 (34.2%)	42 (14.5%)	**<0.001**
CV death (*N*, %)	17 (14.2%)	16 (5.5%)	**0.004**
Nonfatal MI (*N*, %)	6 (5.0%)	7 (2.4%)	0.215
Stent thrombosis	3 (2.5%)	1 (0.3%)	0.078
Stroke (*N*, %)	0	4 (1.4%)	0.326
TLR (*N*, %)	16 (13.3%)	32 (11.1%)	0.518
TVR (*N*, %)	20 (16.7%)	37 (12.8%)	0.304

**RA in AMI vs. RA in non-AMI.*

[#]Death, nonfatal myocardial infarction, stroke, or target vessel revascularization (TVR).

[†]Cardiovascular death, nonfatal myocardial infarction, stroke, or target vessel revascularization (TVR).

One patient in RA in the AMI group was lost to follow-up after discharge from ward.

[§]Another patient in RA in the non-AMI group was lost to follow-up after 1 month.

MACE, major adverse cardiovascular events; TLR, target lesion revascularization; TVR, target vessel revascularization. Bold values meant Statistically significant ($p < 0.05$).

German cohort with an event rate of 0.8% (23) or ROTATE registry in the setting of ACS with an event rate of 3.3% (25). The difference was probably attributed to the definition among these studies. In the German cohort, only persistent slow flow or reflow at the end of the procedure was documented (23), whereas in our study, any transient slow flow or no-reflow during

TABLE 5 | Predictors of cardiovascular major adverse cardiovascular events (CV MACE) during hospitalization and at 1-year follow-up from the multivariable models.

Predictors	In-hospital CV MACE			1-year CV MACE		
	Adjusted OR	95% CI	*p*-Value	Adjusted OR	95% CI	*p*-value
Age	1.10	1.02–1.18	**0.017**	0.99	0.97–1.02	0.590
Male gender	0.23	0.07–0.75	**0.015**	0.70	0.42–1.18	0.184
Hypertension	1.42	0.42–4.79	0.577	0.89	0.51–1.55	0.687
Diabetes	0.79	0.26–2.45	0.688	1.11	0.66–1.87	0.687
PAD	1.06	1.54–23.18	**0.010**	1.09	0.49–2.42	0.831
Serum creatinine	1.06	0.85–1.32	0.627	1.12	1.03–1.22	**0.009**
AMI	12.72	2.86–56.58	**0.001**	1.79	1.02–3.15	**0.042**
Cardiogenic shock	9.18	2.15–39.24	**0.003**	2.41	1.29–4.53	**0.006**
SVD		Reference			Reference	
DVD			0.996	1.77	0.76–4.13	0.186
TVD			0.996	2.75	1.16–6.52	**0.022**
Hemodynamic support	1.87	0.48–7.25	0.364	1.42	0.71–2.83	0.322
SYNTAX score	0.98	0.92–1.04	0.497	0.99	0.97–1.02	0.410
SYNTAX score post-PCI	1.07	1.01–1.13	**0.022**	1.01	0.98–1.04	0.669

95% CI, 95% confidence interval; ACS, acute coronary syndrome; CM, cardiomyopathy; DM, diabetes mellitus; DVD, double vessel disease; OR, odds ratio; PAD, peripheral artery disease; SVD, single vessel disease; disease; TVD, triple vessel disease. Bold values meant Statistically significant (p < 0.05).

the procedure was counted when we retrospectively reviewed the angiography in detail. Nevertheless, most slow flow or no-reflow events in our cohort were relieved by intracoronary use of adenosine without persistent hemodynamic deterioration. The risk of slow flow or no-reflow was also comparable between our AMI and non-AMI groups, supporting that RA is a relatively safe procedure in AMI.

Study Limitations

Our study had several limitations. First, the retrospective design was inherently associated with selection bias and other confounding factors. Some critical parameters, such as LVEF and detailed analysis of intracoronary imaging, could not be collected well in every patient and utilized for outcome analysis. Second, the enrollment of consecutive all-comers, especially those with unstable hemodynamics at initial presentation, might influence the clinical results. However, this allowed us to investigate the safety and efficacy of RA in AMI in real-world practice and confirmed the feasibility in this complex scenario. Third, the incidence of RA-associated periprocedural myocardial infarction in our patients was difficult to determine, given that we only recruited patients with AMI with positive troponin assays. Despite cardiac enzymes being regularly followed up after RA in our cohort, we could not differentiate the extent of myocardial injury from AMI *per se* or from the procedure of rotablation. Fourth, although our study enrolled 23 patients presenting with STEMI and was probably the largest cohort in single center to date for this unique group (12, 23, 24, 26, 29), the enrolled number was still limited and the amount of thrombus burden could not be precisely measured. The application of RA in moderate to large burden of thrombus remains to be confirmed in larger studies for STEMI.

CONCLUSION

Despite very high-risk clinical and anatomical features in patients with AMI, RA was feasible with comparable high procedure success and low complications compared with the patients without AMI. The incidence of in-hospital and 1-year CV MACE events was still higher in the AMI group compared with the non-AMI group. AMI at initial presentation and cardiogenic shock were predictors of both in-hospital CV MACE and 1-year CV MACE for those undergoing RA in the study periods.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board for Human Research of Taichung Veterans General Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

W-LL and Y-WC contributed to the conception and design of the study. C-HL, C-SS, W-CC, C-YW, W-JC, T-HL, K-WL, and T-JL contributed to data collection. W-LL analyzed and interpreted the data. Y-WC drafted the report, which was critically revised for important intellectual content by W-LL. All authors have participated in the work, have reviewed and agreed with the content of the article, and approved the final version of the report.

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REVIEW
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Ventricular Unloading Using the Impella™ Device in Cardiogenic Shock

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Cardiogenic shock (CS) remains a leading cause of hospital death. However, the use of mechanical circulatory support has fundamentally changed CS management over the last decade and is rapidly increasing. In contrast to extracorporeal membrane oxygenation as well as counterpulsation with an intraaortic balloon pump, ventricular unloading by the Impella™ device actively reduces ventricular volume as well as pressure and augments systemic blood flow at the same time. By improving myocardial oxygen supply and enhancing systemic circulation, the Impella device potentially protects myocardium, facilitates ventricular recovery and may interrupt the shock spiral. So far, the evidence supporting the use of Impella™ in CS patients derives mostly from observational studies, and there is a need for adequate randomized trials. However, the Impella™ device appears a promising technology for management of CS patients. But a profound understanding of the device, its physiologic impact and clinical application are all important when evaluating CS patients for percutaneous circulatory support. This review provides a comprehensive overview of the percutaneous assist device Impella™. Moreover, it highlights in depth the rationale for ventricular unloading in CS and describes practical aspects to optimize care for patients requiring hemodynamic support.

Keywords: cardiogenic shock, ventricular unloading, mechanical circulatory support device, Impella, hemodynamics, expert group, review

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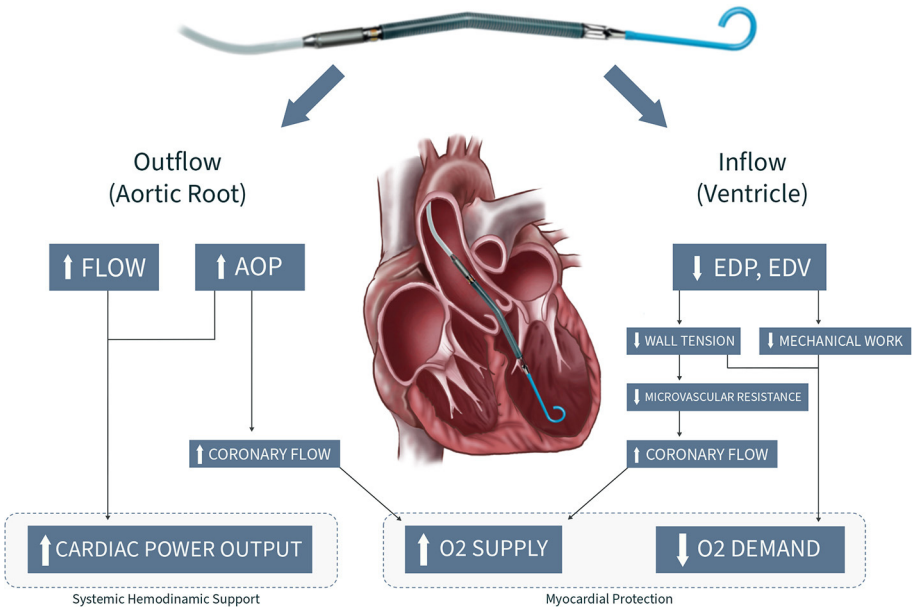
INTRODUCTION

Ventricular dysfunction despite normal or elevated filling pressures associated with hypoperfusion of end organs and tissue hypoxia defines cardiogenic shock (1–3). Acute myocardial infarction (AMI) represents the most common trigger of CS. Other common causes include acute valvular heart disease, ventricular arrythmias, fulminant myocarditis, post-cardiotomy shock and acute or chronic heart failure (HF).

Despite multiple advances including early revascularisation strategies, mortality rates in CS patients remain high (up to 50%) (4, 5).The cornerstones of contemporary CS management include prompt diagnostic workup and initiation of directed therapy aiming to re-establish tissue perfusion and halt the shock spiral. Therapeutic options remained limited for decades, and generally only involved inotropes, vasopressors, ventilatory support and reperfusion therapies. However, the introduction of mechanical circulatory support (MCS) has fundamentally changed CS management over the last decade. This is also reflected by the current European Society of Cardiology (ESC) guidelines with a IIa recommendation for short-term MCS (6). Whereas, particularly in the early MCS era, counterpulsation with an intraaortic balloon pump (IABP) as well as extracorporeal



GRAPHICAL ABSTRACT | Central illustration. Design principles and hemodynamic effects of the Impella™ device. AOP, Aortic pressue; EDP, Enddiastolic pressure; EDV, Enddiastolic volume.

membrane oxygenation (ECMO) represented the preferred devices for refractory CS, the micro-axial Impella™ (Abiomed, Danvers, Massachusetts) is an emerging percutaneous ventricular assist device (pVAD), that has increasingly been used in Western countries (7). In fact, there is a paradigm shift in CS management, which not solely aims for enhancing coronary blood flow (IABP) and maintaining systemic perfusion (ECMO), but also incorporates ventricular unloading ultimately aiming for myocardial recovery.

With this background, this comprehensive review highlights the rationale for ventricular unloading in CS. Moreover, it summarizes important practical aspects, possible complications and current evidence one needs to be aware of, when managing patients requiring hemodynamic support with an Impella™ device.

PATHOPHYSIOLOGY OF CARDIOGENIC SHOCK

CS represents a complex interplay between the heart and all other organ systems. Rapidly deteriorating myocardial contractility results in a spiraling process of ventricular dysfunction, hypotension, reduced venous return and diminished coronary perfusion leading to pulmonary congestion, hypoxia, decreased organ perfusion and worsening ischemia (3). Compensatory peripheral vasoconstriction initially improves coronary and peripheral perfusion. However, it contributes to increased cardiac afterload that overburdens damaged myocardium further diminishing circulating oxygenated blood flow (3, 8). Systemic hypoperfusion triggers endothelial dysfunction, systemic inflammatory response syndrome (SIRS) and coagulopathies, which all promote multiorgan dysfunction syndrome (MODS) (3). Activated systemic inflammatory mediators (e.g., interleukins, TNF-alpha) result in vasodilation and additional hypotension. Consequently, these mechanisms add up to the high mortality associated with cardiogenic shock (9).

Abbreviations: AMI, Acute myocardial infarction; HF, Heart failure; CS, Cardiogenic shock; ECMO, Extracorporeal membrane oxygenation; LVEF, Left ventricular ejection fraction; LVAD, Left ventricular assist device; MCS, Mechanical circulatory support; MODS, Multiorgan dysfunction syndrome; PCI, Percutaneous coronary intervention; pVADs, Percutaneous ventricular assist devices; RHF, Right heart failure; SIRS, Systemic inflammatory response syndrome; STEMI, ST-elevation myocardial infarction.

ROLE OF pVADs IN CARDIOGENIC SHOCK

The management of CS should focus on preventing and reversing organ failure through hemodynamic resuscitation and simultaneously addressing treatable causes.

Vasoactive and inotropic drugs, especially those with adrenergic mechanisms, have the burden to increase afterload, aggravate myocardial ischemia and trigger arrhythmias, which all ultimately worsen the patient's prognosis. Therefore, they must be cautiously titrated in the setting of CS (10, 11). Consequently, in patients presenting with impeding or already established cardiogenic shock, immediate MCS may be the first choice to rapidly re-establish stable hemodynamics and potentially prevent related MODS.

To date, three basic concepts have commonly been used for percutaneous MCS in acute CS management: (1) counterpulsation using the IABP, (2) ventricular unloading

provided by Impella™ technology or by the pulsatile PulseCath iVAC2L device, and (3) veno-arterial extracorporeal membrane oxygenation (VA-ECMO) circulatory support. The mechanisms and hemodynamic effects of currently available MCS are highlighted in **Table 1**.

THE IMPELLA™ DEVICE

The Impella™ is a percutaneous, microaxial pump that continuously draws blood from its inlet inside the ventricle and expels it in the ascending aorta (*Central Illustration*) (12–15). Owing its properties, the Impella™ unloads the left ventricle (LV) while simultaneously augmenting cardiac output (CO). The power connections for the pump motor and sensors are contained inside the 9F guiding catheter. The end of the catheter is connected to an external console consisting of an integrated controller for the pump and purge system. Unlike IABP, the Impella™ does not require ECG or arterial waveform triggering, facilitating stability even in the setting of ongoing tachyarrhythmias or electromechanical disassociation.

TABLE 1 | Characteristic features of cardiogenic shock.

Clinical features of cardiogenic shock
Myocardial contractile dysfunction
• Low CO (CI <2.2L/min/m^2) despite normal or elevated pre-load (LVEDP ≤ 15mmHg)
Prolonged hypotension requiring support by catecholamine
• SBP <90mmHg for ≥ 30 minutes
Clinical signs of impaired end-organ perfusion*
• Cool extremities
• Altered mental status
• Oliguria (<30 ml/h)
• Rising lactate levels (>2.0 mmol/L)
Pulmonary congestion

**Despite normovolemia or hypervolemia.*
CO, Cardiac output; CI, Cardiac index; LVEDP, Left ventricular enddiastolic pressure; SBP, Systolic blood pressure.

Currently, four devices are available: Impella™ 2.5, Impella™ CP and Impella™ 5.0/5.5 and Impella™ RP (**Table 2**). While the Impella™ 2.5 and CP are inserted percutaneously, the Impella™ 5.0 requires a surgical cutdown for insertion. Thus, in many institutions, the Impella™ 2.5 or CP reflect the first choice for mechanical support. The Impella™ RP is a 22 French, three-dimensional catheter-based micro-axial pump approved for use in acute right heart failure (RHF). The inflow of the Impella™ RP is positioned in the inferior vena cava (IVC) and the outflow in the pulmonary artery (PA) expelling blood from the IVC into the PA at a rate of up to 4.6 L/min.

HEMODYNAMIC EFFECTS OF pVADs AND THE CONCEPT OF VENTRICULAR UNLOADING

From Ventricular Venting to Unloading

Ventricular "venting" has been used in cardiac surgery for decades and refers to strategies to treat ventricular distension and prevent pulmonary edema occurring during cardiopulmonary bypass support and VA-ECMO (16). Different techniques have been applied including trans-septal septostomy (17), and surgical placement of an LV vent. Counterpulsation using is an alternative percutaneous option, thought to decompress the LV.

Since ventricular volume and pressure overload represents the hallmark of patients in CS, the concept of ventricular "venting" was adopted for CS patients. For many years, the IABP was the preferred and only support device for patients presenting with AMI and CS. However, efficacy of circulatory support by IABP is often insufficient considering the results of the randomized IABP-SHOCK II trial and a large meta-analysis with 2,123 patients showing no mortality reduction (18, 19).

In contrast to ventricular "venting", "unloading" is an active process reducing volume and pressure by pumping blood from the right or left ventricle to the pulmonary artery or aortic root, respectively. Historically, ventricular unloading in CS has been technically challenging, and a series of devices including the TandemHeart remained prototypes or never found widespread clinical use due to their complicated mode of implantation. The introduction of the catheter-based

TABLE 2 | Impella devices and pump characteristics.

	IMPELLA 2.5	**IMPELLA CP**	**IMPELLA 5**	**IMPELLA RP**
Access	Percutaneous	Percutaneous	Surgical	Percutaneous
Access site	Femoral; (axillary)	Femoral; (axillary)	Axillary; Femoral/ascending aorta	femoral vein
Guiding catheter size	9 F	9 F	9 F	11 F
Motor size	12 F	14 F	21 F	22 F
Introducer size RPM	13 F peel away	14 F peel away	23 F peel away*	23 F peel away
RPM (max.)	51,000	46,000	33,000	33,000
Duration of support (days)#	5	5	10	14

**Surgical cutdown and insertion through a Dacron graft (8-10 mm) recommended.*
#European approval (CE Mark).
F, French; RPM, Revolutions per minute.

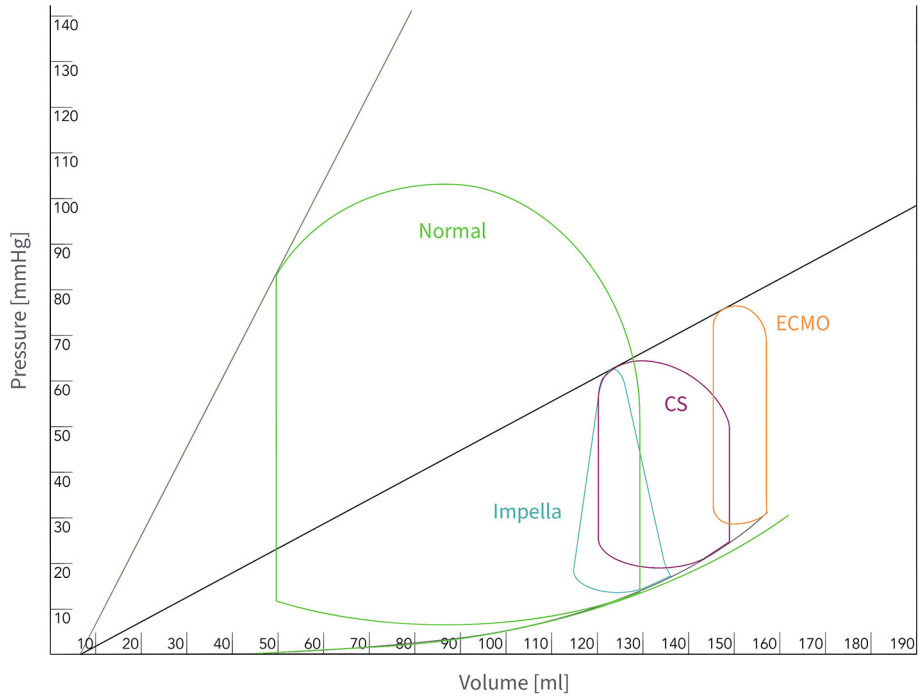


FIGURE 1 | Pressure-volume relationship: Normal conditions (CO 5l; green), CS (CO 3l, PAWP 27 mmHg; purple), CS on VA-ECMO support (3l flow, orange); CS on Impella™ CP support and "P" Level 9 (4 l flow; turquoise). The pressure-volume area represents an estimate of mechanical work performed by the ventricle. The pressure-volume area is only reduced with the Impella™, thus decreasing LV work. *CO, Cardiac output; CS, Cardiogenic shock; LV, Left ventricular; PAWP, Pulmonary artery wedge pressure; VA-ECMO, veno-arterial extracorporeal membrane oxygenation*.

ventricular assist device Impella™ helped to overcome some of those hurdles.

Hemodynamic Effects of the Impella Device

There are four physiologic effects of left sided Impella support: (1) With the inflow of the device drawing blood directly from the ventricle (ventricular unloading), it reduces ventricular end-diastolic volume (EDV) and pressure (EDP) (20). Decreasing EDV and EDP leads to a reduction of myocardial wall tension and workload, both of which diminish myocardial oxygen demand (21–24). This is further highlighted by the progressive loss of isovolumic phases during increasing Impella support illustrated by the conversion of pressure-volume loop into a triangular shape (**Figure 1**). (2) The outflow of the Impella™ device in the aortic root provides active flow increasing mean arterial pressure (AOP), diastolic pressure, CO and thus cardiac power output (20, 25, 26). If properly placed, the outflow of the device resides just above the aortic valve plane and provides before mentioned systemic pressure augmentation in correlation to the level of Impella support ("P" level) (27). (3) The synergistic effect of increased mean AOP and decreased myocardial wall tension leads to augmented coronary flow, thus improving myocardial oxygen supply. Overall, the Impella device favorably alters the balance of myocardial oxygen demand and supply and therefore improves the heart's ability to survive ischemic challenges (28, 29).

In contrast, VA-ECMO decreases preload, but at the same time substantially increases afterload, which adversely impacts myocardial oxygen consumption. While a healthy LV can cope with increased afterload by recruiting more contractility, the impaired LV in CS may further decompensate leading to a vicious cycle of mechanically driven injury with worsen pulmonary congestion, acute lung injury and pulmonary hemorrhage, thereby worsening cardio-pulmonary function (30, 31). (4) Left ventricular Impella™ support results in decreased pulmonary capillary wedge pressure (PCWP) and a secondary reduction in RV afterload (14). (**Table 3**, Central Illustration).

Systemic Hemodynamic Support

The Impella augments both flow and pressure in the aorta leading to improved cardiac power output and increased AOP. The actively generated forward flow depends on (1) the specific device (**Table 3**), (2) the performance ("P") level setting and (3) the pressure gradient across the aortic valve. Higher "P" level settings or lower pressure gradients result in higher flow augmentation (20, 25, 26, 29, 32). Importantly, the increase in systemic CO results from the net effect of native CO reduction after ventricular unloading and the forward flow contribution of the Impella™ pump. As a consequence, the mean AOP correlates with the Impella™ support and can be modified by changes in the "P" level setting, as highlighted in **Figure 2**.

TABLE 3 | Technical properties of percutaneous circulatory assist devices.

	IAPB	IMPELLA 2.5	IMPELLA CP	IMPELLA 5.0	VA-ECMO
Mechanism	Aorta	LV→ aorta	LV→ aorta	LV→ aorta	RA→ aorta
Cannula size (Fr)	7–8	13–14	13–14	22	14–16 arterial 18–21 venous
Flow (L/min)	0.3–0.5	1.0–2.5	3.7–4.0	5.0	3.0–7.0
Pumpmechanism	Pneumatic	Axial flow	Axial flow	Axial flow	Centrifugal
Stable rhythm	Yes	No	No	No	No
Implantation time	+	++	++	+ + ++	++
Risk of ischemia	+	++	++	++	+ + +
Anticoagulation	+	+	+	+	+ + +
Cardiac power	↑	↑↑	↑↑	↑↑	↑↑↑
Afterload	↓	↓	↓	↓	↑↑↑
MAP	↑	↑↑	↑↑	↑↑	↑↑
LVEDP	↓	↓↓	↓↓	↓↓	↔
PCWP	↓	↓↓	↓↓	↓↓	↔
LV preload	–	↓↓	↓↓	↓↓	↓
Coronary perfusion	↑	↑	↑	↑	–

IABP, intraaortic balloon pump; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; LV, Left ventricle, RA, Right atrium; MAP, Mean arterial pressure; LVEDP, Left ventricular end-diastolic pressure; PCWP, Pulmonary capillary wedge pressure.

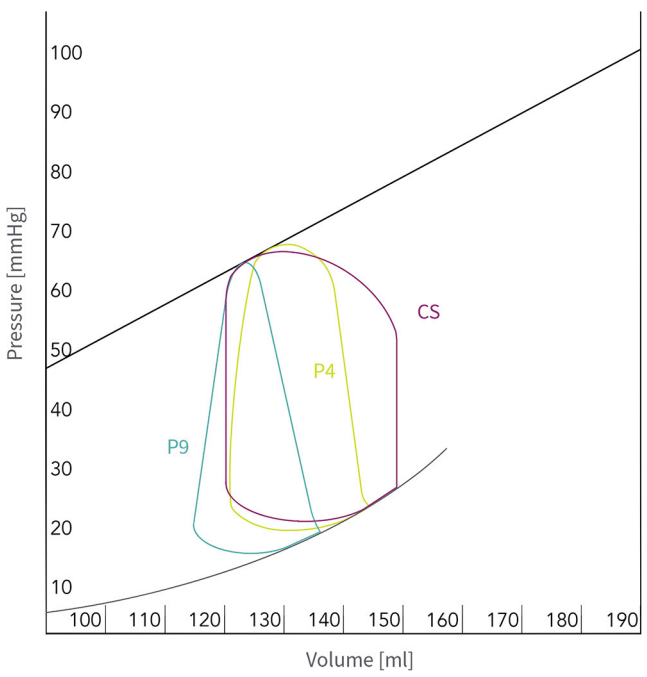


FIGURE 2 | Pressure-volume relationship on Impella™ CP support and different performance ("P") level settings: The evolution of the pressure-volume relationship before (CS: CO 3l, PAWP 27 mmHg; purple) and after support with "P" Level 4 (2.5 l flow; green) and "P" Level 9 (4 l flow; turquoise). *CO, Cardiac output; CS, Cardiogenic shock; PAWP, Pulmonary artery wedge pressure*.

Myocardial Protection: Augmenting Coronary Flow and Increasing O_2 Supply

Coronary artery flow is proportional to the ratio of AOP and microvascular resistance. By drawing blood directly from the ventricle, the Impella™ reduces maximum wall tension and microvascular resistance. Therefore, the synergistic effect of increased AOP and the reduction of microvascular resistance with increasing Impella support levels lead to a subsequent augmentation of the coronary flow (15, 28). Of note, the constant flow of the Impella device provides more sustained augmentation throughout the diastolic period. In contrast, the IABP deflates in late diastole, which leads to transient pressure increase only early in diastole but this augmentation reverses just before systole, lowering end-diastolic pressure. For instance, the positive effects of the Impella™ on coronary microcirculation has been illustrated in a case report from Agel et al. (33). On nuclear perfusion imaging, they demonstrated adequate myocardial perfusion through collaterals while on Impella™ support in a patient with severe three vessel disease, including complete occlusion of the right and left circumflex coronary artery (33).

Ventricular Unloading: Decreasing O_2 Demand

Myocardial oxygen demand is determined by the amount of mechanical work the muscle produces and the amount of myocardial potential energy, which is related to wall tension (21–24, 28). By drawing blood from the ventricle, the Impella™ reduces total filling volume and pressure, which leads to a reduction in stroke volume according to the Frank-Starling mechanism: "If the heart fills less, it expands less and reduces its subsequent stroke output, which corresponds to a reduction in mechanical work" (Central Illustration).

Oxygen Demand-Supply Ratio

The reduction in EDP, EDV and wall stress lead to reduced microvascular resistance and increased myocardial perfusion (increasing myocardial oxygen supply). In addition to this perfusion effect, ventricular unloading results in reduced

mechanical work and potential energy (reduced myocardial oxygen demand). This impact is expressed in the pressure-volume (PV) loop by a leftward shift in its position and an overall reduction in its area (**Figure 1**). Of note, while significant reduction of ventricular work as well as end-diastolic pressure and volume was shown with the Impella, changes in the same parameters with the IABP were not significant (28).

ACUTE RIGHT HEART FAILURE AND RIGHT VENTRICULAR UNLOADING

RHF is a characterized by the inability of the right ventricle (RV) to sustain pulmonary flow caused by increased RV afterload (e.g., acute pulmonary embolus, severe hypoxia, acidemia, or increased intrathoracic pressures) or decreased RV contractility (e.g., RV ischemia, myocarditis, post-cardiotomy CS, or LVAD support) (34–36). RHF is associated with high morbidity, mortality, and longer hospital length of stay (37). The thin walled RV differs markedly from the LV in architecture, mechanics, metabolism, and recovery from injury (38). The RV is exquisitely susceptible to failure under conditions of ischemia and pressure overload. However, the RV is remarkably resilient and tends to recover once hemodynamics improve and the underlying insulting cause is eliminated. But in some patients RHF persists and, similar to LV related shock, outcome in patients requiring multiple and prolonged inotropic and vasopressor support is poor (10, 11). Moreover, 10–40% of patients undergoing isolated left ventricular assist device (LVAD) implantation experience some degree of RHF (39). While RHF associated with LVAD insertion may be partially caused by the underlying cardiomyopathy, the pathophysiology of RHF after LVAD implantation is complex.

In this context, the Impella™ RP provides an opportunity for mechanical support in the downward spiral of refractory RHF and may serve as a bridge to recovery or heart transplant. Since survival after impella™ RP insertion strongly depends on timing and patient selection (37, 40, 41), early identification of RHF and careful consideration of patient's clinical status and comorbidities is key to obtain the best clinical outcomes. Device implantation requires some expertise and, in contrast to LV pumps, can only be performed under fluoroscopy guidance. Frequent monitoring of RV function using echocardiography and pulmonary artery catheter measurements is crucial to guide Impella™ RP therapy. Based on the inclusion and exclusion criteria of the RECOVER RIGHT trial (37) and a series of smaller clinical studies and case series (42–45), a dedicated checklist for patient selection has been proposed, see **Table 4**.

TABLE 4 | Impella RP heart pump patient selection recommendations.

Clinical conditions in which the Impella RP is not recommended
Active infection with positive blood cultures
RA, RV or PA thrombus
Mechanical valves in the right heart*
Unrepaired ASD, PFO, or aortic dissection
PA conduit
Anatomic abnormalities precluding insertion
Moderate to severe pulmonary valve stenosis or insufficiency
Severe pulmonary hypertension (PAPs > 60mmHg)
Documented DVT and/or presence of IVC filter
Patients on right-sided support or ECMO
Allergy or intolerance to contrast
HIT or sickle cell disease
Definition of RHF
CI <2.2 l/min/m^2 despite continuous infusion of high dose inotropes# and any of the following: • CVP > 15 mmHg or • CVP/PCWP > 0.63 or • Moderate to severe global RV dysfunction on echocardiography defined as one of the following criteria: ○ Global RV hypokinesis ○ TAPSE score of ≤14 mm ○ RV diameter at basis >42 mm ○ RV short axis (or mid-cavity) diameter >35 mm

Table adapted from Abiomed® recommendations for Impella RP patient selection.
**Presence of a tricuspid ring or bio-prosthesis is not a contra-indication, but it may result in a difficult implantation depending on the valve strut orientation within the RVOT.*
#Dobutamine of ≥ 10 μg/kg/min or equivalent for more than 15 min (120 min for milrinone) and/or administration of more than one inotrope/vasopressor.
ASD, Atrial septal defect; CVP, Central venous pressure; PCWP, Pulmonary capillary wedge pressure; DVT, Deep vein thrombosis; HIT, Heparin induced thrombocytopenia; PA, Pulmonary artery; PAPs, Pulmonary artery systolic pressure; PFO, Persistent foramen ovale; RA, Right atrium; RV, Right ventricle.

CURRENT EVIDENCE

The only two randomized clinical trials comparing the Impella™ vs. IABP have both been neutral with respect to survival. However, both were underpowered, the ISAR-SHOCK trial mainly targeted hemodynamic improvements (46). The small IMPRESS trial also showed similar outcomes with both Impella CP and IABP in patients with ST-elevation myocardial infarction (STEMI) and CS undergoing primary percutaneous coronary intervention (PCI) (47). One must take in account that this trial included critically ill patients and the major cause of death was anoxic brain injury, suggesting that mechanical hemodynamic support may be of limited utility in this patient cohort. Also, the trial was underpowered (47). Although, some centers have reported better survival rates in CS after implementation of a comprehensive shock protocol using pVADs (48, 49), the use of Impella™ has been associated with higher risks of bleeding, stroke, and death, as well as higher costs compared to IABP in propensity-matched analyzes from registry data (7, 50, 51). However, confounding due to the use of pVADs in sicker patients cannot be ruled out (51). Despite neutral results in randomized clinical trials and the remaining high mortality rates in this severely ill population there is some evidence that the use of larger Impella™ pumps (e.g., Impella™ CP), the initiation of Impella™ prior to PCI and its use in patients without cardiac arrest may be correlated with outcome improvements (52).

In comparison to VA-ECMO, the incidence of major complications, such as bleedings, might be lower with Impella™ use (53). The data supporting the use of RV pVADs, namely the Impella™ RP, is even more limited and randomized data is not yet available. The RECOVER RIGHT study was the first to

suggest feasibility and safety of the Impella™ RP in patients with severe RHF (13). A series of recent studies indicated possible clinical benefit with the Impella™ RP demonstrating 30-day survival rates of of 64–72% (37, 40, 41). However, the survival rate was much lower among patients in whom Impella™ RP was implanted as salvage support (41). This caused the U.S. Food and Drug Administration to issue a warning advice. This controversy highlights the need for proper patient selection and early initiation of hemodynamic support.

CASE SELECTION

Left Ventricular Impella™ Devices

Contraindications to the placement of the LV Impella™ include mechanical aortic valve, LV thrombus, moderate to severe aortic regurgitation, and severe obstructive peripheral arterial disease.

Visualization of the ventricle before implantation excluding the presence of a thrombus is recommended if time permits using a bed-side echocardiogram. Thrombus may be sucked up by the impeller and interrupts its proper functioning. As with any other catheter placed in the LV, the Impella™ catheter may furthermore dislodge thrombus, potentially causing systemic embolization. Moderate to severe aortic regurgitation (AR) is a relative contraindication. Only a competent aortic valve separating the LV and aorta allows optimal antegrade Impella™ flow. In patients with relevant AR, AOP augmentation by the Impella™ may worsen AR and LV dilation. Given concerns regarding compromise of the remaining valvular orifice and worsening hemodynamics with the introduction of the Impella™ catheter, aortic stenosis (AS) has been considered an exclusion criterion in clinical trials. Also, crossing of a severely stenotic aortic valve with the impella device might be very challenging. Despite these concerns, feasibility of Impella™ insertion in severe AS before high-risk PCI, during balloon valvuloplasty or transcatheter aortic valve replacement (TAVR) and bail-out use as a bridge to TAVR in CS has been demonstrated in several reports (54–60). Peripheral artery disease (PAD) may not be an absolute contraindication for the Impella™ insertion, nevertheless its presence and extent need to be considered prior to device implantation. Femoral angiography in an ipsilateral projection prior to Impella™ insertion to assess puncture height and anatomical suitability of the iliac and femoral arteries allows to identify prohibiting PAD and may prevent access site complications and limb ischemia. Additionally, ultrasound guidance helps to find the ideal puncture site and avoid impeding calcifications. In afflicted patients, alternative access routes (trans-subclavian or -axillary) may be evaluated. However, to avoid complications prudent access site management is crucial. Several strategies for closure of the arteriotomy after removal of the device are utilized dependent on availability and local experience. Manual compression is a cost-effective, although time intensive means to achieve hemostasis. Femoral compression systems (e.g., using FemoStop, Abbott Vascular) can be applied to avoid bleeding after device removal. Latest generation of the Impella™ sheaths allow advancement of a wire for sheath exchange or placement of closure devices, such as the MANTA® 14 F device (Teleflex Inc., Morrisville, North Carolina) or the Perclose ProGlide™ suture-mediated closure System (Abbott Vascular Inc., Santa Clara CA, U.S.A.). In selected cases at high risk for bleeding or ischemic complications surgical removal might be safest.

Impella™ RP

As for the left ventricular devices, only a competent pulmonary valve allows optimal forward flow. However, a certain degree of pulmonary valve regurgitation is often present in the setting of acute RHF and elevated pulmonary artery pressures. Albeit significant tricuspid valve regurgitation (TR) often accompanies RHF, hemodynamic effects of the Impella™ RP are usually not affected if the pulmonary valve is competent. So far, TR represents a relative contraindication for Impella™ RP implantation according to the manufacturer. However, TR might improve after RV unloading, particularly if TR is secondary to annular dilatation in the setting of acute RHF. Therefore, TR should rather be seen as a warning sign than as an absolute contraindication.

INDICATIONS FOR VENTRICULAR UNLOADING

In addition to its application in high-risk PCI and cardiogenic shock complicating AMI, the Impella™ technology has been successfully introduced in a broad variety of clinical scenarios requiring left or right ventricular support. Indication for ventricular unloading and issues to be considered when selecting patients for pVAD support are depicted in **Table 5**.

Timely implantation is often key. Considering the rapidly progressing shock spiral, early identification and treatment are crucial to increase chances of survival. This seems underlined by observational data suggesting that Impella™ implantation before revascularization maximizes the potential benefit (61) and that survival decreases by about 10% for every 60 min of delay (49).

Mechanical Support in Coronary Bypass Surgery and Post-cardiotomy Cardiogenic Shock

Nowadays most patients presenting with CS secondary to myocardial infarction (MI) are revascularized percutaneously. However, there is a subset of patients who need to be referred for urgent or emergent coronary artery bypass grafting (CABG). In a US registry, 129 (2.3%) patients with MI and CS undergoing CABG had MCS inserted (62). Most of these patients were bridged to surgery with an Impella™ device. Although, operative mortality in this emergency setting was very high (37.2%), the data suggests that there may be some benefit to instituting MCS prior to CABG in this very high-risk group of patients. Also, there are reports of prophylactic pVAD utilization in high-risk patients undergoing off-pump CABG to minimize cardiovascular instability following heart positioning for proper suturing of coronary anastomoses (63–65).

TABLE 5 | Indication for ventricular unloading.

Clinical scenarios requiring left or right ventricular support		
Emergency interventions	*Planned interventions*	
AMI complicated by CS	High-risk PCI	
Post-cardiac surgical (bi)ventricular failure	Catheter ablations of VT	
Fulminant myocarditis	High-risk bypass surgery	
Advanced heart failure Valvular heart disease (e.g. AS) with severe LV dysfunction		
Hemodynamic deterioration after TAVR		
Clinical conditions to be considered in patient selection with CS		
Coronary artery disease and treatment considerations	*Clinical considerations*	*Hemodynamic considerations*
Large LAD or RCx related STEMI Adequate peripheral access	Comorbidities (e.g. expected neurological outcome, diabetes, renal failure, PAD)	SBP <90mmHg and/or inotropic pressure-dependance Tachycardia (HR >100/min)
Preferably initiate Impella support before PCI	Bleeding risk (ACT 160–180 s)	LVEDP >30–35 mmHg

ACT, Activated clotting time; AMI, Acute myocardial infarction; AS, Aortic stenosis; CS, Cardiogenic shock; HR, Heart rate; PCI, Percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TAVR, Transcatheter aortic valve replacement; VT, Ventricular tachycardia.

Overall, 0.2–9% of the patients undergoing cardiac surgery experience post-cardiotomy CS, which is associated with a high mortality (66, 67). Early data from 24 patients, who could not be weaned from cardiopulmonary bypass or were hemodynamically unstable and therefore needed support with the Impella™ Recover device (providing 3–4 L/min flow), showed improved outcome compared to IABP alone, if the heart was able to pump >1l/min (68). Thomas et al. (69) reported the first successful use of an Impella™ 5.0 L/min for post-cardiotomy CS after coronary artery bypass grafting and bioprosthetic aortic valve replacement. Support was maintained for 7 days. Noteworthy, no damage to the bioprosthetic aortic valve was seen. Despite these promising reports, VA-ECMO is still much more commonly employed in patients with post-cardiotomy CS and further studies are necessary to support the use of the Impella™ device in the setting of cardiac surgery.

COMPLICATIONS ASSOCIATED WITH IMPELLA™

Overall, the type of complications related to the use of the Impella™ device are similar to those encountered with the IABP. The most common complications include limb ischemia, vascular injury and bleeding requiring blood transfusion (15). The reported incidence of limb ischemia ranges from 0.07–10% and for significant bleeding from 0.05 to 54% (70). The risk of bleeding is also related to the administration of antithrombotics (e.g., unfractionated heparin), thrombocytopenia or consumption of coagulation factors (e.g., von-Willebrand factor) related to shear-stress with the impeller. Moreover, shear stress from the impeller (especially at very high "P" levels) can lead to clinically relevant hemolysis, which in worst case scenario can cause renal failure. This phenomenon has been observed in 5–10% of patients during the first 24 h on Impella™ support. The risk of hemolysis and aortic valve injury may be diminished by proper positioning of the inlet cannula, and thus limited flow turbulences.

Ischemic or hemorrhagic cerebrovascular accidents following Impella™ insertion have also been reported (2.4–6.3%) (70, 71). As with any percutaneous device, there is a risk of access site infection and sepsis, which increases with the duration of support. In the early experience, device migration and malfunction rarely led to injury of the aortic valve or ventricle causing tamponade due to LV perforation. Also, mitral regurgitation secondary to injury of the papillary muscles or chordae have been reported (32). Finally, the pigtail end of the Impella™ within the LV can provoke ventricular arrhythmias potentially further impairing CO and deteriorating CS.

ESCALATION OF SUPPORT AND COMBINATION OF IMPELLA™ WITH OTHER DEVICES

MCS is a key element of most modern cardiogenic shock care pathways (3). It is recommended to define triggers for initiation of MCS, choice of MCS modality, and escalation steps in CS patients. Such pathways should certainly be tailored to local MCS availability and experience. Irrespective of MCS modality, the adequacy of hemodynamic support and ventricular unloading needs to be closely monitored.

Adequate monitoring including a pulmonary artery catheter (measurement of central venous pressure (CVP), PCWP, CO) in combination with standard clinical measures such as blood pressure, lactate and urine output is mandatory. Frequent echocardiographic assessments of LV/RV size, function, and aortic valve opening can help to optimize pharmacologic treatment and guide escalation of mechanical circulatory support.

According to the anticipated degree of support required, the Impella™ 2.5, Impella™ CP, or the surgically implanted Impella™ 5.0/5.5 may be considered. The support requirements depend on body size as well as the degree of hemodynamic compromise. It is crucial to be aware, that due to the Anrep effect the intended Impella™ flow cannot be simply added to the pre-insertion native CO. Reduced contractility of the ventricle after pump insertion will result in a smaller total CO than expected. Among patients with profound LV dysfunction an Impella™ pump might unload the LV to the point of continuous aortic valve closure resulting in a non-pulsatile arterial curve on the monitor.

The Impella™ 2.5 and CP, which can rapidly be inserted percutaneously, are usually the first choice in the setting of CS. However, in patients with severe LV failure, low CO might persist for several days, sometimes even weeks or months. In such cases, upgrading to a larger device (e.g., Impella™ 5.0 or 5.5)

TABLE 6 | Combination of Impella™ with other devices.

	Indication	Effect	Limitations
Impella™ + VA-ECMO (ECMELLA)	- Gas exchange failure - Refractory CS/inadequate support - Concomitant RHF* following LV Impella™ insertion - RHF and severely elevated PVR - Recurrent tachyarrhythmias - Pulmonary hemorrhage	Hemodynamic support ↑ Oxygenation ↑ and CO_2 elimination RV unloading	- Access site complications - Increased LV afterload - Bleeding diathesis - Post-implantation management complexity - Cost-intensive
VA-ECMO + Impella™ (ECMELLA)	- LV stasis with thrombus formation - Pulmonary failure due to high PAP - LV distension - Myocardial ischemia	LV/RV unloading Myocardial perfusion ↑	- Reduction of VA-ECMO flow required - Post-implantation management complexity - Cost-intensive
Impella™ + Impella™ RP (BiPella)	- Biventricular failure - Concomitant RHF* following LV Impella™ insertion	RV output ↑ LV suction alarms ↓ (at maximal LV pump speed) CO ↑	- Implantation of Impella™ RP requires expertise and fluoroscopy guidance - Limited efficacy in severely elevated PVR - Cost-intensive
Impella™ + IABP	Refractory CS	Myocardial perfusion ↑ Oxygen demand–supply ratio ↓	- Limited hemodynamic support - Possible overall reduction in the Impella flow

**Which is not volume responsive.*

CS, Cardiogenic shock; CO, Cardiac output; IABP, intraaortic balloon pump; VA-ECMO, Veno-arterial extracorporeal membrane oxygenation; LV, Left ventricle, RV, Right ventricle; PAP, Pulmonary artery pressure; PVR, Pulmonary vascular resistance.

might be a wise strategy (72). With these devices the patient can even be ambulated while awaiting recovery, cardiac transplant or LVAD implantation.

Simultaneous RHF results in reduced LV preload and therefore limits the flow of the LV Impella by recurrent suction events, which necessitates down-titration of the Impella™ pump power level. In case of inadequate hemodynamic response after LV unloading and recurrent suction alarms irresponsive to volume challenge, the insertion of an VA-ECMO or Impella™ RP may be considered. The latter augments RV output and therefore increases LV preload (BiPella approach), which in turn improves CO. Although, there are only small case series available (45, 73–78), the BiPella approach seems to be feasible and safe und might be used as a salvage treatment modality for refractory biventricular failure. VA-ECMO might be primarily considered in the setting of inappropriate oxygenation due to acute lung congestion or MODS. Also, VA-ECMO implantation might be evaluated in case of refractory shock and inadequate support from the Impella™.

Conversely, some patients on VA-ECMO support may benefit from additional LV unloading by an Impella™ device. Although potentially lifesaving in patients with CS, VA-ECMO burdens the already impaired LV by increasing afterload. This may further compromise the LV contractile function due to ventricular distension and impaired myocardial blood flow (79, 80). When deployed in combination with VA-ECMO, the Impella™ (ECMELLA approach) reduces filling pressures, ventricular distension, and maintains flow from the LV to the aorta even in the absence of LV ejection and a closed aortic valve (81–83). There is data proposing the combined use of VA-ECMO with an Impella™ device in severe CS cases to unload the LV, facilitate myocardial recovery and improve clinical outcomes. Yet, the evidence supporting the ECMELLA approach derives only from observational studies and has accordingly some limitation (81–84). Also, the increased risks of hemorrhagic and vascular complications due to the additional large bore vascular access required need to be considered.

Finally, there are small case series endorsing the combination of an Impella™ device and IABP as a bail out strategy in refractory CS (28, 85). However, further clinical investigations will be needed to assess if the combination of LV unloading and counterpulsation using the IABP brings any incremental physiological and clinical benefit. Possible combinations of different MCS devices, their indications, clinical effect and possible pitfalls are depicted in **Table 6**.

FUTURE PERSPECTIVES

With respect to the limited evidence supporting the use of the Impella™, especially in patients with AMI and/or CS, there are several trials in progress. For instance, the DanGer Shock trial (ClinicalTrials.gov Identifier: NCT01633502) is a prospective, multicenter, open-label trial randomizing AMI patients with CS 1:1 to Impella™ CP support or current guideline-driven therapy with a planned enrollment of 360 patients (86).

Also, following encouraging pre-clinical studies (87, 88), which suggest a reduction in infarct size by applying early ventricular unloading in patients with AMI, the STEMI-DTU trial (ClinicalTrials.gov Identifier: NCT03947619) will study the impact of ventricular unloading by the Impella™ device during 30 min before primary PCI on infarct size in patients with acute anterior MI.

Besides new treatment concepts, also new devices are currently under investigation or development. Since the actual versions of percutaneously implanted LV Impella™ devices

bear the risks of bleeding and vascular injury, there have been efforts to downsize the catheter size. There is now a nine french device – the Impella™ ECP – under clinical investigation (ClinicalTrials.gov Identifier: NCT04477603). Also, new devices allowing LV unloading with integrated batteries are under development, ensuring long-term hemodynamic support for several months and enabling patients to leave the hospital while awaiting heart transplant or as a destination therapy.

CONCLUSION

Albeit randomized evidence supporting its clinical use remains scarce, the Impella™ device is an emerging MCS device for treatment of CS. The Impella™ actively unloads the impaired left or right ventricle and maintains systemic pressure. If immediately applied, these devices not only unload the ventricle but also improve myocardial and peripheral oxygen supply and therefore have the potential to halt the shock spiral and reverse MODS. Owing to its design, the Impella™ relieves the battered ventricle, which appears to improve myocardial recovery. Profound understanding of the device, its physiologic impact, but also its limitations are important when considering a CS patient for percutaneous circulatory support.

AUTHOR CONTRIBUTIONS

AA-T has drafted and corrected the manuscript. MB, GC, GT, MM, AB, RK, and FC revised the manuscript critically for important intellectual content. All authors contributed to the article and approved the submitted version.

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A Novel Strategy to Simplify the Procedures in Treating Complicated Coronary Bifurcation Lesions: From a Bench Test to Clinical Application

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Background: Although provisional stenting strategy based on jailed balloon side branch (SB) protection could be useful for high-risk bifurcation lesion in certain clinical scenarios, its complexity still gives rise to procedure complications. We proposed a novel strategy, the jailed balloon proximal optimization technique (JB-POT), to simplify the procedures in treating complex coronary bifurcation lesions (CBLs). The present study was designed to verify the safety and efficacy of JB-POT under bench testing and clinical circumstances.

Methods: After a stent was deployed in main vessel (MV) with a balloon jailed in SB, POT and post-dilation of the stent were performed without retrieving the jailed balloon. A re-POT was performed 2 mm away from SB branching point to minimize proximal stent malapposition. The JB-POT procedure was performed on 10 samples of a silicone bifurcation bench model, and optical coherence tomography (OCT) was utilized to evaluate stent deployment. From December 2018 to July 2021, a total of 28 consecutive patients with true CBLs treated with JB-POT were enrolled. Immediate procedure results were observed, and clinical follow-ups were performed.

Results: The bench test showed that JB-POT did not induce significant stent malapposition, underexpansion or distortion, as indexed by the malapposition rate, minimum stent area (MSA), eccentricity index and symmetry index determined through OCT. Under clinical circumstances, JB-POT did not induce significant malapposition, underexpansion or distortion. Among the 30 lesions, there was no primary endpoint event defined as SB occlusion, need to rewire the SB with a polymer-covered guide wire, or failure to retrieve a jailed wire or balloon. One rewiring event and 0 double stenting events occurred as secondary endpoint events. One patient died of heart failure in the 8th month after discharge.

Conclusions: The JB-POT protocol, which tremendously simplifies the current standard provisional stenting procedure in complicated bifurcation lesions, shows acceptability in safety and efficacy. Hence, it might become an applicable strategy for treating high-risk bifurcation lesions, especially those with multiple risked SBs.

Keywords: bifurcation, bench test, jailed balloon technique, proximal optimization technique, provisional stenting

INTRODUCTION

Coronary bifurcation lesions (CBLs) are involved in 15–20% of all percutaneous coronary interventions (1). A provisional stenting strategy based on jailed balloon side branch (SB) protection could be useful for high-risk bifurcation lesions in certain clinical scenarios according to the recent studies (2, 3). In the traditional jailed balloon-based provisional stenting (JB-PS) protocol, SB rewiring, stent dilation after deployment (post-dilation), proximal optimization technique (POT), SB dilation (if necessary), final kissing and repeated POT are frequently required. Although POT was proven to optimize proximal main vessel (MV) stent apposition and SB opening in some bench studies (4, 5), further research showed that POT caused 6–10% SB strut jailing in bench studies and 30% SB FFR < 0.75 in clinical trials (6, 7). Although the jailed balloon technique (JBT), including both conventional and modified JBT (8), prevents carina and plaque shifts during stent deployment, POT could still cause SB narrowing by the carina or plaque shift mechanism after the jailed balloon has been retrieved when POT is not accurately positioned. As a result, rewiring SB and SB dilation become routine manipulations before POT and post-dilation. However, these manipulations are often time-consuming and troublesome, especially when they need to be repeated to protect each SB from occlusion in diffuse MV bifurcation lesions accompanied by multiple endangered SBs.

Hereby, we simplified the provisional stenting strategy from JB-PS to the jailed balloon proximal optimization technique (JB-POT) by performing post-dilation and POT with a balloon jailed in the SB. This strategy limits carina/plaque shift during post-dilation and POT, and it saves the steps of SB rewiring, SB dilation and final kissing, which would substantially shorten the procedure time and reduce the complexity of the CBL intervention under certain circumstances. Our concern about this strategy is whether it would induce unacceptable malapposition, underexpansion and/or distortion and whether it would effectively protect the SB from occlusion. The present study utilized a silicosis CBL model to test the proximal stent apposition, proximal stent expansion and proximal stent formation. A retrospective observation was performed to examine the efficacy and safety of JB-POT in real-world applications.

Abbreviations: SB, side branch; JB-POT, jailed balloon proximal optimization technique; CBLs, coronary bifurcation lesions; MV, main vessel; OCT, optical coherence tomography; MSA, minimum stent area; JB-PS, jailed balloon-based provisional stenting; POT, proximal optimization technique; JBT, jailed balloon technique; Re-POT, repeated POT; EBC, European Bifurcation Club; TIMI, thrombolysis in myocardial infarction; LM, left main coronary artery; QCA, quantitative coronary angiography; IVUS, intravascular ultrasound; MACE, major adverse cardiovascular events; TLR, target lesion revascularization; MI, myocardial infarction; STEMI, ST segment elevation myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; D1, the first diagonal branch; D2, the second diagonal branch; OM, obtuse marginal branch; ELCA, excimer laser coronary angioplasty.

MATERIALS AND METHODS

JB-POT Rationale and Protocol

In CBLs of higher angiographic complexity, the amount of atherosclerotic plaque located in the polygon of confluence is higher. Stenting the MV is known to have the potential to compromise the SB due to the occurrence of plaque and carina shifts. JBT is an effective strategy to prevent plaque and carina shifts (3, 9, 10). In the standard JB-PS protocol, the jailed balloon is retrieved after stent deployment and cannot protect the SB from carina/plaque shift and narrowing during POT and post-dilation. Hence, rewiring the SB, dilating the SB ostium and final kissing are often required to avoid SB complications. As shown in **Figure 1**, the JB-POT technique was designed to avoid SB rewiring and final kissing to simplify the provisional stenting protocol. After jailed balloon MV stenting, a non-compliant balloon of the proximal MV diameter was used to perform POT with the jailed balloon maintained. SB blood flow was then checked by angiography, and the SB jailed balloon was dilated if SB flow was degraded at the time. Furthermore, the jailed balloon was retrieved gently, and repeated POT (re-POT) was performed 2 mm away from the SB branching point (avoiding influencing SB ostium) to revise the probable malapposition or underexpansion. After initial jailed balloon POT, rewiring, side branch dilation and kissing would be performed if side branch thrombolysis in myocardial infarction (TIMI) flow degraded (<3), side branch residual stenosis was over 90% for non-left main (LM) lesions or over 75% for LM lesions, or dissection type over A (11, 12). As the previous trials showed, SB [except large left circumflex coronary artery (LCX)] residual stenosis was often not functionally meaningful. In side branch of small territory, it is only necessary to keep it (side branch) open (13).

Bifurcation Phantom

3D printing semitransparent silicone models of the coronary bifurcation artery were made by Ningbo Trando 3D Medical Technology Co., Ltd. Their inside diameters were 3.7 mm for proximal MV (D_{pMV}), 3.0 mm for distal MV (D_{dMV}), and 2.5 mm for SB (D_{SB}), complying with Finet's law ($D_{pMV} = 0.678\ [D_{dMV} + D_{SB}]$) (**Figure 2**) (14, 15). The silicone material had similar elastic characteristics according to the EBC bench test consensus (16). The semitransparent characteristic was appropriate for testing or observing the simulated intervention procedures.

Patients

In our hospital, 30 patients underwent JB-POT-based provisional stenting from December 2018 to July 2021. Twenty eight patients were enrolled in this study by a retrospective analysis. One patient was excluded due to angiographically visible thrombus, and another was excluded due to unstable hemodynamics (**Figure 3**). The indications for PCI included stable coronary disease and acute coronary syndrome, which were further determined by the results of preprocedural exercise electrocardiography, quantitative coronary angiography (QCA) or intravascular imaging. In this study, bifurcation lesions with risked SBs and significant MV stenosis as indicated by the 2018 European Society of

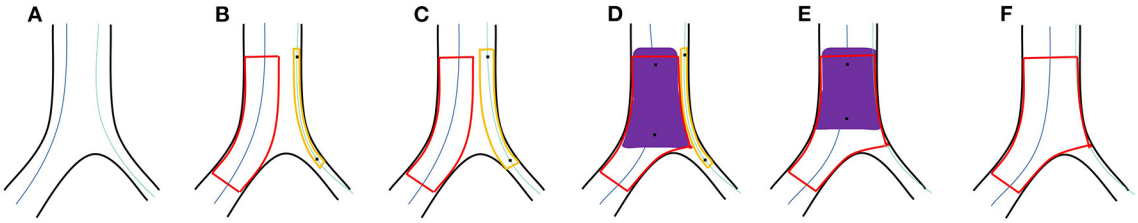

FIGURE 1 | (A) Both the MV and SB are wired. **(B)** The MV stent is then deployed with a balloon jailed in the SB. **(C)** The jailed balloon is dilated at 6–8 atm if SB blood flow is degraded. **(D)** POT and post-dilation of the distal stent were performed with non-compliant balloons of corresponding sizes. **(E)** The jailed balloon is retrieved and rePOT is performed 2 mm away from the SB branching point. **(F)** Final effects are examined.

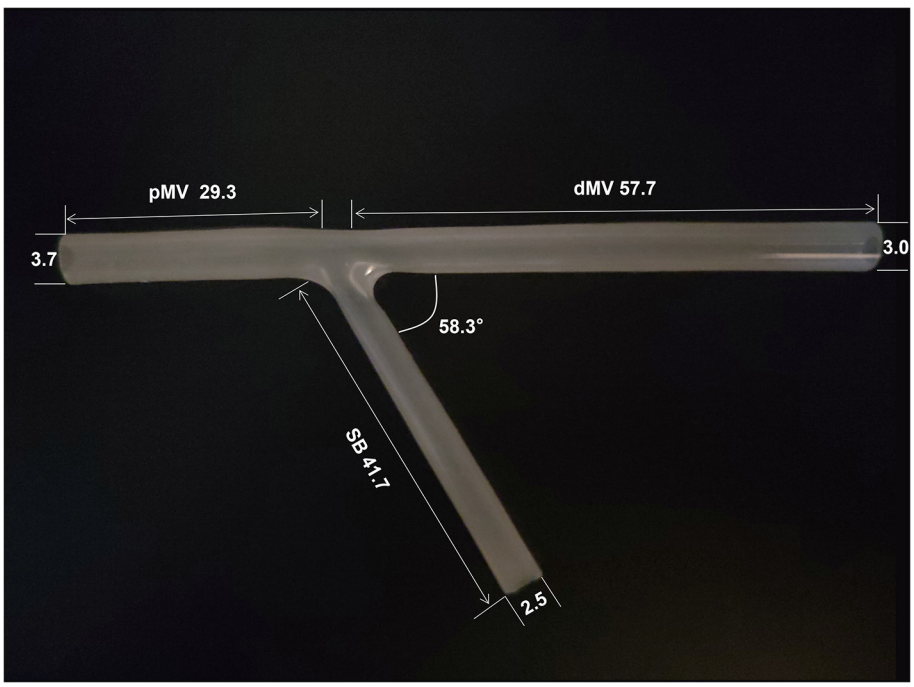

FIGURE 2 | Bench test model of bifurcation stenting. The length of the pMV, dMV and SB is 29.3, 57.7 and 41.7 mm respectively. The inner lumen diameter of the pMV, dMV and SB is 3.7, 3.0 and 2.5 mm respectively. The bifurcation angle is 58.3°. pMW, proximal main vessel; dMV, distal main vessel; SB, side branch.

Cardiology/European Association for Cardiothoracic Surgery guidelines on myocardial revascularization were selected (17). Risked SB was defined as true bifurcation lesions (Medina 1,1,1; 0,1,1; or 1,0,1) complying with carina mismatch according to the Vassilev theory (18), which referred to carina length equal to or longer than ostial residual width determined by QCA.

The exclusion criteria were as follows: (a) unstable hemodynamics; (b) severe calcified lesions in the CBL (significant haziness in coronary angiography, $\geq 90^{\circ}$ or over 300 μm thick in intravascular ultrasound or OCT images); (c) previously stented lesion; (d) angiographically visible thrombus; and (e) lesions in which the SB reference diameter was <1.5 mm.

Diagnostic and Therapeutic Procedure

Coronary angiography was performed in all patients after intracoronary administration of nitroglycerin (0.5 mg). The SB ostial segment was evaluated using two orthogonal coronary angiographic images, showing the SB ostium as clearly as possible. The baseline QCA was performed with images obtained before stent implantation. All lesions were treated using the JB-POT-based provisional stenting technique. Post-dilatation of the distal MV stent was performed by choosing a non-compliant balloon according to the distal MV diameter, and POT was performed by choosing a balloon according to the proximal MV diameter. The two orthogonal angiographies selected in the diagnostic phase were repeated after stent implantation to evaluate the SB ostial region.

Intracoronary Imaging Measurement

OCT or intravascular ultrasound (IVUS) was performed based on the operators' criteria before, during and after the PCI

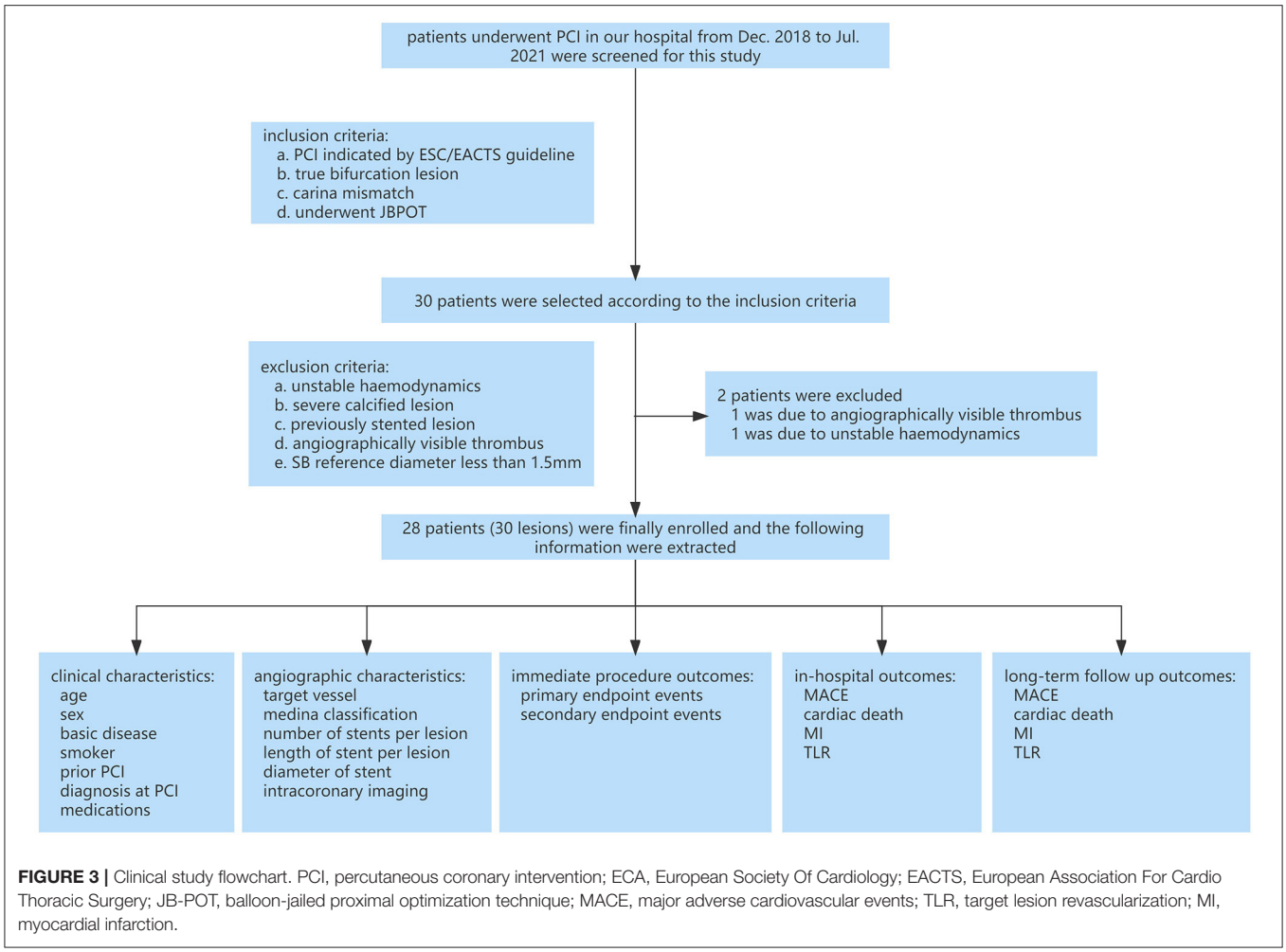

FIGURE 3 | Clinical study flowchart. PCI, percutaneous coronary intervention; ECA, European Society Of Cardiology; EACTS, European Association For Cardio Thoracic Surgery; JB-POT, balloon-jailed proximal optimization technique; MACE, major adverse cardiovascular events; TLR, target lesion revascularization; MI, myocardial infarction.

procedure. OCT imaging was obtained using a Dragonfly™ Duo OCT imaging catheter (LightLab™ Imaging, Inc., Westford, MA, USA) and C7™XR system/OPTIS™ system (C7™XR system, LightLab™ Imaging, Inc., Westford, MA, USA; OPTIS™ system, Abbott Medical, Westford, MA, USA). Briefly, the OCT imaging catheter was advanced distal to the MV target lesion over a 0.014-inch conventional angioplasty guide wire through a 6 or 7 Fr guiding catheter. Pullbacks were performed during a continuous injection of 3.5–4 ml/s contrast media through the guiding catheter to remove blood from the field of view after the intracoronary administration of 0.5 mg nitroglycerin. Images were acquired at 100 fps/180 fps and an automated pullback speed of 20 mm/s. The IVUS catheter was advanced at least to the distal (> 10 mm) of lesion or stent edge after intracoronary administration of nitroglycerin. Automated pullback was set at 0.5 mm/s on a commercially available imaging system with a 40-MHz mechanical transducer (Boston Scientific Corporation, Natick, MA, USA).

For the bench test, three OCT pullbacks were acquired after retrieving the jailed balloon, retrieving the jailed wire and performing the final POT respectively (**Figure 4**). Longitudinal sections and cross-sections were analyzed. The malapposition rate was calculated as the percentage of the total number of malapposed struts divided by the total number of proximal struts (SB ostium struts not included) (19). The minimum stent area (MSA) was defined as the minimum stent area of the frames within the proximal MV. The eccentricity index was computed as the ratio of the maximum to minimum scaffold diameter (8); the symmetry index was defined as the maximum scaffold diameter divided by the minimum scaffold diameter in the minimum frame (7, 20). Briefly, malapposition was defined as a lack of contact of at least 1 strut with the underlying vessel wall (at least 300 μm, in the absence of a side branch) with evidence of blood flow behind the strut according to the expert consensus document of the European Association of Percutaneous Cardiovascular Interventions on intravascular imaging (20).

Endpoint Events

Primary endpoint events were defined as SB TIMI grade 0–1, SB rewiring failure, a need to rewire the SB by guide wire with polymer tip and sleeve, failure to retrieve SB jailed balloon

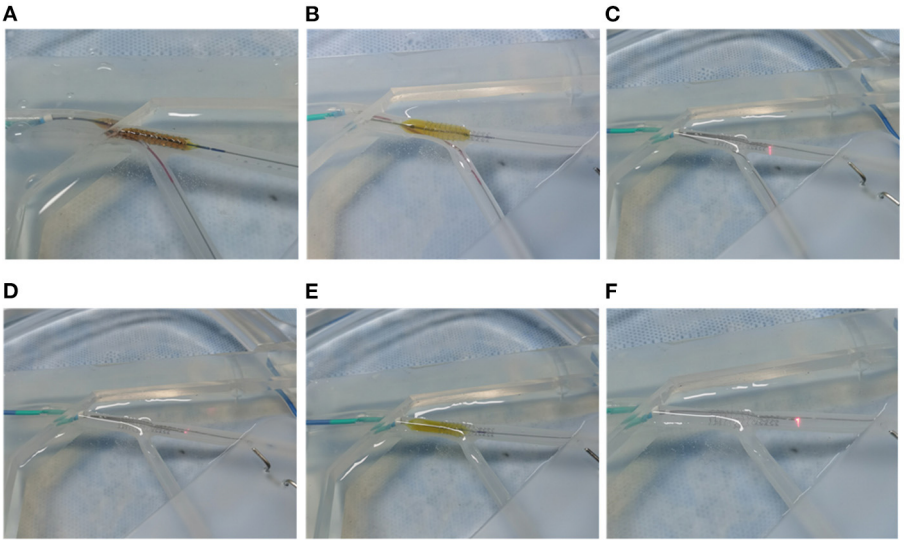

FIGURE 4 | JB-POT bench test procedures. **(A)** Perform MV stenting with a balloon jailed in the SB. **(B)** Perform POT pullback at the carina level with the jailed balloon maintained. **(C)** Retrieve the jailed balloon and perform OCT evaluation with the jailed wire remaining. **(D)** Perform OCT pullback after retrieving the jailed wire (experimental arm). **(E)** Perform POT at the carina level to correct the potentially JB-POT-induced stent distortion. **(F)** Perform the final OCT run (self-control arm).

and/or wire, malapposition distance $\geq$ 300 μm (SB ostium not included), minimal stent area (MSA) $\leq$ 5.5 mm^2 for left main or $\leq$ 4.5 mm^2 for non-LM lesions, and stent expansion rate $\leq$ 80%. The secondary endpoint events included SB TIMI grade 2, a need to rewire the SB by working-horse guide wire, final kissing, and/or rescue double stenting as decided by operators (21).

In-hospital and Long-Term Clinical Outcomes

In-hospital clinical outcomes were defined as major adverse cardiovascular events (MACE) including target lesion revascularization (TLR), myocardial infarction (MI) and cardiac death before discharge. All patients were followed up after discharge to observe the rate of MACEs as an indicator of long-term clinical outcomes (22).

Statistical Analysis

Statistical analyses were performed using SPSS 26.0. Paired *t* test was used to analyze the bench test data and *P*-value < 0.05 was considered significant.

RESULTS

Bench Test

Ten bench tests were conducted as shown in **Figure 4**. After the JB-POT procedure, OCT was used to determine the parameters of stent deployment, which were taken as the experimental arm. The non-compliant balloon for POT was reused to fully dilate the proximal stent following jailed balloon and wire retrieval, and the corresponding stent deployment status was regarded as self-control. Typical OCT images are shown in **Figure 5**. After retrieval of the jailed balloon and wire, the gap between the stent and vessel during the JB-POT maneuver vanished. The stent apposition, expansion and formation between the two arms were compared. Malapposition rates were 0.011 ± 0.027 in the experimental arm and 0.001±0.004 in the self-control arm. The MSAs were 9.687 ± 1.043 and 9.896 ± 0.761 mm^2 for the experimental and control arms, respectively. The eccentricity indices were 1.292 ± 0.136 and 1.324 ± 0.194 for the experimental and control arms, respectively. The symmetry indices were 1.181 ± 0.146 and 1.161 ± 0.109 for the experimental and control arms, respectively. There were no statistically significant differences between the 2 arms regarding malapposition rates, MSAs, eccentricity indices or symmetry indices. However, a distanced re-POT was designed to be positioned 2 mm proximal to the SB branching point to avoid closing the SB ostium. Hence, the 2 mm segment apposition was not fixable in the present JB-POT protocol. There were no significant differences between the 2 arms regarding malapposition rates, MSAs, eccentricity rates or symmetry indices (**Figure 6**).

Patients' Clinical and Angiographic Characteristics

The patients' clinical characteristics are summarized separately in **Table 1** in terms of SB complications. Most patients were men with hypertension and dyslipidemia and were smokers, and all of them were diagnosed with acute coronary syndrome. According to our experience and previous studies (23–25), these patients are vulnerable to SB complications during one-stent crossover intervention. The angiographic characteristics are listed in **Table 2**. Most bifurcation lesions were located at the left

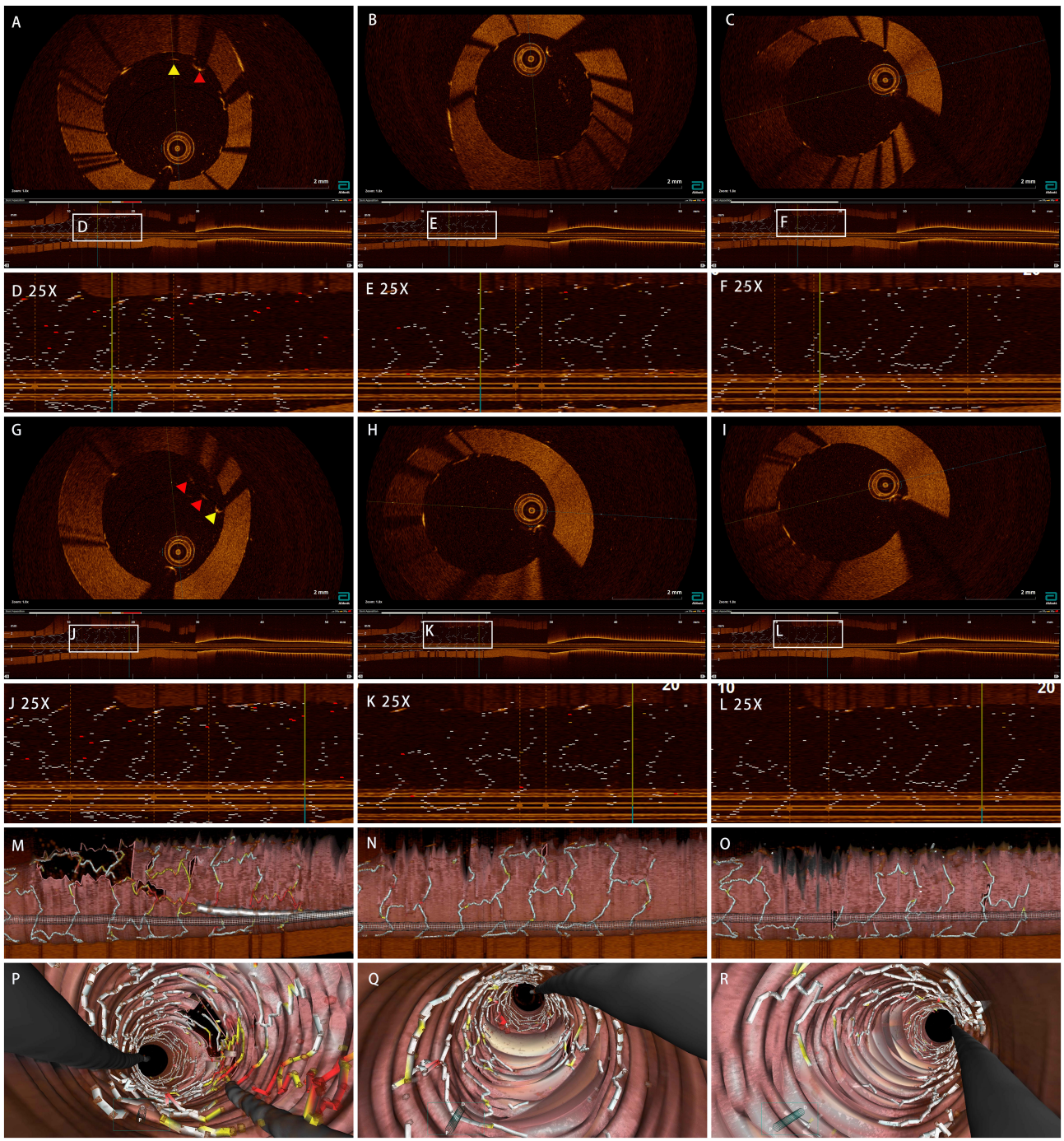

FIGURE 5 | Effect of JB-POT procedures on stent deployment examined by OCT. **(A,G)** Cross-sections of JB-POT run before jailed wire retrieved. **(B,H)** Cross-sections of JB-POT final run. **(C,I)** Cross-sections of self-control run. **(D,J)** Longitudes of JB-POT run before jailed wire retrieved. **(E,K)** Longitudes of JB-POT final run. **(F,L)** Longitudes of self-control run. **(M,P)** 3D images of JB-POT run before jailed wire retrieved. **(N,Q)** 3D Images of JB-POT final run. **(O,R)** 3D Images of self-control run. Red arrows, malapposition distance ≥300 μm; yellow arrows, 200 μm≤Malapposition distance <300 μm. JB-POT, jailed balloon proximal optimization technique; OCT, optical coherence tomography.

anterior descending (LAD) coronary artery and classified into the Medina (1,1,1). In the present study, all of the bifurcation lesions had longer carina lengths complying with carina length mismatch. These characteristics indicate that the present study included bifurcation lesions with SBs mostly vulnerable to closure during the one-stent crossover strategy.

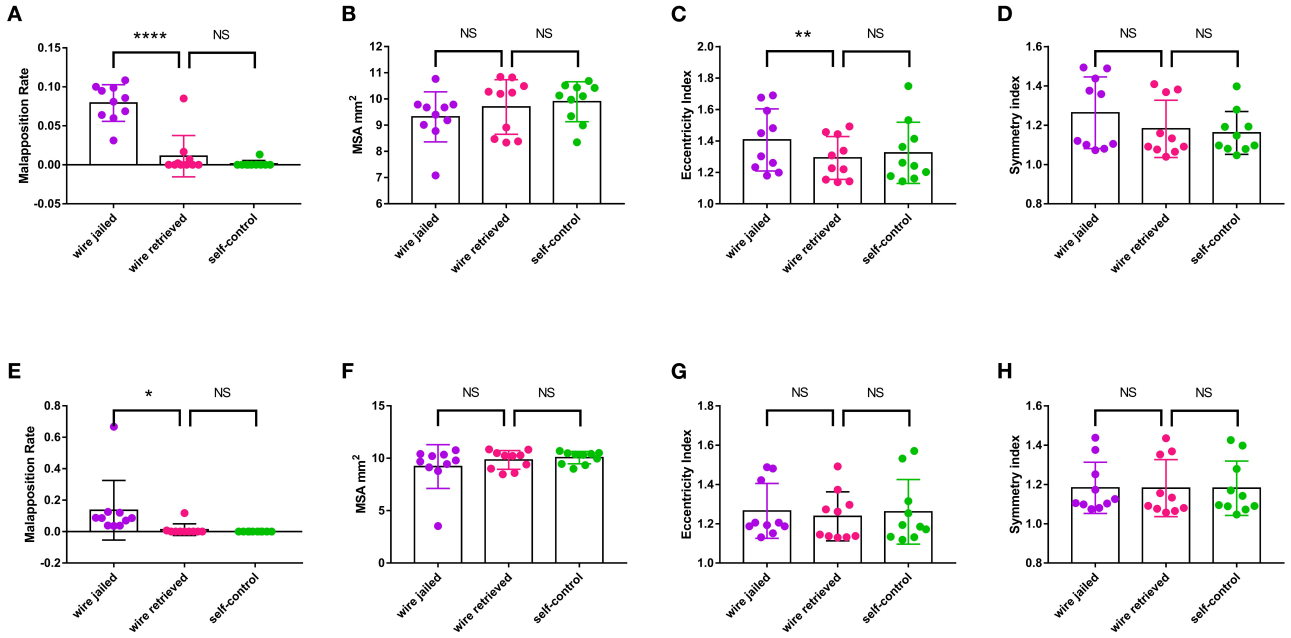

FIGURE 6 | Effect of JB-POT procedures on stent deployment parameters determined by OCT. **(A–D)** Malapposition rate, MSA, eccentricity and symmetry of the whole stent. **(E–H)** Malapposition rate, MSA, eccentricity and symmetry of the 2 mm stent segment adjacent to SB take-off. MSA, minimum stent area. NS, no significant. *$p < 0.1$. **$p < 0.05$, ****$p < 0.0001$. $n = 10$.

Application of JB-POT in Clinical Circumstances

JB-POT was performed in 30 bifurcation lesions of 28 patients from December 2018 to July 2021. There were no primary endpoint (JB-POT failure) events among these procedures, including SB TIMI grade 0–1, SB rewiring failure, a need to rewire the SB by guide wire with a polymer tip and sleeve, failure to retrieve the SB jailed balloon and/or wire, clinically relevant malapposition, MSA of $\leq$ 5.5 mm^2 for LM or $\leq$ 4.5 mm^2 for non-LM lesions, and stent expansion rate $\leq$ 80%. There was only one secondary endpoint event involving rewiring the SB by a working-horse guiding wire and final kissing (**Table 3**). There was no SB TIMI grade 2 occurrence, and rescue double stenting was performed. Specifically, MSA was 6.5 $\pm$ 2.6 mm^2, the malapposition rate was 0, and the expansion rate (defined as MSA divided by distal stent area) was 85.4 $\pm$ 2.6% in the proximal stent segment. The mean amount of contrast medium was 90 $\pm$ 25 ml and the mean duration was 50 $\pm$ 18 min.

No MACE (including MI, TLR and cardiac death) occurred during the in-hospital period. There were 28 patients enrolled in this study, among whom two patients were lost in the follow up and the other 26 patients were contacted successfully for at least 6 months. The mean duration of follow up is 619 days. Of the 26 patients, 19 patients had reached 1 year follow-up. One patient died of heart failure in the 8th month and no patient suffered from MI or underwent TLR. In total, no patient suffered from MACE during the 6-month follow up and 1 (5.2%) patient suffered from cardiac death and MACE during the 1-year follow-up (**Table 4**).

Representative Case of JB-POT Application

Figure 7 shows a representative case of JB-POT application in a coronary bifurcation lesion with risked SBs. Baseline coronary angiography LAD had diffused stenotic lesions from medium LAD to LAD ostium branching 2 diagonal branches and 1 septal branch. LAD-D1 was below 2 mm, and its territory was limited; hence, LAD-D1 did not need to be protected during the procedure. The other 2 bifurcation lesions were both Medina classifications (1,1,1). Baseline angiography showed both bifurcation lesions had a narrow carina angle and a short branching point-carina tip complying with carina length mismatch (18), which was demonstrated to be highly related to SB compromise after MV stent crossover implantation (21). Two sequential JB-POT procedures were performed sequentially on the LAD-D2 and LAD-S1 lesions, as shown in **Figure 7**. A third stent was then deployed in the proximal LAD-LM with a wire jailed in the LCX because the LCX was thought to be safe during stent crossover. Postprocedure IVUS examination showed that the stents had quite satisfactory apposition and expansion after JB-POT interventions. The struts just proximal to the branching point also showed good apposition and expansion, although they were avoided by re-POT (**Figure 8**). The whole procedure protected 3 SBs (1

TABLE 1 | Patient characteristics.

Characteristics	*n* = 28 patients
Age, years	58.7 ± 12.0
Male, n (%)	19 (67.9%)
Hypertension, n (%)	18 (64.3%)
Diabetes mellitus, n (%)	7 (25.0%)
Dyslipidemia, n (%)	19 (67.9%)
Smoker, n (%)	14 (50.0%)
Prior PCI or CABG, n (%)	7 (25.0%)
Diagnosis at PCI, n (%)	
STEMI	8 (28.6%)
NSTEMI	8 (28.6%)
UA	12 (42.9%)
Pharmaceutical medications, n (%)	
Aspirin	28 (100%)
Clopidogrel	12 (42.9%)
Ticagrelor	16 (57.1%)
Beta blocker	17 (60.7%)
ACEI/ARB	13 (46.4%)
Statin	28 (100%)

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; STEMI, ST segment elevation myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; UA, unstable angina; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

TABLE 2 | Angiographic and procedural characteristics.

Characteristics	*n* = 30 lesions
Target vessel, n (%)	
LAD-D1	17 (56.7%)
LAD-D2	9 (30%)
LCX-OM	3 (10%)
LM-LCX	1 (3.3%)
Medina classification, n (%)	
(1,1,1)	20 (66.6%)
(1,0,1)	7 (23.3%)
(0,1,1)	3 (10%)
Number of stents per lesion, n	1 (100%)
Length of stent per lesion, mm	26.43 ± 5.83
Diameter of stent, mm	2.93 ± 0.45
IVUS	23 (76.7%)
OCT	7 (23.3%)
Procedure duration, min	50 ± 18
Consumption of contrast medium, ml	90 ± 25

LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery; D1, the first diagonal branch; D2, the second diagonal branch; OM, obtuse marginal branch; IVUS, intravascular ultrasound; OCT, optical coherence tomography.

diagonal branch, 1 septal branch and 1 LCX) by the same guide wire, costing only 40 min, 100 ml of contrast media and 350 mGry X ray radiation. No rewiring and kissing were required.

TABLE 3 | Immediate postoperative endpoint events.

Characteristics	*n* = 30 lesion
Primary endpoint events (JB-POT failure events)	
SB TIMI grade 0–1	0
SB rewiring failure	0
Needing to rewire SB by wire with polymer tip and sleeve	0
Re-wire SB with polymer-covered guide wire	0
Failure to retrieve SB jailed balloon and/or wire	0
Clinically relevant malapposition	0
Stent expansion rate ≤80%	0
MSA ≤5.5 mm^2 for LM or ≤4.5 mm^2 for non-LM lesions	0
Secondary endpoint events	
SB TIMI grade 2	0
Needing to rewire SB by working-horse guiding wire and final kissing	1 (3.3%)
Rescue double stenting	0

JB-POT, jailed balloon proximal optimization technique; SB, side branch; MSA, minimal stent area; LM, left main; TIMI, thrombolysis in myocardial infarction.

TABLE 4 | Clinical outcomes.

Characteristics	
Immediate clinical outcomes	*n* = 28 patients
MACE	0
Cardiac death	0
MI	0
TLR	0
Long-term clinical outcomes of 6 months	*n* = 26 patients
MACE	0
Cardiac death	0
MI	0
TLR	0
Long-term clinical outcomes of 1 year	*n* = 19 patients
MACE	1 (5.2%)
Cardiac death	1 (5.2%)
MI	0
TLR	0

MACE, major adverse cardiovascular events; MI, myocardial infarction; TLR, target lesion revascularization.

DISCUSSION

Repeated jailed balloon and rewiring SB are often troublesome in coronary stent implantation on bifurcation lesions with multiple risked SBs. The JB-POT protocol removes the rewiring maneuver and simplifies JB-PS to 3 main steps: jailed balloon stent implantation, jailed balloon POT and final re-POT. The major findings of this study were as follows: (a) JB-POT does not lead to imperfect stent implantation, as indexed by stent apposition and expansion in the bench test and clinical observation; (b) the success rate of JB-POT is quite satisfactory, as shown by the low endpoint event rate; and (c) JB-POT saves time, contrast media

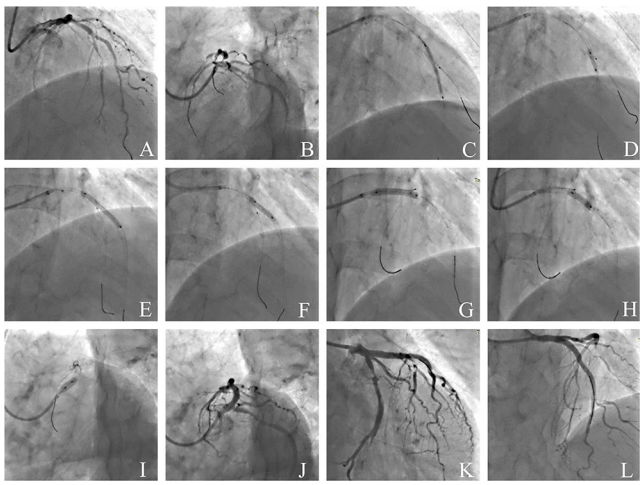

FIGURE 7 | Coronary angiography illustrating the JB-POT in the intervention of a complicated bifurcation lesion. **(A,B)** Baseline angiography of diffused LAD-LM lesions with 3 true bifurcations (LAD-D1, LAD-S1, LAD-D2); **(C)** deploying a 2.5 × 29mm DES crossing D2 with a 1.5 × 15mm balloon jailed in D2; (D) post-dilation and JB-POT of the first stent with 2.5 × 12mm and 3.0 × 12 non-compliant balloons; **(E)** deploying a 3.0 × 29mm DES crossing D2 with a 1.5 × 15mm balloon jailed in D2; **(F)** JB-POT of the 3.0 stent with a 3.5 × 12 NC balloon, re-POT the 2.5mm stent and post-dilation of the 3.0mm stent with a 3.0 × 15 NC balloon; **(G)** deploying a 3.5 × 24mm DES crossing LCX with a wire jailed in LCX; **(H)** post-dilation of the 3.5mm stent and re-POT of the 3.0mm stent with a 3.5 × 12 NC balloon; **(I)** performing POT in LM with a 5.0 × 10 NC balloon; **(J–L)** final angiographic results. JB-POT, jailed balloon proximal optimization technique; LAD, left anterior descending coronary artery; LM, left main coronary artery; D1, the first diagonal -branch; D2, the second diagonal branch; S1, the first septal branch.

and radiation dosage and is easy to perform, especially for those who are just starting their career in coronary intervention.

The mechanism of SB complications during bifurcation stenting includes atheromatous plaque shift from MV to SB, carina shift toward the SB lumen, the presence of stent struts covering the SB ostium, coronary vasospasm, and the formation of a local thrombus covering the SB ostium. Based on the results from earlier studies, plaque shift and carina shift are considered to play a major role in this complication. Further studies also indicate that a shift of carina, but not of atheromatous plaque, was the main cause for SB narrowing. Previously, several studies were designed to explore risk factors for SB complications in crossover stenting protocols. Many risk factors, such as a small bifurcation angle, carina tip-branching point length and stenosis at the SB ostium, were associated with a significantly higher incidence of SB ostial stenosis (23–25). However, the overwhelming workload of clinicians requires a simple way to predict SB complications. Vassilev et al. and Longobardo et al. proposed a simple model to predict SB compromise called carina mismatch by QCA (18, 21). Unless the carina length was less than the SB ostium diameter, the SB would be liable to be blocked by carina or plaque shifts during MV stent implantation, similar to the relationship between a door and a doorframe. Because many factors, such as bifurcation angle and stenosis at SB ostium, influence the relationship between carina length and SB ostium diameter, the carina mismatch model is quite a comprehensive and easy-to-grasp model to predict SB compromise during MV stenting. We found that this model was quite applicable in real-world clinical practice not only in true bifurcation lesion (Medina 0,1,1; 1,0,1; 1,1,1) but also in false bifurcation lesion (Medina 0,1,0; 1,0,0 or 1,1,0) interventions. Therefore, the current study adopted the carina mismatch model to predict whether the SB was endangered and needed jailed balloon protection.

A few strategies have been proposed to protect an endangered SB from closure during MV stent crossover implantation, namely, predilation of the SB, the jailed wire technique and the JBT. Predilation of the SB was applied to prevent SB compromise but was shown to have limited effects on SB protection. The main reason is that predilation cannot prevent stent-induced carina shift, so EBC expert consensus recommends predilation only when the SB ostium is severely stenotic (26). Another constantly used SB protective measure was the jailed wire technique, which also has limited effects on SB complication prevention. Unlike the unsatisfactory protective effects of the former 2 strategies, the JBT was proven to be the most effective strategy in the prevention of SB compromise (3, 9, 10). In addition, provisional stenting was recommended for most bifurcation lesion interventions. Therefore, JB-PS became a useful strategy in treating bifurcation lesions with endangered SBs in certain clinical scenarios. The traditional JB-PS protocol includes stent deployment with a jailed balloon in the SB, rewiring the SB, proximal optimization, post-dilation of the stent, SB ostium dilation, the kissing balloon technique, and rePOT, which greatly increase contrast medium use and procedure duration times. Saito et al. presented a modified jailed balloon technique, which showed more satisfactory effects than conventional JBT (8). Theoretically, side branch was at risk if balloon for POT was not positioned accurately. When there were 2 or more risked SBs needing sequential protection, rewiring and other steps were supposed to be repeated. With repeated rewiring, device delivery might cause device entanglement, SB protection failure and even procedure failure, which sometimes are very troublesome for interventionists. Our modified JB-POT protocol includes only 3 steps: MV stent deployment with a jailed balloon in the SB, post-dilation and POT with a jailed balloon in the SB, and final distanced rePOT (POT balloon positioned 2 mm from the branching point). The cordial modification of this protocol prevents the most troublesome and time-consuming steps of the rewiring, cross-strut SB ostial dilation and final kissing in complicated bifurcation lesion treatment.

One concern about this simplified protocol is that retrieval of the jailed balloon might leave a "gap" (malapposition) between the struts and vessel wall. A previous study showed that OCT could conveniently be acquired from silicon bifurcation phantoms, and OCT had quite strong resolution power to recognize malapposition (27). Therefore, this silicon bifurcation phantom is suitable for testing the reliability of the simplified protocol. In this bench test model, we found that the stent struts rebounded and narrowed the "gap" after the jailed balloon was retrieved. However, slight malapposition sometimes existed after JB retrieval in the bench test if we pulled the jailed balloon

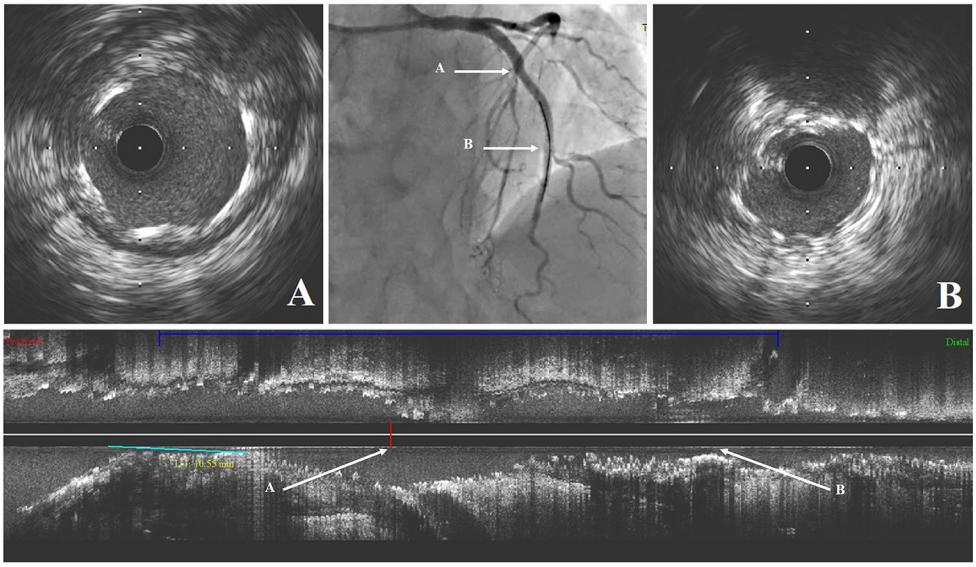

FIGURE 8 | The intravascular ultrasound findings after stenting. **(A)** Cross-sectional intravascular image of LAD stent just proximal to the septal branch branching point; **(B)** Cross-sectional intravascular image of LAD stent just proximal to the 2nd diagonal branch branching point. LAD, left anterior descending coronary artery.

with force. Therefore, jailed balloon retrieval might leave a "gap" when there is a calcification lesion underneath the stent under clinical circumstances. For the best safety in clinical observation, we added a distanced re-POT in the final design to eliminate the gap as best we could. Distanced re-POT was realized by positioning the POT balloon 2 mm away from the SB branching point to avoid POT dilation-induced carina shift and subsequent SB compromise. As a result, the simplified JB-POT protocol did not induce significant differences in the malapposition rate or expansion rate in the present bench study. Another concern is whether the modified JB-POT could effectively prevent SB compromise. If the SB blood flow was blocked or could hardly be restored, it was defined as a JB-POT failure event (primary endpoint event). There were no such events occurring in the present observation. If SB ostium stenosis was aggravated and could be easily repaired, it was defined as a secondary endpoint event. Under clinical circumstances, most SB compromises occur in LAD-D bifurcation lesion interventions. The SBs of Medina (1,1,1) bifurcation lesions are mostly vulnerable to SB closure during MV single-stent crossover interventions. There was 1 such event in our observation, which is acceptable for bifurcation intervention. According to previous studies, the incidence of SB complications was 5–15% using jailed wire-based provisional stenting in bifurcation interventions. The application of the JBT could decrease the incidence to below 5% (23). In the present study, we did not find any non-rescuable SB closure, suggesting that the JB-POT protocol is an effective strategy for the protection of risked SBs in provisional stenting.

It might be not safe for severe calcified lesions because jailed balloon might be difficult to retrieve after POT and post-dilation. However, we think it would be safer if we correctly utilized atherosclerotic plaque debulking techniques like rotational atherectomy or excimer laser coronary angioplasty (ELCA). In respect to in-stent lesions, the sandwich formed by two layers of metal struts and jailed balloon might cause detrimental results. Therefore, we do not think it appropriate to routinely use JB-POT under such circumstances.

CONCLUSIONS

The JB-POT protocol, which tremendously simplifies the current standard provisional stenting procedure in complicated bifurcation lesion treatment, shows acceptability in safety and efficacy. Hence, it might help save time, reduce contrast consumption and reduce complications in the intervention of high-risk bifurcation lesions, especially those with multiple risked SBs.

Limitations

First, we were not able to accurately compare JB-POT with the standard JB-PS protocol because the present study was not a prospective randomized controlled trial. Second, the patient count was limited to those with SB complications during JB-POT, and a multicenter RCT is anticipated to obtain a more reliable conclusion. Third, we used one brand of phantom to allow a reliable comparison in the bench test. Stent selection is critically important when performing JB-POT since marked differences exist between stent platforms, including stent strut thickness, elongation capability and the number of connections between struts in the real world. We chose one stent known for its platform performance in terms of crossability, stent strut thickness, deformation capability and early endothelial coverage in animal models. For this reason, we could not include any comparison with other stent platforms in the present

study. Finally, we have not acquired angiographically follow-up results and the MACE data of long term follow-up. Further observation was still needed to determine the efficacy and safety of this protocol.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Tangdu Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WG proposed this strategy and applied it clinically from December 2018. DL conducted the bench test. WM and HL analyzed the data. PL and BB assisted WG to carry out the operation. DL and MZ drafted this paper. All authors contributed to the article and approved the submitted version.

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Surgical Turned-Downed CHIP Cases—Can PCI Save the Day?

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Current guidelines, rarely if at all, address decision-making for revascularization when bypass surgery is not a possibility for high-risk cases. Patients who are surgically turned down are routinely excluded from clinical trials, even though they remain symptomatic. Furthermore, the reasons for surgical ineligibility are often times not captured in standardized risk models. There is no data regarding health status outcomes following PCI procedures in these patients and the ultimate question remains whether the benefits of PCI outweigh its risks in this controversial subpopulation. When CHIP (Complex High risk Indicated Percutaneous coronary interventions) is selected for these very complex individuals, there is no unanimity regarding the goals for interventional revascularization (for instance, the ambition to achieve completeness of revascularization vs. more targeted or selective PCI). The recognition that, worldwide, these patients are becoming increasingly prevalent and increasingly commonplace in the cardiac catheterization labs, along with the momentum for more complex interventional procedures and expanding skillsets, gives us a timely opportunity to better examine the outcomes for these patients and inform clinical decision-making.

Keywords: multivessel disease, complex PCI, high risk, surgical ineligible, surgical turndown, CHIP, hemodynamic support devices

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INTRODUCTION

The proportion of percutaneous coronary intervention (PCI) to coronary artery bypass graft surgery (CABG) varies by nation. Still, it is commonly agreed that CABG is the revascularization technique of choice in the setting of left main disease (LMD) or multivessel disease (MVD) when clinically viable. This derived on account of randomized controlled trials which compared revascularization strategies in MVD and found that CABG is associated with fewer repeat revascularization procedures and improved survival (1, 2), even if PCI is performed using the latest generation drug-eluting stents and is guided by fractional flow reserve (FFR) (3–5). Nonetheless, in medical practice, physicians frequently encounter patients who would have been excluded from clinical trials because of significant medical comorbidities. In such patients, CABG and thus the findings of these trials are not applicable. As a consequence, the undisputed performance of CABG in LM and MVD decreases in front of frail patients with multiple comorbidities. With an aging patient population, a growing challenge remains the management of these patients, with severe ischemic heart disease. Comorbidities increase the patient's surgical risk and can negate the benefits of surgical revascularization, around one in five patients with left main and/or multivessel disease being declared surgically ineligible (6). Current guidelines rarely, if at all, address decision-making for revascularization when bypass surgery is not a possibility, and patients who are surgically turned

down are routinely excluded from clinical trials, even though they remain symptomatic. Further, the reasons for surgical ineligibility are seldom captured in standardized risk models. There is no existing data regarding health status outcomes following PCI procedures in such patients, and the ultimate question remains whether the benefits of PCI outweigh its risks in this subpopulation. It should not be forgotten that this topic addresses a particular category of patients: mostly octogenarians, with multiple comorbidities, fragile, some with a history of neoplastic disease, some with reduced mobility and a survival less than a year. Nonetheless, with revascularization, both survival and quality of life can increase (**Figure 1**).

Finally, when CHIP (Complex High risk Indicated Percutaneous coronary interventions) is selected for these very complex individuals, there is no unanimity regarding the goals for interventional revascularization (for instance, the ambition to achieve completeness of revascularization vs. more targeted or selective PCI). The recognition that, worldwide, these patients are becoming increasingly prevalent and increasingly commonplace in the cardiac catheterization labs, along with the momentum for more complex interventional procedures and expanding skillsets, gives us a timely opportunity to better examine the outcomes for these patients and inform clinical decision-making.

THE OPTIMUM TRIAL—REVIEW OF RESULTS

The OPTIMUM study (*clinicaltrials.gov identifier: NCT02996877*), the first to investigate this category of patients, was an investigator-initiated prospective multicenter study conducted at 22 centers in the United States. It included up to 750 patients who, after evaluation, were deemed by the site heart team (comprised of both an interventional cardiologist and a cardiothoracic surgeon) to be unsuitable for surgery. Of these, 726 underwent PCI, while 24 were assigned to medical therapy. The outcomes were presented at the Transcatheter Cardiovascular Therapeutics 2021 Scientific Sessions (7).

The baseline characteristics of the study cohort imply a very high-risk population with complex disease and associated comorbidities. Most of the patients were over the age of 70, and 31.5% were female. At baseline, more than half (56.6%) of the patients were diagnosed with diabetes mellitus, while 48.2% had a history of myocardial infarction, and 32.8% had received prior PCI. Other traits included prior CABG (16.4%), current smoking (18.2%), renal failure (37.2%), atrial fibrillation (23.1%), and New York Heart Association (NYHA) class III/IV heart failure (23.4%). The heart team rated them as high-risk for the following reasons: 16.8% had severe left ventricular dysfunction or non-viable myocardium, 18.9% had poor distal targets, 16.8% had advanced lung disease, and 10.1% were reportedly frail and/or advanced in age. The most common reason for revascularization was stable or unstable angina. Not only was the patient population at high risk, but the coronary anatomy was complex: 80% of patients had severe calcification, bifurcation disease, and lesions >20 mm in length. The average SYNTAX score was 32.4, with 45.3% of patients having a high SYNTAX score (≥33). Chronic total occlusions were frequent (57.0%), and LMD cases were not uncommon either (38.2%). Mechanical circulatory support (MCS) was used in 27% of the cases—contrary to popular belief, the enrolled American centers were not excessive of this. Furthermore, unlike other studies testing for PCI performance, intravascular imaging was often used (63.9%). Complications were reported in 9.8% of the cases.

The primary end-point was to compare the 30-day and in-hospital mortality in the PCI cohort with the predicted Society

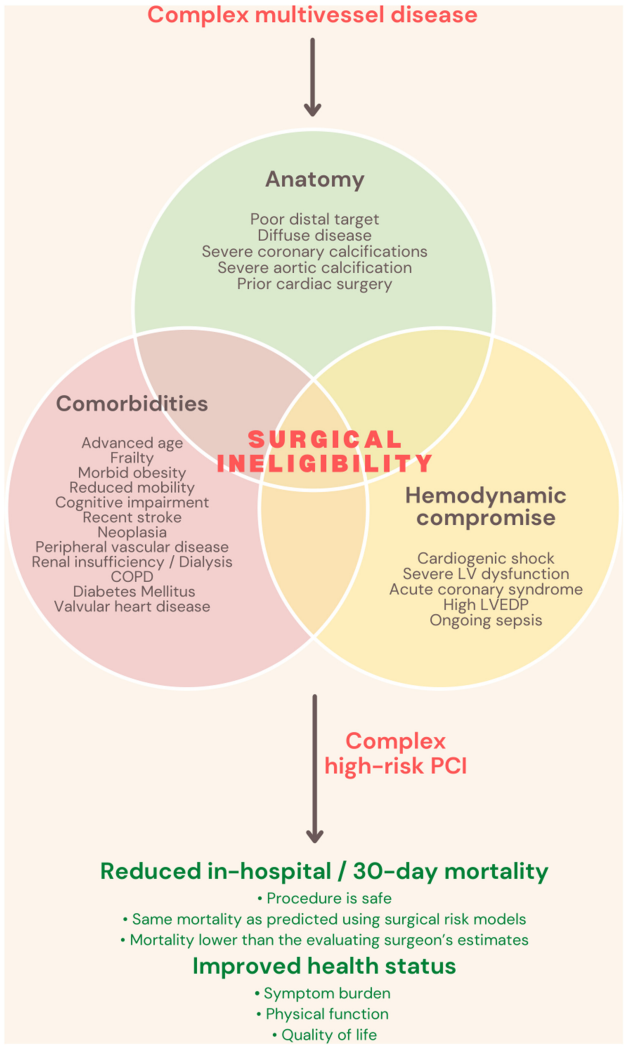

FIGURE 1 | Complex high-risk indicated procedures definition and benefits. COPD, Chronic obstructive pulmonary disease; LV, left ventricle; LVEDP, left ventricular end-diastolic pressure; PCI, Percutaneous coronary intervention.

Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LMD, left main disease; MVD, multivessel disease; FFR, fractional flow reserve; CHIP, complex high risk indicated PCI; NYHA, New York Heart association; MCS, mechanical circulatory support; STS, Society of Thoracic Surgeons; MACCE, major adverse cardiac and cerebrovascular events.

of Thoracic Surgeons (STS) surgical risk. For the secondary objective, the investigators analyzed and compared the 30-day and in-hospital mortality in the PCI cohort with the EuroSCORE II and the Surgeon's predicted risk. The results were also compared according to the level of completeness of the revascularization. Another important aspect was the quality of life of these patients, and this was assessed using two questionnaires: the Seattle Angina Questionnaire (quality of life) and the Kansas City Cardiomyopathy Questionnaire (angina frequency and heart failure).

The observed death rate at 30 days was 5.6%, which matched the predicted risk of death using the STS and EuroSCORE II risk calculators (5.3 and 5.7%, respectively). On the other hand, the site surgeon's predicted mortality was 10.4%. The actual death rate was 40% lower than that predicted by the site surgeons, at least with surgery. Tellingly, however, by 6 months, the mortality more than doubled in the PCI cohort (12.3%).

At 6 months, the investigators detected significant improvements in patient-reported health status amongst the survivors, including marked improvements in quality of life and reductions in angina frequency. More than 82% of patients had no angina at 6 months compared with 40.5% at baseline, while 11.6% reported monthly episodes, down from 31.9% at baseline. In total, 6% reported weekly or daily angina, which was down from 27.7% before PCI.

SHOULD MORTALITY BE THE ONLY POINT OF FOCUS?

Given the overestimation of risk during the CABG rejection decision, the inevitable question is whether these patients should be reconsidered for surgery. OPTIMUM suggests that the outcomes are similar to the current risk models and appreciably lower than surgeons' assessments. Caution should be taken as the STS and EuroSCORE II scores were intended to assess surgical mortality, and OPTIMUM looked at the relationship to PCI-related mortality. Moreover, in such a sickly population, it would be misleading to expect that the actual surgical mortality rates would be exactly what the STS and EuroSCORE II risk scores predict. Perhaps one interpretation might be that PCI mitigates the risk anticipated by the surgeons given the lack of periprocedural morbidity and complications associated with invasive surgery. Lastly, STS and EuroSCORE II do not capture all of the risk characteristics that impact a surgeon's reasons for turning down patients (for example, poor distal target/conduit, non-viable myocardium, obesity, prior stroke).

The concept of CHIP remains somewhat ill-defined with considerable variability among operators, making it difficult to delineate the difficulties of such a procedure and how they may be related to prognosis. A recent multiple logistic regression model of a large British population found 7 patient factors (age >80 years, female sex, previous stroke, previous myocardial infarction, peripheral vascular disease, ejection fraction <30%, and chronic renal disease) and 6 procedural factors (rotational atherectomy, left main PCI, 3-vessel PCI, dual arterial access, MCS, and total lesion length >60 mm) associated with increased in-hospital major adverse cardiac and cerebrovascular events (MACCE) and attempted to construct a CHIP score (8). Interestingly, MCS had the strongest association with MACCE. Even though MCS aimes to reduce MACCE, we concur with the investigators that the increased risk reported is mainly related to the fact that LV support is preferentially used in patients with an intrinsically high-risk profile. Indeed, CHIP is closely related to MCS, similar to those of the OPTIMUM patients were recruited in the MCS studies (9–11). In addition to their main results, all advocating for supported PCI, PROTECT II (9), BCIS-1 (10) and the Roma-Verona Registry (11) univocally found a significant increase in LVEF and a significant improvement in functional status after revascularization. Although guidelines support the use of mechanical LV support during high-risk PCI (12, 13), the observed low rate of planned MSC use in OPTIMUM or other large CHIP registries (8) could be explained by the increasing operator comfort in CHIP over time, a lack of robust clinical data supporting their use, cost, concerns regarding the safety and morbidity of the devices themselves, and, of course, the ambiguous definition of CHIP that we mentioned earlier.

Because more than half of the OPTIMUM patients were elective (stable angina or atypical angina), in light of the results of the ISCHEMIA trial (14, 15), one could argue why these patients cannot remain on medical therapy. As aforementioned, it is crucial to analyze what type of population these results can be applied to. Among the exclusion criteria of the ISCHEMIA trial, we mention left ventricle ejection fraction < 35%, NYHA class III-IV heart failure, exacerbation of chronic heart failure within the previous 6 months, LM stenosis, prior CABG, recent acute coronary syndrome, recent stroke, estimated glomerular filtration rate <30 mL/min, severe valvular disease, and life expectancy <5 years. This criterion is similar to the type of patients recruited into OPTIMUM. This would make the plea for conservative treatment in these patients inappropriate. OPTIMUM did not randomize 1:1 with medical treatment, due to the short follow-up limitation and the variety of comorbidities and anatomical complexity in this population. In a similar study, Graham et al. managed to cast a glance at this detail, demonstrating that elderly patients with ischemic heart disease who underwent revascularization with either PCI or CABG had better outcomes at 4 years than those treated with medication alone (16). However, given the improvements in techniques for PCI, most patients turned down for surgery will undergo PCI, thus, the number of patients with MVD treated medically who are ineligible for CABG is likely quite small. It was also the case with OPTIMUM, where initially, the investigators intended to include a group of patients who had no revascularization options, namely patients treated with medical therapy alone. Still, given the increasing prevalence of PCI patients, they later modified the protocol to include only those patients who underwent CHIP.

In a retrospective analysis from 2008 to 2012, Danson et al. showed that in a rather morbid population, the MACCE rate at 30 days is similar between the group treated with PCI and the group treated with medical therapy alone. However, after 1 year, MACCE were significantly higher in the medical treatment group (17). Furthermore, the residual SYNTAX score (an index of incomplete revascularization) was independently associated with

TABLE 1 | Distribution of percutaneously treated coronary artery disease in surgical turndowned patients, comorbidity and anatomical stratification—6 studies across 10 years.

Study	McNulty et al. (21)	Danson et al. (22)	Waldo et al. (6)	Sukul et al. (23)	Danson et al. (17)	Shields et al. (18)	OPTIMUM (7)
Year	**2011**	**2014**	**2014**	**2016**	**2018**	**2020**	**2021**
Study design	Retrospective, single-center	Retrospective, single-center	Retrospective, multicenter	Retrospective, multicenter	Retrospective, multicenter	Retrospective, single-center	Prospective, multicenter
Number of patients	55	77	218	1922	133	137	750
Age (years)	75 ± 10	74 ± 1.2	72±12	64.5 ± 11.8	76±9	71 ± 11.1	70.0 ± 10.9
At least 5 comorbidities	55%	–	44.6%	28.4%	49.7%	45.8%	31.9%
LVEF	45 ± 17%	–	–	53.6 ± 12.0%	–	44.3 ± 15.1%	42.6 ± 16.3%
LM PCI	100%	–	33%	1%	45.8%	40%	38.2%
High SYNTAX score (>33 pcts)	39%	–	41%	8.4%	43.5%	14%	45.3%
ACS presentation	62%	–	22%	24.3%	58%	–	37.7%
30 day MACCE	3.6%	6 ± 1.1%	7%	0.83%	12.2%	2.9%	5.6%
6 months MACCE	–	–	–	–	–	–	12.3%
1 year MACCE	–	22 ± 1.9%	–	–	26.7%	27.7%	–

Where nominal values are used, they are presented as mean standard deviation.
LVEF, left ventricle ejection fraction; LM, left main; PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; MACE, major adverse cardiac and cerebrovascular events.

MACCE at 1 year. The fact that in-hospital mortality did not increase in the PCI group, along with the long-term outcomes, supports the hypothesis that PCI with complete revascularization may confer the greatest predicted benefit from revascularization. Indeed, OPTIMUM and the Roma-Verona Registry also noted a trend toward better in-hospital/30-day mortality, left ventricle ejection fraction and 6-month health status improvement in those with a lower residual SYNTAX score (7, 11).

Shield et al. have similarly focused on patients with advanced CAD who were deemed to be ineligible for surgery, retrospectively reviewing a smaller cohort (137 patients) and showing even better results for PCI (mortality 2.2% at 30 days and 11% at 1 year) but in a healthier population (Syntax Score >33 pcts in 14% of patients vs 45% in OPTIMUM, STS >8% only 17%) (18). It is not surprising that mortality increases with the level of comorbidity but also with the complexity of the coronary disease. On the other hand, the operator cannot influence the first factor, but mechanical support, debulking devices, less iodine-contrast, full revascularization, or centers with experience in CHIP are all aspects which can make the risk of the procedure go down (19). The SYNTAX trial included a nested registry of patients ineligible for surgery who were treated with PCI (20). Among those patients, the EuroSCORE II was 5.8%, similar to that of OPTIMUM. At 30 days, the rate of all-cause mortality was 3.1%. A 10-year follow-up in these patients would be interesting to see, although it must be clearly acknowledged that at the time of enrollment in the SYNTAX, most patients were over 70 years old, so we should not be surprised at a possible mortality of 50% at present. Maybe mortality alone should not be our only point of focus in trials that test the performance of PCI in general, but especially in this old, fragile population of patients who are already living with low life expectancy, but in whom, through PCI, the quality of life is improved.

At 6 months, the mortality rate more than doubled, reflecting the high-risk nature of this population, but the risks (compared to those calculated by STS and EuroSCORE II) of the intervention did not exceed the net benefits in terms of significant improvement in patients' reported health status. Should we be doing PCI in high-risk patients with 30-day mortality following PCI, which is around 5–6%? We learn from this study that marked improvement in severe angina and quality of life can be achieved (at 6 months, 80% of patients had no angina, 11% had monthly residual angina only). We can immediately see that, effectively, for over 90% of our patients, we are reducing the symptom burden to less than once a month. This is a crucial aspect as, in randomized controlled trials, our pivotal objective addresses only if "there is a mortality benefit in these patients." Still, we must acknowledge that, often in this particular morbid population, it is unlikely we are going to impact on their longer-term prognosis, but the quality of life and symptoms are still important to patients, and the sight of that should not be lost. OPTIMUM and other registries of its kind (6, 9–11, 16, 18) show that we should reflect on the patients' cohort that we are undertaking these procedures on and think about what really matters to them.

Needless to say, we consider the 6-month data from OPTIMUM preliminary as the investigators will have to wait for the 1-year results. As **Table 1** shows, a major limitation that reigns over this controversial population is the lack of data on intermediate and long-term outcomes. In the last 10 years, 6 studies have been found describing outcomes in patients undergoing PCI who have been turned down for CABG on

the basis of prohibitive risk. Of these, Sukul et al.'s criteria for surgical ineligibility may have been biased due to a lack of clear referral documentation and how patients were extracted from the registry, hence, their much lower event rate (**Table 1**).

PERSPECTIVES

The reported lower frequency of angina, improvement in overall quality of life and reduction in in-hospital/30-day mortality rates suggest there is room for high-risk PCI in patients with no other options and that this procedure is in fact safe. The potential of CHIP has changed significantly for the better in recent years, and the credit goes both to technological progress and to the tertiary, high-volume centers that have trained skilled operators in this regard. There is no data comparing the difference in outcomes between centers of expertise and medium-volume centers when performing CHIP, but it can be clearly seen that the OPTIMUM cohort represents tough cases/complex patients and a collateral finding from OPTIMUM which provokes the reader is where and who should do these procedures. Currently, CHIP can be performed, but the operators must be circumspect and judicious. The safety of the procedure and its outcome can only be improved by the decision of the Heart Team. Postoperative care should not be neglected. The cause of early mortality has not been revealed, but surely factors such as contrast-induced nephrotoxicity or sepsis can negatively affect it.

Further studies are needed to assess technical considerations in the surgical turndown population; such issues include the impact of completeness of revascularization, the value of MCS for safer and optimal revascularization, and even the possibility of very short dual antiplatelet or single antiplatelet therapy. And of course, a question remains whether this single study is sufficient to change guidelines to include CHIP for patients with prohibitive risk.

AUTHOR CONTRIBUTIONS

AA, MM, and ZR contributed to the conception and design of the study. AA organized the database and wrote the first draft of the manuscript. MM and ZR wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Percutaneous Coronary Intervention vs. Coronary Artery Bypass Grafting for Treating In-Stent Restenosis in Unprotected-Left Main: LM-DRAGON-Registry

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Background: Data regarding management of patients with unprotected left main coronary artery in-stent restenosis (LM-ISR) are scarce.

Objectives: This study investigated the safety and effectiveness of percutaneous coronary intervention (PCI) vs. coronary artery bypass grafting (CABG) for the treatment of unprotected LM-ISR.

Methods: Consecutive patients who underwent PCI or CABG for unprotected LM-ISR were enrolled. The primary endpoint was a composite of major adverse cardiac and cerebrovascular events (MACCE), defined as cardiac death, myocardial infarction (MI), target vessel revascularization (TVR), and stroke.

Results: A total of 305 patients were enrolled, of which 203(66.6%) underwent PCI and 102(33.4%) underwent CABG. At 30-day follow-up, a lower risk of cardiac death was observed in the PCI group, compared with the CABG-treated group (2.1% vs. 7.1%, *HR* 3.48, 95%*CI* 1.01–11.8, $p = 0.04$). At a median of 3.5 years [interquartile range (*IQR*) 1.3–5.5] follow-up, MACCE occurred in 27.7% vs. 29.6% (*HR* 0.82, 95%*CI* 0.52–1.32, $p = 0.43$) in PCI- and CABG-treated patients, respectively. There were no significant differences between PCI and CABG in cardiac death (9.9% vs. 18.4%; *HR* 1.56, 95%*CI* 0.81–3.00, $p = 0.18$), MI (7.9% vs. 5.1%, *HR* 0.44, 95%*CI* 0.15–1.27, $p = 0.13$), or stroke (2.1% vs. 4.1%, *HR* 1.79, 95%*CI* 0.45–7.16, $p = 0.41$). TVR was more frequently needed in the PCI group (15.2% vs. 6.1%, HR 0.35, 95%*CI* 0.15–0.85, $p = 0.02$).

Conclusions: This analysis of patients with LM-ISR revealed a lower incidence of cardiac death in PCI compared with CABG in short-term follow-up. During the long-term follow-up, no differences in MACCE were observed, but patients treated with CABG less often required TVR.

Visual overview: A visual overview is available for this article.

Registration: https://www.clinicaltrials.gov; Unique identifier: NCT04968977.

Keywords: left main, in-stent restenosis (ISR), coronary artery bypass graft (CABG), stents (Coronary), percutaneous coronary intervention (complex PCI)

INTRODUCTION

The left main coronary artery (LM) supplies a large myocardial area, therefore, atherosclerotic disease in the LM may lead to significant ischemia associated with high morbidity and mortality. Evidence from randomized controlled trials has shown that LM percutaneous coronary intervention (PCI) with drug-eluting stents (DES) is a feasible alternative to coronary artery bypass grafting (CABG) (1, 2); however, in-stent restenosis (ISR) after DES in unprotected LM disease continues to occur with an incidence of 9.7–17.6% (3, 4). A number of mechanical, biological, and technical factors predispose percutaneously revascularized patients to an increased risk of ISR. The use of intravascular imaging, proper stenting techniques, and calcium plaque modification improve outcomes of LM-PCI. Since LM-ISR can present as acute coronary syndrome (ACS) in substantial number of cases, treatment and decision-making process is often challenging. Although surgical revascularization is considered a standard treatment for this kind of stent failure, owing to a higher risk of perioperative morbidity and mortality, particularly in patients with high risk, as those with ACS, the restoration of flow with PCI may be a reliable alternative. The exact risk profile of unprotected patients with LM-ISR and variations of treatment choice remains a matter of an ongoing debate due to limited data in this clinical setting. Additionally, it is not clear whether repeat PCI is safe in these patients. Therefore, the purpose of the current study was to compare long-term outcomes following PCI or CABG for unprotected LM-ISR disease.

METHODS

The LM-DRAGON registry is a multi-center, observational study conducted in 16 high-volume centers in Poland and Italy between January 2000 and July 2020. Consecutive patients with LM-ISR defined as ≥50% diameter stenosis on angiography with or without multivessel coronary artery disease were included in the registry. Patients with LM distal bifurcation disease within the proximal 5 mm of the left anterior descending artery (LAD) or left circumflex artery (LCx) ostium (in the absence of significant angiographic stenosis in the LM) were also eligible (LM equivalent). Patients with protected LM-ISR, defined as the occurrence of ≥1 patent arterial or venous graft to the left coronary artery, or other concomitant non-CABG procedure during surgery were excluded.

The choice of the type of revascularization (PCI or CABG) was at the discretion of heart team or individual invasive cardiologist, if the patient was unstable (acute LM occlusion). The choice of techniques for LM PCI or CABG was at the operator's discretion as well. The 4-stage classification (5) was used to determine the degree of restenosis on the basis of restenosis in relation to stented length based on the angiographic manifestation: (i)

focal (≤10 mm length); (ii) diffuse (>10 mm within the stent); (iii) proliferative (>10 mm extending outside the stent); and (iv) occlusive ISR. Angiographic visual estimation or intravascular imaging was used to diagnose LM restenosis. Significant stenosis was defined as intravascular ultrasound (IVUS) imaging of the target lesion with a minimum lumen area (MLA) of ≤6 mm^2 for the left main lesions was defined as significant stenosis. Angiographic data of patients included in the study were collected and recorded in the central cardiovascular information registry. Bifurcation lesions were classified according to the Medina classification (6). The European Bifurcation Club consensus document was used to define the one or two stent strategy of LM PCI (7). Patient data were anonymized in each center, combined into a database, and statistically analyzed as a single cohort. The institutional review board at each center approved the study protocol; however, due to the retrospective nature of the study, no written informed consent was needed. The patient data were protected according to the requirements of country law and hospital standard operating procedures. The data that support the findings of this study are available from the corresponding author upon reasonable request. The study was conducted in accordance with the Declaration of Helsinki and was registered at ClinicalTrials.gov (NCT04968977).

Endpoints

The primary endpoint was a composite of major adverse cardiac and cerebrovascular events (MACCE), defined as cardiac death, myocardial infarction (MI), target vessel revascularization (TVR), or stroke assessed during a median of 3.5 year follow-up [interquartile range (*IQR*) 1.3–5.5]. TVR was defined as any repeat intervention (PCI or CABG) of the treated vessel caused by ischemia driven stenosis of the LM. Data regarding long-term outcomes were obtained by phone call or clinical visit as well as from the National Health Fund Service (Ministry of Health) database.

Statistical Analysis

Continuous data are presented as mean ± standard deviation or median with IQR (Q1–Q3). Categorical data are expressed as count and percentage. Normal distribution was verified by the Kolmogorov–Smirnov test. Continuous data were compared by the Student *t*-test or by Mann–Whitney *U* test, depending on the data distribution. Categorical data were analyzed with the χ^2 or Fisher exact test. Kaplan–Meier survival curves were performed to present the unadjusted time-to-event data for investigated endpoints and were compared using the log-rank test. Finally, Cox regression for 30 days, 1 year, and long-term follow-up event rates of MACCE, cardiac death, TLR, TVR, MI, and stroke were calculated for both groups. A p-value < 0.05 was considered statistically significant. The statistical analysis was performed using MedCalc version 17.9.2 (MedCalc Software, Ostend, Belgium) and SPSS version 21 (IBM Corp, Armonk, NY).

RESULTS

The LM-DRAGON registry included 305 patients, of whom 203 (66.6%) were treated with PCI and 102 (33.4%) with CABG (**Table 1**). After verifying missing outcomes with multiple datasets, 12 (5.9%) patients in the PCI group and 4 (3.9%) in the CABG group were lost to follow-up. A comparison between PCI and CABG groups demonstrated significant differences in baseline characteristics and clinical presentation. Patients treated by PCI were older (68.9 ± 10.3 vs. 65.0 ± 8.9, $p < 0.001$) more often had diabetes mellitus (49.8% vs. 35.3%, $p = 0.02$), and chronic kidney disease (25.6% vs. 13.7%, $p = 0.02$), compared with CABG patients. STS score for mortality and morbidity was

TABLE 1 | Patient characteristics, risk factors, and clinical presentation according to the type of treatment.

	PCI ($n = 203$)	CABG ($n = 102$)	*p*-value
Age, y	68.9 ± 10.3	65.0 ± 8.9	<0.001
Male sex	148 (72.9)	72 (70.6)	0.67
Body mass index, kg/m^2	28.4 ± 3.9	27.7 ± 3.7	0.22
Discharge diagnosis			
Chronic coronary syndrome, n (%)	80 (39.4)	19 (18.6)	<0.001
Unstable angina, n (%)	46 (22.7)	62 (60.8)	<0.001
Non–ST-segment elevation myocardial infarction	72 (35.5)	21 (20.6)	0.007
ST-segment elevation myocardial infarction	4 (2.0)	0 (0)	0.15
Previous myocardial infarction	134 (66.0)	65 (63.7)	0.69
Previous CABG	33 (16.3)	1 (1.0)	<0.001
Previous stroke	15 (7.4)	4 (3.9)	0.24
Diabetes mellitus	101 (49.8)	36 (35.3)	0.02
Insulin requiring	35 (17.2)	19 (18.6)	0.77
Hypertension	170 (83.7)	92 (90.2)	0.13
Hyperlipidemia	167 (82.3)	85 (83.3)	0.82
Chronic kidney disease*	52 (25.6)	14 (13.7)	0.02
Dialysis	3 (1.5)	2 (2.0)	0.75
Atrial fibrillation	29 (14.3)	13 (12.7)	0.71
Current smoker	30 (14.8)	16 (15.7)	0.83
Family history of coronary artery disease	35 (17.2)	22 (21.6)	0.36
Pulmonary disease	24 (11.8)	2 (2.0)	0.003
Peripheral artery disease	46 (22.7)	16 (15.7)	0.15
Cardiac arrest before PCI/CABG	9 (4.4)	1 (1.0)	0.11
Time to restenosis, months	10.0 (5.0–19.0)	6.5 (4.0–33.0)	0.22
Recurrent in-stent restenosis	42 (20.7)	10 (9.8)	0.02
Number of in-stent restenosis events	1.2 ± 0.4	1.1 ± 0.4	0.03
STS score mortality and morbidity	4.5 (2.5–8.4)	7.2 (5.1–9.9)	<0.001
EuroSCORE II	1.5 (0.9–3.5)	1.6 (1.0–3.3)	0.52
Left ventricular ejection fraction, %	50.0 (40.0–60.0)	49.0 (40.0–55.0)	0.46

*Values are mean ± standard deviation, n (%), or median (interquartile range). *Estimated glomerular filtration rate of <60 ml/min/1.73 m^2 calculated using the modification of diet in renal disease method. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; STS, society of thoracic surgeons.*

TABLE 2 | Angiographic, procedural, and medication data according to the type of treatment.

	PCI ($n = 203$)	CABG ($n = 102$)	*p*-value
Restenosis in drug-eluting stents	185 (91.1)	78 (76.5)	<0.001
Restenosis in bare metal stents	18 (8.9)	24 (23.5)	
SYNTAX score I	22.0 (13.2–27.0)	21.5 (15.0–27.0)	0.47
SYNTAX score II (PCI)	32.5 (22.4–44.8)	32.5 (25.9–41.6)	0.75
SYNTAX score II (CABG)	39.2 (24.7–48.6)	29.1 (21.7–37.0)	<0.001
Number of diseased vessels			
1	31 (15.3)	9 (8.8)	0.12
2	76 (37.4)	28 (27.5)	0.08
3	96 (47.3)	65 (63.7)	0.006
Previous left main PCI strategy			
One-stent strategy	157 (77.3)	70 (68.6)	0.10
Two-stent strategy	46 (22.7)	32 (31.4)	
In-stent restenosis left main segment			
Proximal/medial	18 (8.9)	4 (3.9)	0.12
Distal	185 (91.1)	98 (96.1)	
Medina classification			
1,1,1	87 (47.0)	28 (28.6)	<0.001
1,1,0	23 (12.4)	34 (34.7)	
1,0,1	41 (22.2)	13 (13.3)	
0,1,1	8 (4.3)	11 (11.2)	
1,0,0	8 (4.3)	10 (10.2)	
0,1,0	13 (7.0)	2 (2.0)	
0,0,1	5 (2.7)	0 (0)	
Type of in-stent restenosis			
Focal	113 (55.7)	40 (39.2)	0.02
Diffuse	63 (31.0)	50 (49.0)	
Proliferative	26 (12.8)	12 (11.8)	
Occlusive	1 (0.5)	(0)	
Restenotic stent length, mm	18.0 (16.0–23.0)	22.2 (18.0–27.0)	0.11
Restenotic stent diameter, mm	3.5 (3.5–4.0)	3.5 (3.5–4.0)	0.82
Thrombus	3 (1.5)	(0)	0.26
Stenosis, %	70.0 (60.0–90.0)	90.0 (80.0–90.0)	<0.001
Number of stent layers	1.2 ± 0.4	1.0 ± 0.2	<0.001
PCI data			
PCI with drug-eluting stents*	121 (59.6)	—	—
PCI with drug-coated balloon	78 (38.4)	—	—
Plain old balloon angioplasty	4 (2.0)	—	—
Intravascular lithotripsy	3 (1.5)	—	—
Procedural use of intracoronary imaging	81 (39.9)	—	—
Residual stenosis	18 (8.9)	—	—
TIMI 3 post-PCI	199 (98.5)	—	—
Perforation	1 (0.5)	—	—
Dissection	1 (0.5)	—	—
Stent thrombosis during hospitalization	1 (0.5)	—	—
Complications during PCI	15 (7.4)	—	—
CABG data			
Off-pump coronary artery bypass	—	16 (15.7)	—
Minimally invasive coronary artery bypass	—	1 (1.0)	—
Left internal mammary artery to LAD	—	92 (90.2)	—
Aorta to LAD	—	10 (9.8)	—
Aorta to obtuse marginal	—	69 (67.6)	—
Aorta to right coronary artery	—	40 (39.2)	—
Arterial grafts	-	0.9 ± 0.3	—
Vein grafts	-	1.2 ± 0.7	—
CABG–other type	—	11 (10.8)	—
Complications during CABG, n (%)	—	15 (16.1)	—
Complete revascularization, n (%)	—	91 (89.2)	—
Mechanical circulatory support	4 (2.0)	6 (7.8)	0.02
Glycoprotein IIb/IIIa inhibitors	9 (4.4)	(0)	—

*Values are mean ± standard deviation, n (%), or median (interquartile range). CABG, coronary artery bypass grafting; LA, left anterior descending artery; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; *all drug eluting stents were 2nd generation.*

lower in the PCI group [4.5 (*IQR* 2.5–8.4) vs. 7.2 (*IQR* 5.1–9.9), $p < 0.001$]; however, there were no differences in EuroSCORE II [1.5 (0.9–3.5) vs. 1.6 (1.0–3.3), $p = 0.52$].

Angiographic, procedural, and medication data are shown in **Table 2**. The SYNTAX score I did not differ between the two groups [22.0 (13.2–27.0) vs. 21.5 (15.0–27.0), $p = 0.47$]. Recurrent ISR was more common in the PCI group (20.7% vs. 9.8%, $p = 0.02$). Procedurally, the most common location of LM-ISR was the distal segment including the bifurcation. True bifurcation lesions (Medina 1,1,1) were more prevalent in the PCI, compared with the CABG group (47.0% vs. 28.6%, $p < 0.001$). Patients treated with PCI had a higher prevalence of focal ISR (55.7% vs. 39.2%, $p = 0.02$) and proliferative ISR (12.8% vs. 11.8%, $p = 0.02$), while those in the CABG group had a higher prevalence of diffuse ISR (31.0% vs. 49.0%, $p = 0.02$). Number of stent layers in the target segment was higher in PCI (1.2 ±0.4 vs. 1.0 ± 0.2, $p < 0.001$). In the PCI group, 59.6% of patients underwent DES implantation, 38.4% were treated with a drug coated balloon, and 2% were treated with plain old balloon angioplasty; additionally, 3 patients had

intravascular lithotripsy during PCI. TIMI 3 flow post-PCI was observed in 98.5% of patients and residual stenosis was observed in 8.9%. In the CABG group, 90.2% patients had left internal mammary artery to left anterior descending grafts, 9.8% had vein to left anterior descending grafts, and 67.6% had grafts to obtuse marginal branch or distal Cx. Periprocedural mechanical circulatory support was needed more often in the CABG group (7.8% vs. 2.0%, $p = 0.02$).

30 Days and 1-Year Outcomes

At 30-day follow-up, there was a lower risk of cardiac death in the PCI group (2.1% vs. 7.1%, *HR* 3.48, 95% *CI* 1.01–11.8, $p = 0.04$) as compared to CABG treatment group. However, worth mentioning, patients who died in CABG group were at median EuroSCORE II 3.4 (2.3–4.5) and median STS score for mortality and morbidity 9.4 (8.6–11.4). There were no differences with respect to MACCE (3.1% vs. 7.1%, *HR* 2.32, 95% *CI* 0.77–6.90, $p = 0.13$), TVR (PCI−0.5% vs. CABG−0%), MI (PCI−0% vs. CABG−0%), and stroke (PCI−0.5% vs. CABG−0%) through 30-days. During 1-year follow-up a trend toward a higher rate of TVR in the PCI group (7.9% vs. 2.0%; *HR* 0.25, 95% *CI* 0.05–1.09, $p = 0.07$) was observed, with no differences in MI (3.7% vs. 2.0%, *HR* 0.54, 95% *CI* 0.11–2.60, $p = 0.44$), cardiac death (4.2% vs. 8.2%, *HR* 1.98, 95% *CI* 0.74–5.27, $p = 0.17$), stroke (1.6% vs. 1.0%, *HR* 0.64, 95% *CI* 0.06–6.16, $p = 0.70$) and MACCE (14.7% vs. 12.2%, *HR* 0.81, 95% *CI* 0.41–1.59, $p = 0.54$) (**Table 3**).

Long-Term Outcomes

The median follow-up period was 3.4 years (1.3–5.2) in the PCI group and 3.8 years (2.3–6.5) in the CABG group ($p = 0.046$). The study's primary endpoint occurred in 27.7% of patients in PCI group and 29.6% of patients in CABG group (*HR* 0.82, 95% *CI* 0.52–1.32, $p = 0.43$) (**Table 3**). There were no significant differences between PCI and CABG in terms of cardiac death (9.9% vs. 18.4%; *HR* 1.56, 95% *CI* 0.81–3.00, $p = 0.18$), MI (7.9% vs. 5.1%; *HR* 0.44, 95% *CI* 0.15–1.27, $p = 0.13$), or stroke (2.1% vs. 4.1%; *HR* 1.79, 95% *CI* 0.45–7.16, $p = 0.41$); however, TVR occurred less frequently in the CABG group than in the PCI group (6.1% vs. 15.2%, *HR* 0.35, 95% *CI* 0.15–0.85, $p = 0.02$). The treatment strategy of TVR after PCI and CABG is reported in **Supplementary Material**. Kaplan–Meier curves for the cumulative incidence of selected outcomes are shown in **Figures 1**, **2**. The results of the combined clinical outcome measures and MACCE were consistent across most of the pre-specified subgroups (**Figure 3**). Patients at lower preoperative risk (EuroSCORE II < 2) had significantly less MACCE in the CABG group than in the PCI group.

DISCUSSION

We present the largest registry of patients with unprotected LM-ISR reporting long-term data on the safety and efficacy of revascularization with either PCI or CABG. In the current report, both PCI and CABG provided favorable clinical outcomes; however, a lower incidence of cardiac death at 30-day follow-up was observed in the PCI group compared with the CABG group. This was reflected in the subgroup analysis, where

TABLE 3 | One-year and long-term follow-up according to the type of treatment.

	30 days follow-up				1-year follow-up				Long-Term follow-up*			
	PCI	CABG	*HR* (95%*CI*)	*p*-value	PCI	CABG	*HR* (95%*CI*)	*p*-value	PCI	CABG	*HR* (95%*CI*)	*p*-value
TVR	1 (0.5)	-	-	-	15 (7.9)	2 (2.0)	0.25 (0.05–1.09)	0.07	29 (15.2)	6 (6.1)	0.35 (0.15–0.85)	0.02
MI	-	-	-	-	7 (3.7)	2 (2.0)	0.54 (0.11–2.60)	0.44	15 (7.9)	5 (5.1)	0.44 (0.15–1.27)	0.13
Cardiac death	4 (2.1)	7(7.1)	3.48 (1.01–11.8)	0.04	8 (4.2)	8 (8.2)	1.98 (0.74–5.27)	0.17	19 (9.9)	18 (18.4)	1.56 (0.81–3.00)	0.18
Stroke	1(0.5)	-	-	-	3 (1.6)	1 (1.0)	0.64 (0.06–6.16)	0.70	4 (2.1)	4 (4.1)	1.79 (0.45–7.16)	0.41
MACCE	6 (3.1)	7 (7.1)	2.32 (0.77–6.90)	0.13	28 (14.7)	12 (12.2)	0.81 (0.41–1.59)	0.54	53 (27.7)	29 (29.6)	0.82 (0.52–1.32)	0.43

**PCI median follow-up period 3.4 (IQR 1.3–5.2) years; CABG median follow-up period 3.8 (IQR 2.3–6.5) years.*
CABG, coronary artery bypass grafting; CI, confidence intervals; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

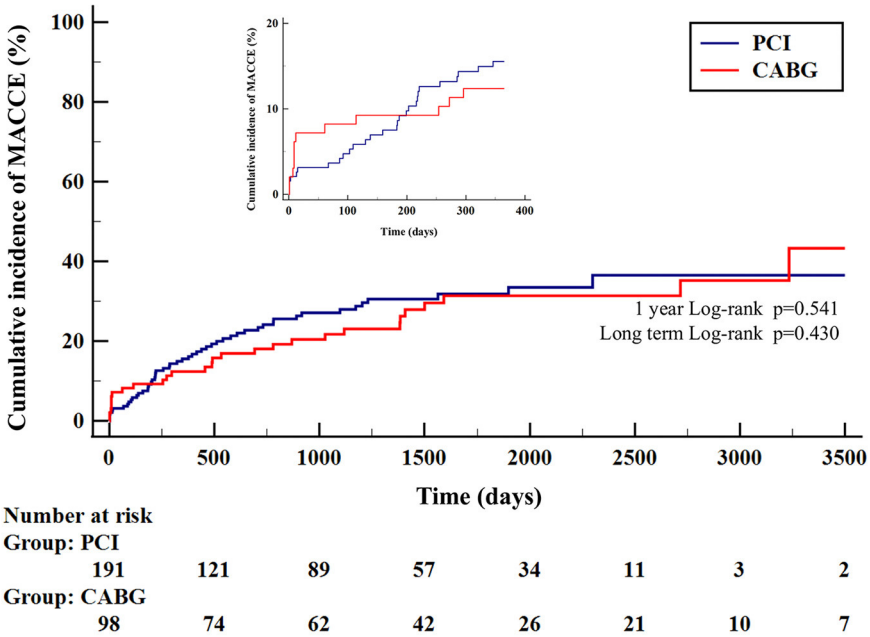

FIGURE 1 | Kaplan–Meier curves for MACCE according to type of treatment. Major adverse cardiac and cerebrovascular events (MACCE) is the composite of target vessel revascularization, myocardial infarction, stroke, or cardiac death. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

high EuroSCORE II favored PCI treatment. The elevated risk of the patients with CABG treatment was also indicated by a substantial proportion of mechanical circulatory support use. Clinically compromised patients characterized by such a procedural profile could therefore drive the short-term excess mortality in the CABG-revascularized group. At the long-term follow-up patients receiving PCI treatment, compared with those treated with CABG, had similar rates of cardiac death but a higher rate of TVR. Our long-term results provide evidence for the use of PCI in unprotected LM-ISR and suggest its safety and efficacy in reducing recurrent stent failure.

Despite favoring results, LM-ISR PCI is, undoubtedly, a challenging treatment option. Those with LM-ISR are a specific subset of patients who already underwent high-risk procedure of PCI in LM and now experience a subsequent stent failure. Previous reports addressed a combination of multiple factors contributing to an increased risk of LM-ISR and the subsequent adverse events: female sex, a previous restenotic lesion, a total number of stents employed, distal bifurcation lesions, and the use of complex bifurcation stenting technique (4), whereas the use of IVUS was protective (8). To systematically apprise the phenomenon, ISR classification including variables contributing to in different angiographic manifestation of ISR lesion length and the location of the neointimal proliferation, was proposed (9). To date, many large-scale clinical studies have evaluated treatment strategies for patients with *de novo* unprotected LM disease. Generally, guidelines recommend CABG revascularization in patients with *de novo* unprotected LM disease with high SYNTAX scores, downplaying the role of PCI (10). Although the less invasive PCI has a lower rate of periprocedural adverse events and provides more rapid recovery compared with CABG (11), it exposes patients to an increased risk of myocardial ischemia in LM-ISR. A previous study demonstrated that DES implantation or drug-coated balloon angioplasty could be effective in patients with ISR (12, 13); however, the effectiveness of repeat PCI for LM-ISR following previous DES implantation remains controversial. The Milan and New-Tokyo (MITO) registry evaluated the prognostic role of restenosis in unprotected distal LM bifurcation coronary lesions and revealed that the patients with LM main branch ISR have higher risk of cardiac mortality compared with patients without LM main branch ISR (14). As limited data are available on the LM-ISR optimal revascularization, this clinical setting remains a matter of discussion. The Failure in Left Main Study (FAILS) study showed satisfactory results using PCI revascularization strategy at 27 months of follow-up, with major adverse cardiac events (MACE; death, MI, or TLR) occurring in 26% of patients and TLR occurring in 22%; however, the analyzed groups were too small to allow for a comparison between the two treatment strategies (3). Promising results of PCI were also reported in the long-term results of the CORPAL registry, where few patients were treated by CABG over the course of 46 ± 26 months (15). The rate of

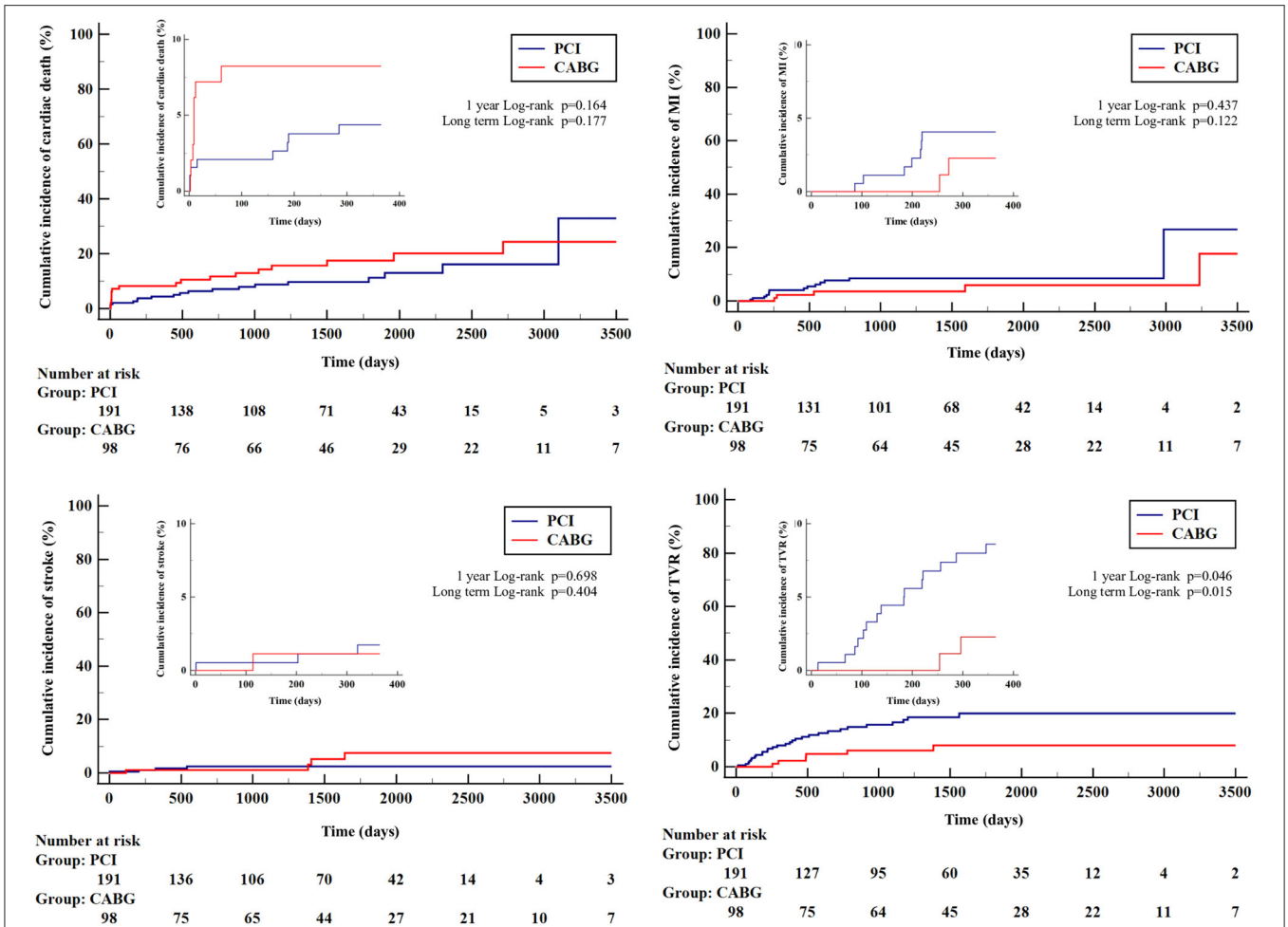

FIGURE 2 | Kaplan–Meier curves for cumulative incidence of secondary outcomes according to type of treatment. CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

outcomes in PCI patients was 22% MACE (cardiac death, TLR, and MI), 8% cardiac death, 4% non-fatal MI, and 15% repeat revascularization. The optimal management of patients with LM-ISR focuses on maintaining a balance between the long-term risk of TVR in PCI and perioperative complications in CABG; however, the PCI in LM-ISR is oftentimes performed as a first-line, life-saving treatment in unstable patients with acute LM occlusion compared with emergency cardiac surgery. Safety and efficacy of both revascularization methods were evaluated in many studies in *de novo* unprotected LM lesions, showing a comparable rate of clinical outcomes in terms of MACCE (1, 11, 16). Long-term results of the LE MANS, PRECOMBAT, and EXCEL trials showed that at 1-year and 5-year follow-up, patients undergoing revascularization for unprotected LM experienced similar rate of the composite clinical outcome. The rate of target vessel failure in the LE MANS and the rate of mortality, MI, and stroke in PRECOMBAT were also comparable between PCI and CABG (11, 16). The results of TVR varied between studies, with a hint of more frequent occurrence in the PCI vs. CABG, also observed in the current LM-DRAGON registry. None of the previous randomized controlled trials directly compared PCI and CABG for reintervention for ISR in LM lesions; indeed, ISR or prior LM intervention has universally been imposed as exclusion criterion in these trials (17).

Limitations

There are several limitations to this study. First, we had no intravascular imaging data and thus limited insight into the mechanisms of restenosis. We had no comprehensively reported data on initial PCI strategy, nor on completeness of revascularization in the PCI group. Angiographic follow-up was not systematically performed. In the PCI group, 16% of patients had previous CABG, which may also affect further revascularization options, furthermore the decisions on the choice of treatment were

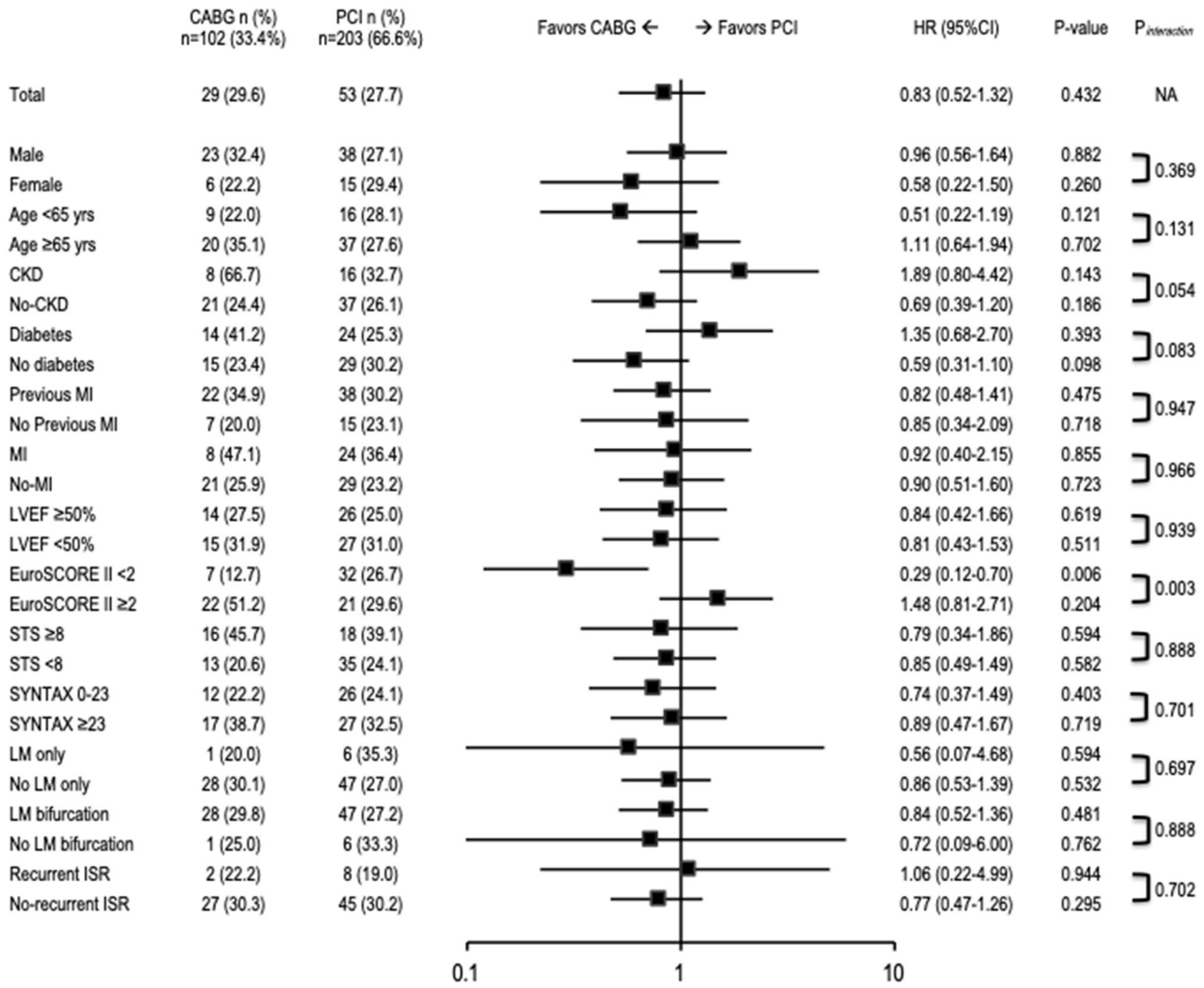

FIGURE 3 | Risk of MACCE at long-term follow-up. CABG, coronary artery bypass grafting; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; ISR, in-stent restenosis; LM, left main coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons.

not random but based on the heart team or operator's preference; selection bias was inevitable and may limit our interpretation. The study was a retrospective analysis with inherent limitations; however, this was balanced by an "all-comer" design with broad inclusion criteria and a large sample size.

CONCLUSIONS

This analysis of a real-life unprotected LM-ISR registry revealed a lower incidence of cardiac death in the PCI treatment group compared with the CABG treatment group at short-term follow-up. Long-term follow-up showed similar incidences of cardiac death, MACCE, MI, and stroke regardless of revascularization strategy, but patients who underwent CABG less often required TVR compared with patients who underwent PCI.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical University of Silesia, Katowice, Poland. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Data curation: JB, AK, DH, RG, RJ, TF, MM, BT, PKÜ, PD, ŁK, KM, BG, AŁ, JK, AW, MA, PKL, RL, AB, and GS. Formal analysis

and methodology: WWA, MKOŁ, and MKOW. Supervision: WWA, WWO, MG, ML, FD'A, MA, KR, MGR, RG, MJ, KB, PS, SD, DD, SB, MGĄ, JL, AO, AL, MD, and EK. Writing—original draft: WWA and MKOŁ. All authors have read and agreed to the published version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.849971/full#supplementary-material

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Switching From Proximal to Distal Radial Artery Access for Coronary Chronic Total Occlusion Recanalization

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Background: Distal radial access (DRA) was recently introduced in the hopes of improving patient comfort by allowing the hand to rest in a more ergonomic position throughout percutaneous coronary interventions (PCI), and potentially to further reduce the rate of complications (mainly radial artery occlusion, [RAO]). Its safety and feasibility in chronic total occlusion (CTO) PCI have not been thoroughly explored, although the role of DRA could be even more valuable in these procedures.

Methods: From 2016 to 2021, all patients who underwent CTO PCI in 3 Hungarian centers were included, divided into 2 groups: one receiving proximal radial access (PRA) and another DRA. The primary endpoints were the procedural and clinical success and vascular access-related complications. The secondary endpoints were major adverse cardiac and cerebrovascular events (MACCE) and procedural characteristics (volume of contrast, fluoroscopy time, radiation dose, procedure time, hospitalization time).

Results: A total of 337 consecutive patients (mean age 64.6 ± 9.92 years, 72.4% male) were enrolled (PRA = 257, DRA = 80). When compared with DRA, the PRA group had a higher prevalence of smoking (53.8% vs. 25.7%, SMD = 0.643), family history of cardiovascular disease (35.0% vs. 15.2%, SMD = 0.553), and dyslipidemia (95.0% vs. 72.8%, SMD = 0.500). The complexity of the CTOs was slightly higher in the DRA group, with higher degrees of calcification and tortuosity (both SMD >0.250), more bifurcation lesions (45.0% vs. 13.2%, SMD = 0.938), more blunt entries (67.5% vs. 47.1%, SMD = 0.409). Contrast volumes (median 120 ml vs. 146 ml, $p = 0.045$) and dose area product (median 928 mGy×cm² vs. 1,300 mGy×cm², $p < 0.001$) were lower in the DRA group. Numerically, local vascular complications were more common in the PRA group, although these did not meet statistical significance (RAO: 2.72% vs. 1.25%, $p = 0.450$; large hematoma: 0.72% vs. 0%, $p = 1.000$). Hospitalization duration was similar (2.5 vs. 3.0 days, $p = 0.4$). The procedural and clinical success rates were comparable through DRA vs. PRA ($p = 0.6$), moreover, the 12-months rate of MACCE was similar across the 2 groups (9.09% vs. 18.2%, $p = 0.35$).

Conclusion: Using DRA for complex CTO interventions is safe, feasible, lowers radiation dose and makes dual radial access more achievable. At the same time, there was no signal of increased risk of periprocedural or long-term adverse outcomes.

Keywords: distal radial access, snuffbox approach, chronic total occlusion, CTO, radiation dose, proximal radial access, radial artery occlusion

INTRODUCTION

Distal radial access (DRA), a technique that can no longer be called "novel" in terms of its widespread adoption, has already been declared feasible and safe in various types of coronary, structural and peripheral procedures (1–7). The most notable advantages are the low rate of radial artery occlusion, few local complications, short hemostasis time and better ergonomics, both for the patient and for the operator (1, 2), especially in the case of left radial artery access.

In recent times, coronary chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has become widely adapted and is currently being performed at large scale, with a significant positive clinical impact on malignant ischemic arrhythmias and adverse clinical outcomes in patients with acute myocardial infarction and incomplete revascularization (8–10). Dual arterial access is necessary in almost every case. Furthermore, these procedures are usually long and arduous. For these reasons, adopting dual DRA and bringing both hands in a physiological position of pronation in close proximity to each other, seems an attractive option. Nonetheless, compared to other well-studied interventions, knowledge about the safety and feasibility of DRA in CTO PCI remains limited (11). The present multicenter, retrospective study aimed to perform a head-to-head comparison between proximal radial access (PRA) and DRA in CTO PCI. We specifically assessed the impact of access strategy on vascular complications, procedural times, and irradiation exposure, provided that procedural efficacy and outcomes remained non-inferior.

METHODS

Study Patients

All consecutive patients who underwent CTO PCI between May 2016 and October 2021 in 3 Hungarian institutions were included. Because our local protocol has been changed in 2019, switching from PRA to DRA, 2 cohorts could be formed retrospectively, the PRA group ($n = 257$) and the DRA group ($n = 80$). We collected deidentified data of all patients in whom at least one arterial access was either PRA or DRA, in a standardized form. The indication for CTO PCI was established by the local heart team, as well as the recanalization strategy. There were 3 main operators responsible for all the procedures, the learning curve of the DRA as well as its technique being described elsewhere (2). Patients with ultrasound evidence of arterial occlusion, severe calcification, and a lumen of <1 mm were excluded. Baseline patient characteristics, procedural details, puncture-related complications, CTO-related complications, major events at 30 days and 12 months were all recorded in a common database. Before discharge, the patency of the radial artery was verified by duplex ultrasound. After discharge, patients were followed-up by outpatient visits or phone call at 1, 6 and 12 months after the procedure. Written informed consent was obtained from all patients, and the Institution's Ethics Committee approved the study.

Endpoints

Because our study was a vascular access-related study, focused on the safety, feasibility and performance of DRA in PCI CTO, 2 types of endpoints were defined. The primary outcomes of the study were the success (procedural plus clinical) and access site complications (severe arterial spasm, forearm hematoma, radial artery occlusion, bleeding, pseudoaneurysms and fistulae). The secondary endpoints included were major adverse cardiac and cerebrovascular events (MACCE) and procedural performance characteristics (volume of contrast, fluoroscopy time, radiation dose, procedure time, hospitalization time).

The total procedure time referred to the time interval between the administration of the local anesthetic until the completion of the procedure. For the classification of the forearm hematomas, we used a modified version of the EASY (Early Discharge After Transradial Stenting of Coronary Arteries Study) classification (12). Large hematomas were considered $\geq$EASY II. Bleeding was considered significant if Bleeding Academic Research Consortium $\geq$2.

The components of MACCE were defined as non-fatal myocardial infarction (MI), acute stent thrombosis, target lesion revascularization (TLR), stroke or transient ischemic attack, and cardiovascular mortality.

Statistical Analyses

For the entire cohort ("Before Matching"), continuous variables were evaluated for normality using the Shapiro-Wilk test and reported as mean $\pm$ standard deviation or median (interquartile range), as appropriate, while categorical variables were reported as frequencies and percentages. Patients were stratified by approach (PRA vs. DRA) and compared using parametric (Student's paired t) or non-parametric (Mann-Whitney U) tests, as appropriate, for continuous variables and the Chi-squared test for categorical variables.

Propensity score matching was used to adjust for pre-specified baseline characteristics that were potentially confounding

Abbreviations: DRA, distal radial access; CTO, chronic total occlusion; PCI, percutaneous coronary intervention; PRA, proximal radial access; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; TLR, target lesion revascularization; SMD, standardized mean difference; DAP, dose area product; RAO, radial artery occlusion; JCTO, Japanese chronic total occlusion.

variables. We calculated propensity scores using logistic regression models with all baseline variables listed in **Table 1**, including patient comorbidities and lesion characteristics. The C-statistic for the model was 0.92. PRA cases were matched 1:1 with DRA cases, using the propensity score with a caliper of 0.1 of the standard deviation of the logit of the propensity score, without replacement (13, 14). Standardized mean differences (SMD) were determined to compare baseline characteristics of all patients; a standardized mean difference <0.25 was considered an indicator of good balance between groups (15).

For the matched cohort ("After Matching"), data were again presented as described above. Both approaches (PRA vs. DRA) were compared by paired univariate analysis. Categorical variables were compared using McNemar's test and continuous variables were compared by Wilcoxon signed rank test. All analyses were completed with R Statistical Software (version 4.1.1, Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population

A total of 337 consecutive patients (mean age 64.6 ± 9.92 years, 72.4% male) underwent PCI between May 2016 and October 2021 at our institutions. Of these, access was obtained using PRA in 257 and using DRA in 80 cases. Baseline characteristics of the unmatched cohort are presented in **Table 1**. When compared with DRA, the PRA group had a higher prevalence of smoking (53.8% vs. 25.7%, SMD = 0.643), family history of cardiovascular disease (35.0% vs. 15.2%, SMD = 0.553), and dyslipidemia (95.0% vs. 72.8%, SMD = 0.500). The prevalence of the other risk factors was similar. The complexity of the CTOs was slightly higher in the DRA group, being characterized by higher degrees of calcification and tortuosity of the target lesions (both SMD > 0.250), and a higher prevalence of bifurcation lesions (45.0% vs. 13.2%, SMD = 0.938) and blunt entry shape (67.5% vs. 47.1%, SMD = 0.409). Propensity score matching resulted in 44 pairs, which showed adequate overall balancing in the baseline characteristics (SMD < 25%), except for very minor residual imbalances in male sex and family history of cardiovascular disease (SMD for PRA compared to DRA of −0.261 and −0.253, respectively) (**Table 1**, **Figure 1**).

Intraprocedural Characteristics

Intraprocedural characteristics are summarized in **Table 2**. In the unmatched cohort, the distribution of CTO was significantly different between both groups: anterograde dissection reentry was more frequent in the DRA group (27.8% vs. 3.89%, $p < 0.001$) whereas anterograde wire escalation, retrograde dissection reentry, and retrograde wire escalation were more frequent in the PRA group (all $p < 0.001$). Cases in the DRA group had higher use of intravascular ultrasound (IVUS, 16.2% vs. 7.39%, $p = 0.032$), greater use of guidewires (median 3.00 vs. 2.00, $p = 0.001$), and longer stents (median 56.5 mm vs. 40.0 mm, $p < 0.001$). Furthermore, contrast volumes (median 120 ml vs. 146 ml, $p = 0.045$) and dose area product (DAP) (median 928 mGy × cm² vs. 1,300 mGy × cm², $p < 0.001$) were lower in the DRA group. On the other hand, PRA was characterized by shorter procedure times (median 38.5 min vs. 55.0 min, $p < 0.001$) and fluoroscopy times (median 19.0 vs. 27.5 min, $p = 0.042$).

After matching, anterograde dissection reentry was still more frequent (34.9% vs. 6.82%, $p = 0.001$) and the number of guidewires used was still higher (median 3.00 vs. 2.50, $p = 0.003$) in DRA than in PRA. Lower DAP (median 1,000 mGy × cm² vs. 1,515 mGy × cm², $p = 0.018$) and longer procedure time (median 70.0 min vs. 37.5 min, $p < 0.001$) were also still observed for the DRA group. There was still a trend toward longer stent length ($p = 0.071$) and longer fluoroscopy time ($p = 0.064$) in the DRA group, although this did not reach statistical significance.

The overall complexity of the procedures remained varied across all patients, although most had a Japanese chronic total occlusion (JCTO) score ≤2 ($n = 171$). However, no clear correlation between JCTO score and procedural success could be established (**Figure 2**).

Procedural and Long-Term Outcomes

Procedural and long-term outcomes are presented in **Table 3**. In the unmatched cohort, a shorter hospital length of stay (median 2.00 days vs. 3.00 days, $p = 0.006$) was observed in the DRA group. Furthermore, the 12-months rate of MACCE tended to be lower in the DRA group (10.0% vs. 20.2%, $p = 0.055$), although this did not reach statistical significance. Numerically, local vascular complications were more common in the PRA group, although these did not meet statistical significance (radial artery occlusion [RAO]: 2.72% vs. 1.25%, $p = 0.450$; large hematoma: 0.72% vs. 0%, $p = 1.000$). After matching, no differences were observed in any of the observed outcomes.

DISCUSSION

The main findings of our study were that (1) procedure success rates, complication rates, and long-term outcomes were comparable after CTO recanalization through DRA vs. PRA; and (2) despite longer procedure times, DRA was associated with lower radiation doses. These findings suggest that DRA may be an attractive and ergonomic alternative to PRA that is as safe and effective for CTO procedures. Moreover, although not statistically significant, the RAO rate seems to be lower with DRA, which is of clinical importance because, for many patients, this is not their last intervention in the catheterization room.

Only 2 previous studies tested the feasibility of DRA in CTO recanalization procedures, but none had a PRA control group or quantified the radiation dose (11, 16). In a small, prospective, multicenter study (41 patients), Gasparini et al. (16) demonstrated high procedural success (90.3%) using the 7-French Glidesheath Slender for CTO PCIs through left DRA only, their operators using ultrasound-guided puncture as well. Vascular access-site complications (DRA-related) or MACEs were not recorded. The cohort of Lin et al. (7) was larger (298 patients) and, also often used the Glidesheath system in the majority of their patients (95.5%). The investigators observed low vascular complications rates (RAO 0.5%, large hematomas 0.2%), consistent with our data and those by Gasparini et al. (16). Interestingly, they reported that successful DRA was feasible even

TABLE 1 | Baseline characteristics before and after propensity score matching.

Variable	Before matching				After matching			
	DRA ($n = 80$)	PRA ($n = 257$)	*P*-value	SMD*	DRA ($n = 44$)	PRA ($n = 44$)	*P*-value	SMD*
Age, years	64.1 (9.58)	64.7 (10.0)	0.623	0.061	62.6 (8.76)	64.6 (10.6)	0.326	0.204
Male sex, *n* (%)	52 (65.0%)	192 (74.7%)	0.120	0.223	32 (72.7%)	27 (61.4%)	0.364	−0.261
BMI, kg/m²	29.2 (26.5; 32.3)	29.4 (26.0; 32.3)	0.996	0.005	29.8 (4.80)	29.3 (4.41)	0.586	−0.109
CKD, *n* (%)	16 (20.0%)	34 (13.2%)	0.191	−0.200	12 (27.3%)	10 (22.7%)	0.806	−0.134
Diabetes, *n* (%)	39 (48.8%)	106 (41.2%)	0.292	−0.153	21 (47.7%)	24 (54.5%)	0.670	0.139
AHT, *n* (%)	75 (93.8%)	230 (89.5%)	0.360	−0.139	41 (93.2%)	41 (93.2%)	1.000	0.000
Smoking, *n* (%)	43 (53.8%)	66 (25.7%)	<0.001	−0.643	22 (50.0%)	19 (43.2%)	0.669	−0.156
Family history of CVD, *n* (%)	28 (35.0%)	39 (15.2%)	<0.001	−0.553	14 (31.8%)	10 (22.7%)	0.473	−0.253
Dyslipidemia, *n* (%)	76 (95.0%)	187 (72.8%)	<0.001	−0.500	40 (90.9%)	40 (90.9%)	1.000	0.000
Previous MI, *n* (%)	35 (43.8%)	115 (44.7%)	0.978	0.020	21 (47.7%)	21 (47.7%)	1.000	0.000
Previous CABG, *n* (%)	8 (10.0%)	35 (13.6%)	0.512	0.106	6 (13.6%)	6 (13.6%)	1.000	0.000
PAD, *n* (%)	23 (28.7%)	58 (22.6%)	0.327	−0.148	10 (22.7%)	8 (18.2%)	0.792	−0.109
Diagnosis			0.096				0.761	
Cx, *n* (%)	7 (8.75%)	49 (19.1%)		0.263	6 (13.6%)	8 (18.2%)		0.116
LAD, *n* (%)	31 (38.8%)	88 (34.2%)		−0.095	17 (38.6%)	18 (40.9%)		0.048
RCA, *n* (%)	42 (52.5%)	120 (46.7%)		−0.116	21 (47.7%)	18 (40.9%)		−0.137
Location			0.454				1.000	
Distal, *n* (%)	5 (6.25%)	15 (5.84%)		−0.018	0 (0.00%)	1 (2.27%)		0.097
Mid, *n* (%)	24 (30.0%)	97 (37.7%)		0.160	17 (38.6%)	17 (38.6%)		0.000
Proximal, *n* (%)	51 (63.7%)	145 (56.4%)		−0.148	27 (61.4%)	26 (59.1%)		−0.046
Lesion length, mm	30.0 (20.0; 40.0)	25.0 (20.0; 40.0)	0.076	−0.110	35.0 (25.0; 40.0)	30.0 (25.0; 42.5)	0.859	0.176
Lumen diameter, mm	3.00 (2.50; 3.50)	2.75 (2.50; 3.00)	0.001	−0.544	3.00 (2.50; 3.00)	2.88 (2.50; 3.00)	0.655	−0.033
Calcification			<0.001				1.000	
Extreme, *n* (%)	30 (37.5%)	43 (16.7%)		−0.556	15 (34.1%)	16 (36.4%)		0.061
Severe, *n* (%)	24 (30.0%)	119 (46.3%)		0.327	11 (25.0%)	11 (25.0%)		0.000
Slight, *n* (%)	20 (25.0%)	87 (33.9%)		0.187	14 (31.8%)	14 (31.8%)		0.000
No, *n* (%)	6 (7.50%)	8 (3.11%)		−0.253	4 (9.09%)	3 (6.82%)		−0.131

(Continued)

TABLE 1 | Continued

Variable	Before matching				After matching			
	DRA ($n = 80$)	**PRA ($n = 257$)**	***P*-value**	**SMD***	**DRA ($n = 44$)**	**PRA ($n = 44$)**	***P*-value**	**SMD***
Tortuosity			<0.001				0.890	
Extreme, *n* (%)	5 (6.25%)	7 (2.72%)		−0.217	2 (4.55%)	2 (4.55%)		0.000
Severe, *n* (%)	21 (26.2%)	23 (8.95%)		−0.606	8 (18.2%)	11 (25.0%)		0.239
Slight, *n* (%)	34 (42.5%)	198 (77.0%)		0.821	23 (52.3%)	20 (45.5%)		−0.162
No, *n* (%)	20 (25.0%)	29 (11.3%)		−0.434	11 (25.0%)	11 (25.0%)		0.000
Bifurcation, *n* (%)	36 (45.0%)	34 (13.2%)	<0.001	−0.938	14 (31.8%)	13 (29.5%)	1.000	−0.067
JCTO score			0.080	−0.294			0.433	−0.059
0, *n* (%)	0 (0.00%)	4 (1.56%)			0 (0.00%)	0 (0.00%)		
1, *n* (%)	8 (10.0%)	30 (11.7%)			3 (6.82%)	3 (6.82%)		
2, *n* (%)	37 (46.2%)	134 (52.1%)			20 (45.5%)	18 (40.9%)		
3, *n* (%)	25 (31.2%)	79 (30.7%)			15 (34.1%)	21 (47.7%)		
4, *n* (%)	10 (12.5%)	10 (3.89%)			6 (13.6%)	2 (4.55%)		
Blunt entry shape, *n* (%)	54 (67.5%)	121 (47.1%)	0.002	−0.409	26 (59.1%)	27 (61.4%)	1.000	0.046
Occlusion length >20 mm, *n* (%)	61 (76.2%)	179 (69.6%)	0.319	−0.144	37 (84.1%)	40 (90.9%)	0.519	0.148
Right coronary dominance, *n* (%)	76 (95.0%)	228 (88.7%)	0.151	−0.199	41 (93.2%)	40 (90.9%)	1.000	−0.072

AHT, arterial hypertension; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CVD, cerebrovascular disease; Cx, circumflex coronary artery; DRA, distal radial access; LAD, left anterior descending coronary artery; MI, myocardial infarction; PAD, peripheral artery disease; PRA, proximal radial access; RCA, right coronary artery; SMD, standardized mean difference.
**PRA minus DRA.*

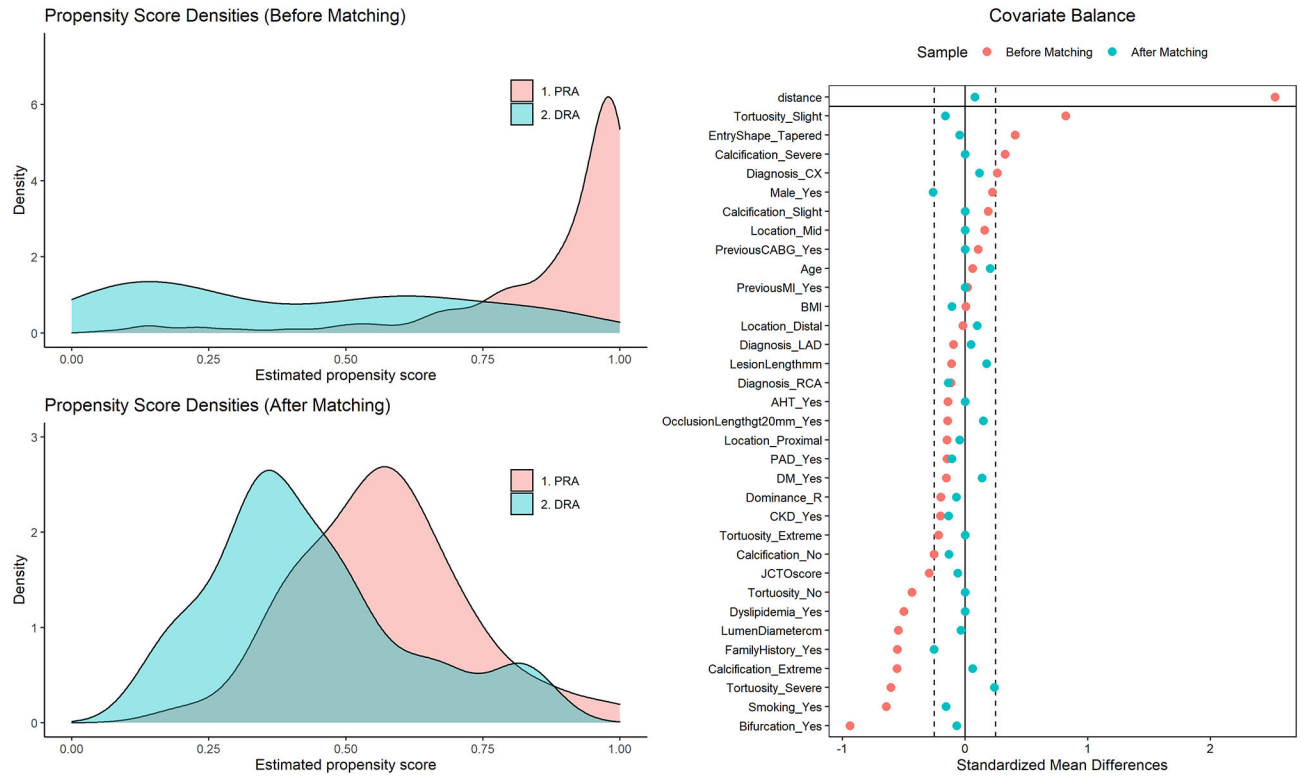

FIGURE 1 | Validation of propensity score matching. (Left) Density of propensity scores for cases in the PRA and the DRA group before and after matching. The propensity scores represent the probability for each patient of belonging to the PRA group. The overlapping area represents patients with similar propensity scores available for close matches. (Right) "Love Plot" illustrating the covariate balance created in the propensity score matched sample. The standardized mean differences comparing covariates between the PRA and DRA groups are shown both in the original sample and after propensity score matching. While there were relevant differences (>25%) in covariates between both groups in the original sample, after matching all are <25%, indicating balance between cases in the PRA and DRA groups for all relevant covariates. DRA, distal radial access; PRA, proximal radial access.

in 2 cases (0.7%) with prior pre-existing RAO at the ipsilateral side, by resolving the ROA by means of angioplasty first.

Our findings are clinically important for several reasons. First, as mentioned earlier, CTO PCI often requires dual arterial access. From the operator's point of view, it is ergonomically easier when using the left radial artery; the arm can be then positioned over the patient's right groin without the need of maintaining a supine position, rather than having to bend over the patient which can become wearisome during long procedures in obese patients. At the same time, it allows a safer distance between the operator and the radiation source. The use of DRA is also more comfortable for the patient as the arm can be put in a neutral position without wrist rotation and no extra support devices are required in cases of left forearm use (**Figure 3**). This may be proven important for patients with orthopedic problems, including frozen shoulders (17). The hemostasis time is shorter in comparison to traditional radial approach as the artery at this level has a smaller diameter and is easily compressible. Furthermore, the patient is able to bend the wrist with no restriction after the procedure, thus making it better tolerated. In a similar population, patients have reported a higher rate of satisfaction post recovery after DRA use in comparison to the conventional radial access (18).

Second, in terms of radioprotection, the lower DAP with DRA in our study (a 34% reduction compared to PRA in matched analyses) is encouraging. In this regard, DRA may help to effectively address one of the main disadvantages of traditional radial access compared to transfemoral access, i.e., greater radiation exposure (19, 20). this imbalance could be equated with DRA. Ultimately, bringing both hands over the patient's pelvis is equivalent to the transfemoral positioning (2).

Third, although statistical significance could not be determined given sample size limitations, the current study suggested a 1.47–2.27% absolute risk reduction of RAO with DRA. Several mechanisms, including vascular injury, blood flow reduction, and thrombosis, have been linked to the occurrence of RAO (21). The 2019 international consensus paper on "Best Practices for the Prevention of Radial Artery Occlusion After Transradial Diagnostic Angiography and Intervention" recommends a 5% RAO rate threshold and proposes DRA as a potential approach to avoid RAO given its anatomic basis and physiological rationale (22). Notably, both groups in our study

TABLE 2 | Intraprocedural characteristics.

Variable	Before matching			After matching		
	DRA ($n = 80$)	PRA ($n = 257$)	*P*-value	DRA ($n = 44$)	PRA ($n = 44$)	*P*-value
CTO technique			<0.001			0.001
Anterograde dissection reentry, *n* (%)	22 (27.8%)	10 (3.89%)		15 (34.9%)	3 (6.82%)	
Anterograde wire escalation, *n* (%)	55 (69.6%)	218 (84.8%)		26 (60.5%)	36 (81.8%)	
Retrograde dissection reentry, *n* (%)	1 (1.27%)	10 (3.89%)		1 (2.33%)	0 (0.00%)	
Retrograde wire escalation, *n* (%)	1 (1.27%)	19 (7.39%)		1 (2.33%)	5 (11.4%)	
Rotational atherectomy, *n* (%)	9 (11.2%)	23 (8.98%)	0.701	3 (6.82%)	5 (11.6%)	0.484
Dual access, *n* (%)	46 (57.5%)	130 (50.6%)	0.340	26 (59.1%)	25 (56.8%)	1.000
Antegrade approach used, *n* (%)	78 (97.5%)	252 (98.1%)	0.672	42 (95.5%)	44 (100%)	0.494
Retrograde approach used, *n* (%)	6 (7.50%)	13 (5.06%)	0.410	6 (13.6%)	2 (4.55%)	0.266
IVUS, *n* (%)	13 (16.2%)	19 (7.39%)	0.032	7 (15.9%)	2 (4.55%)	0.157
Number of guidewires	3.00 (2.00; 5.00)	2.00 (1.00; 4.00)	0.001	3.00 (2.00; 6.00)	2.50 (1.75; 3.00)	0.003
Number of balloons	3.00 (2.00; 4.00)	3.00 (2.00; 4.00)	0.431	3.00 (2.00; 4.25)	3.00 (2.00; 4.00)	0.268
Stent length, mm	56.5 (37.5; 82.0)	40.0 (22.0; 64.0)	<0.001	59.0 (41.5; 79.8)	46.0 (28.0; 68.8)	0.071
Contrast volume, ml	120 (90.0; 190)	146 (100; 218)	0.045	142 (100; 205)	157 (119; 212)	0.447
Procedure time, min	55.0 (33.8; 87.0)	38.5 (20.0; 64.0)	<0.001	70.0 (40.0; 104)	27.5 (15.0; 69.2)	<0.001
DAP, mGy × cm²	928 (400; 1500)	1,300 (593; 2787)	<0.001	1,000 (445; 1500)	1,515 (668; 3097)	0.018
Fluoroscopy time, min	27.5 (10.0; 52.0)	19.0 (10.0; 31.0)	0.042	34.5 (13.0; 61.2)	21.5 (14.8; 32.8)	0.064

CTO, chronic total obstruction; DRA, distal radial access; IVUS, intravascular ultrasound; PRA, proximal radial access; DAP, dose area product.

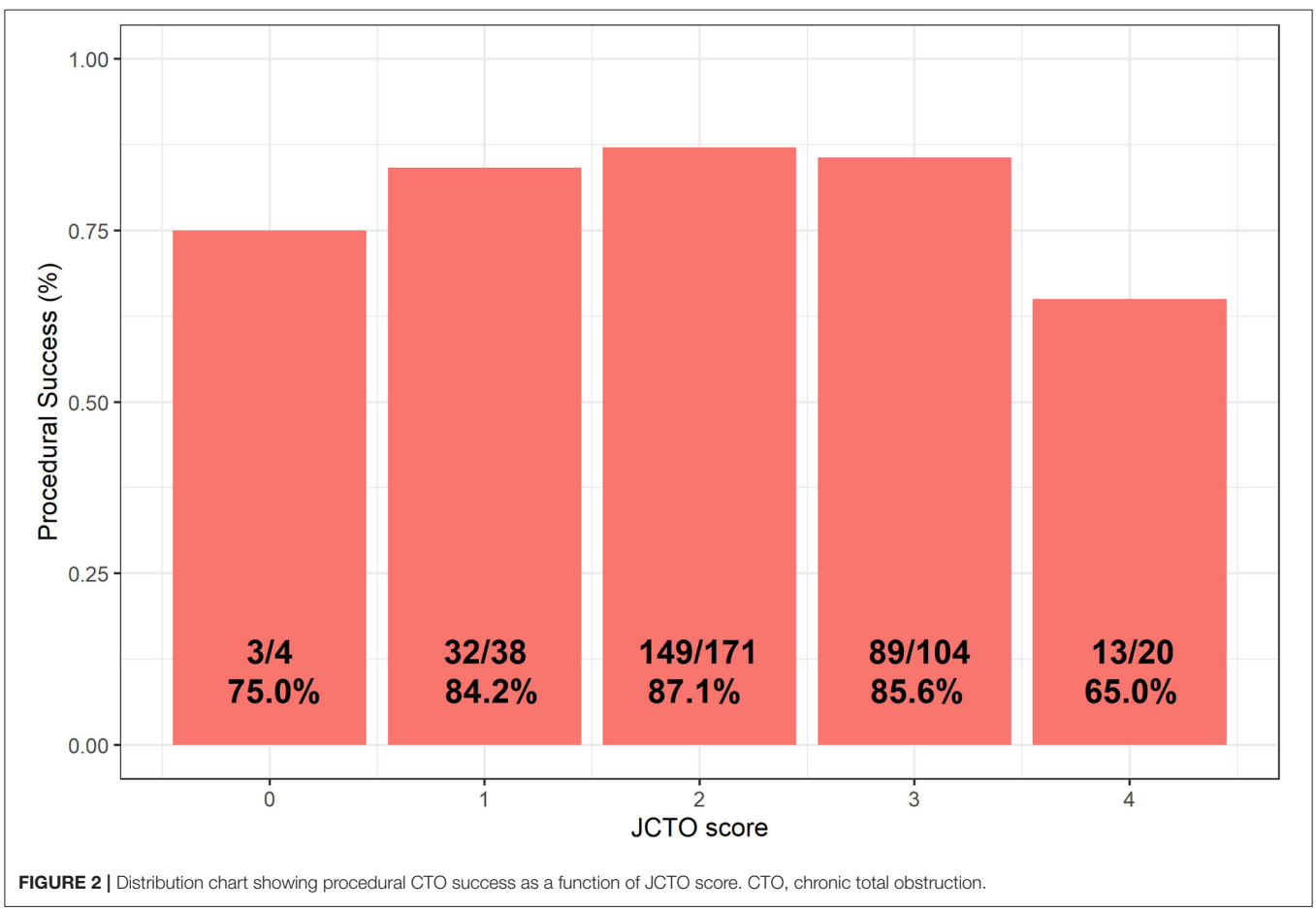

FIGURE 2 | Distribution chart showing procedural CTO success as a function of JCTO score. CTO, chronic total obstruction.

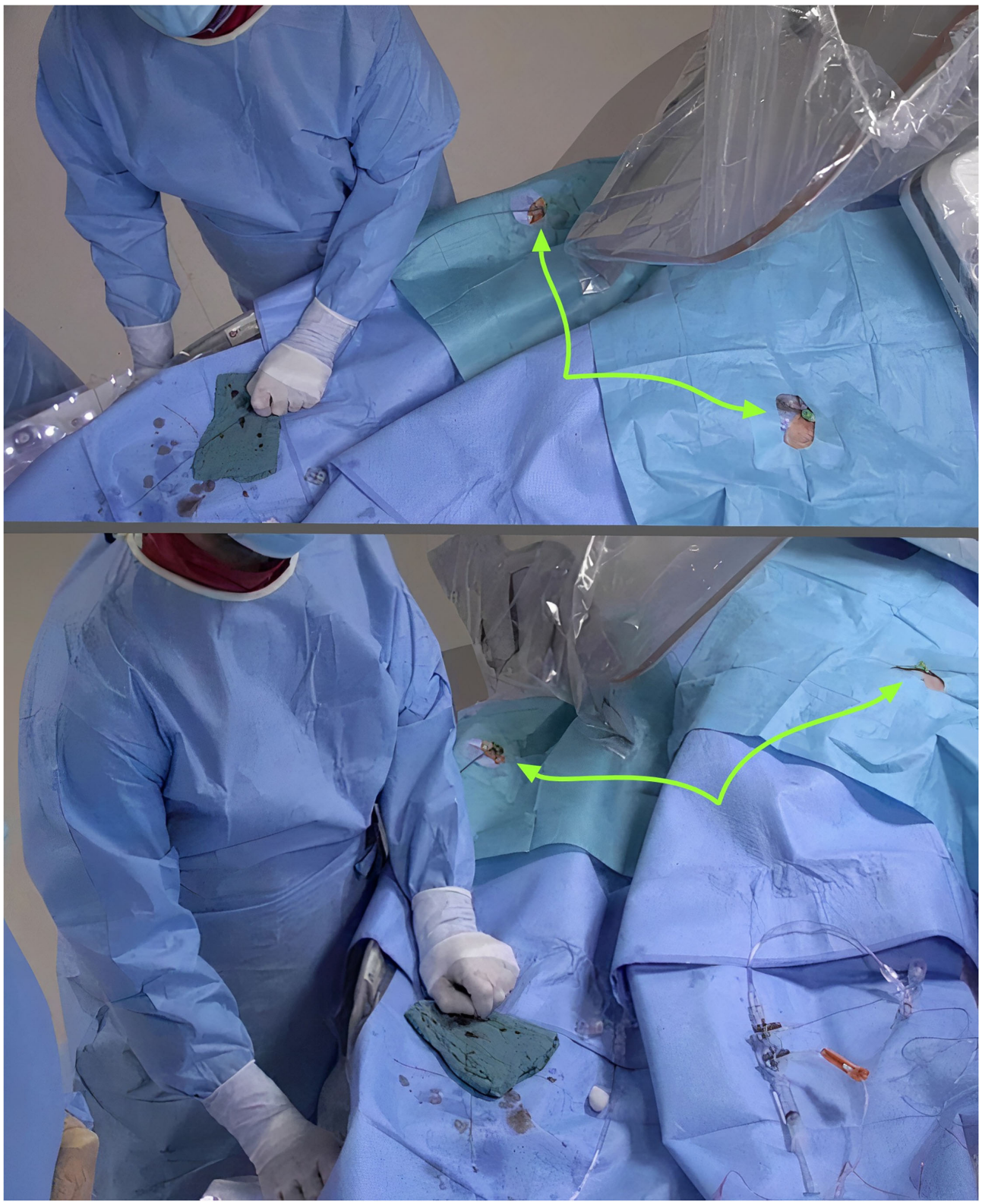

FIGURE 3 | Improved ergonomics during dual distal radial (arrows) in CTO PCI.

TABLE 3 | Procedural and long-term outcomes.

Variable	Before matching			After matching		
	DRA ($n = 80$)	PRA ($n = 257$)	*P*-value	DRA ($n = 44$)	PRA ($n = 44$)	*P*-value
Procedural outcomes						
Access site complications			0.820			1.000
Large hematoma, *n* (%)	0 (0.00%)	2 (0.78%)	1.000	0 (0.00%)	0 (0.00%)	1.000
Small hematoma, *n* (%)	2 (2.50%)	4 (1.56%)	0.577	2 (4.55%)	1 (2.27%)	0.557
RAO, *n* (%)	1 (1.25%)	7 (2.72%)	0.450	0 (0.00%)	1 (2.27%)	1.000
Bleeding, *n* (%)	0 (0.00%)	0 (0.00%)	1.000	0 (0.00%)	0 (0.00%)	1.000
None, *n* (%)	77 (96.2%)	244 (94.9%)	0.631	42 (95.5%)	42 (95.5%)	1.000
Any complications*, *n* (%)	7 (8.75%)	10 (3.89%)	0.138	3 (6.82%)	3 (6.82%)	1.000
Procedural success, *n* (%)	73 (91.2%)	213 (82.9%)	0.100	38 (86.4%)	39 (88.6%)	1.000
Clinical success, *n* (%)	70 (87.5%)	167 (79.5%)	0.161	37 (84.1%)	32 (78.0%)	0.664
Hospital length of stay, days	2.00 (2.00; 3.00)	3.00 (2.00; 4.00)	0.006	2.50 (2.00; 3.25)	3.00 (2.00; 3.25)	0.412
Long-term outcomes						
30-day MACCE	3 (3.75%)	11 (4.28%)	1.000	2 (4.55%)	2 (4.55%)	1.000
6-months MACCE	7 (8.75%)	31 (12.1%)	0.538	4 (9.09%)	4 (9.09%)	1.000
12-months MACCE	8 (10.0%)	52 (20.2%)	0.055	4 (9.09%)	8 (18.2%)	0.351
12-months redo PCI	6 (7.50%)	27 (10.5%)	0.566	5 (11.4%)	5 (11.4%)	1.000
12-months target lesion revascularization	3 (3.75%)	12 (4.67%)	1.000	1 (2.27%)	4 (9.09%)	0.360
12-months stent thrombosis	1 (1.25%)	1 (0.39%)	0.419	1 (2.27%)	0 (0.00%)	1.000
12-months MI	2 (2.50%)	3 (1.17%)	0.340	1 (2.27%)	0 (0.00%)	1.000
12-months TIA or stroke	2 (2.50%)	2 (0.78%)	0.240	1 (2.27%)	0 (0.00%)	1.000
12-months death	0 (0.00%)	9 (3.50%)	0.122	44 (100%)	44 (100%)	1.000

DRA, distal radial access; RAO, radial artery occlusion; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PRA, proximal radial access; TIA, transient ischemic attack.

**These included cardiac decompensation, coronary dissection, coronary perforation, and pericardial fluid/tamponade.*

fell below this limit. Moreover, in the context of using large 7-French sheaths in CTO PCI, the risk of RAO has still dropped. Of course, operator's expertise is equally important to improve procedural success and diminish crossover rate among patients undergoing DRA. Issues such as the appropriate choice of sheath and catheter sizes to minimize arterial wall injury, adequate procedural anticoagulation, non-occlusive techniques, and adequate hemostasis (e.g., "patent hemostasis") are important steps to further improve this technique (23). In one of our previous reports, we found that it takes at least 150 cases to reach the learning curve and maintain a consistently high success rate of >94.0% (2). These findings are also consistent with a Korean report (24).

All the above mentioned aspects have meaningful implications in the CTO procedures. Maintaining a radial-only procedure, efficiently using 7-French catheters, and working comfortably away from the radiation source indeed represent important advances for the CTO community. Nonetheless, appropriate size matching between the catheter and the radial artery diameter may theoretically introduce another challenge when pursuing DRA. In a large registry of over 1,000 patients, the mean diameter in the distal segment was of 2.3 ± 0.5 mm, while the outer diameter of the 7-French Glidesheath is 2.79 mm, and that of the 6-F is 2.46 mm (2). Another study found even smaller diameters (2.01 ± 0.53 mm, 19% smaller than the proximal segment) (25). Nonetheless, none of our patients required crossover due to severe arterial spasm and only one patient developed distal RAO (1.25%). It should be noted, however, that our internal protocol specifies that the DRA should be punctured under guidance of duplex ultrasound. The planning of the procedure by means of pre- and peri-procedural ultrasound certainly helped in this regard. Thus, our data provide further insight into the impressive versatility of the radial artery wall, which can accommodate devices larger than the nominal size regardless of age, body weight and vessel anatomy (7, 26, 27).

Finally, in terms of broader implications, the clinical benefits of DRA over conventional PRA during long-term follow-up are still to be determined. One of the key goals of future research should be to investigate whether this access site may deliver added benefits on "hard" clinical endpoints while maintaining the same efficacy as traditional PRA. Our experience offers a promising first window into these potential benefits.

In terms of the CTO PCI rationale, the authors wish to acknowledge several benefits of such a procedure. It was shown that the presence of a coronary CTO was associated with increased rates of all-cause mortality at midterm follow-up and the composite endpoint of cardiac death at 24 h, recurrent ventricular tachyarrhythmias, and appropriate ICD therapies at 18 months (9). Viable myocardium supplied by a CTO is a persistently ischemic zone (28). Moreover, with respect to complete revascularization, a trend was noted toward better in-hospital/30-day mortality and 6-month health status in patients

with a lower residual Syntax Score (8, 10, 29). This is of particular importance when a patient with a coronary CTO suffers an acute MI in the donor vessel ("double jeopardy" effect). However, improving patient symptoms caused by myocardial ischemia (angina, exertional dyspnea, and sometimes fatigue) despite optimal medical therapy remains the only benefit of CTO-PCI that has been demonstrated in randomized, controlled trials and should therefore currently be the primary indication for offering this procedure to patients (30).

There are several limitations of our study that are worthy of mentioning. First, the retrospective nature of our study is subject to confounding; nevertheless, all included patients were consecutive patients and propensity score matching was performed to balance any clinically meaningful confounders between the two groups. Second, a specific protocol for ultrasound-guided puncture and transradial band air removal to target faster hemostasis was introduced for all DRA cases, while this protocol was not employed for conventional PRA. The potential impact of this protocol can thus not entirely be separated from the observed effect of the approach (DRA vs. PRA). Third, the data were only analyzed based on intention-to-treat whilst the rate of DRA failure and crossover percentage were not registered. We know that the lumen of the radial artery is slightly smaller at the anatomical snuffbox and that inserting a sheath can be more challenging, especially in women (31). Therefore, beyond patient discomfort and increased radiation exposure, transradial access crossover may entail delayed revascularization and worse outcomes compared with successful radial access in acute coronary syndrome patients and abolishes the bleeding benefit offered by radial access over femoral access (32, 33). However, in the setting of CTO, this clinical impact is not of such significant importance.

CONCLUSION

Using DRA for complex CTO interventions is safe, feasible, lowers radiation dose and makes dual radial access more achievable. At the same time, there was no signal of increased risk of periprocedural or long-term adverse outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Hungarian State Ethical Review (OGYÉI/50275/2018). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AA, KK, BM, DB, IÉ, GB, RP, and ZR contributed to the conception and design of the study. AA and JV organized the database. AA wrote the first draft of the manuscript. TS, DO, JV, and ZR wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Cost-Effectiveness in Patients Undergoing Revascularization of Chronic Total Occluded Coronary Arteries—A Cohort Study

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Background: Revascularization of patients with chronic total occluded coronary arteries (CTO) is recommended if they have symptoms despite medical treatment. The cost-effectiveness of treatment with percutaneous coronary intervention (PCI) was investigated in this cohort study.

Materials and Methods: The study was designed as a cohort study enrolling all patients undergoing PCI for a CTO in the Central Region of Denmark and recorded in the EUROCTO database. Major adverse cardio- and cerebrovascular events (MACCE) and admissions for cardiac symptoms were collected in the Western Denmark Heart Registry and through medical Journal Audits. Exposure was defined as successful revascularization of all CTO lesions compared with having one or more remaining CTOs after PCI attempt(s). Cost-effectiveness was evaluated as the net benefit (NB) at the patient level 3 years after treatment and through cost-effectiveness planes. The cost was defined as the cumulative cost of the index procedure and admissions due to MACCE and cardiac symptoms. Effectiveness was defined as the difference in MACCE for the primary analysis and the difference in death and symptomatic admissions for the secondary.

Results: Between 2009 and 2019, 441 patients with $\geq$ 3 years of follow-up were treated with PCI for at least one CTO lesion (342 in the successful arm and 99 in the unsuccessful arm). The technical success rate was 85.4%. In total, 155 MACCE and 184 symptomatic admissions occurred in the follow-up period. The mean total cost was EUR 11.719 (11.034; 12.406) in the successful group vs. EUR 13.565 (11.899; 15,231) (p = 0.02) in the unsuccessful group. Net-benefit was EUR 1.846 (64; 3,627) after successful revascularization for MACCE. The adjusted analysis found an NB of EUR 1,481 (–118; 3,079). Bootstrap estimates showed cost-effectiveness planes in favor of successful revascularization.

Conclusion: Patients fully revascularized for all CTO lesions had a more cost-efficient treatment. However, results need confirmation in a randomized controlled trial due to the risk of residual confounding after adjustment.

Keywords: chronic total occlusion (CTO), chronic coronary syndrome (CCS), ischemic heart disease, complex PCI, coronary artery disease, percutaneous coronary intervention (PCI)

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INTRODUCTION

Revascularization of patients with chronic total occluded coronary artery (CTO) lesions is recommended in patients with angina resistant to medical treatment and/or large ischemic burden (1). The decision to perform percutaneous coronary intervention (PCI) should always balance the risks and benefits. Adequately powered trials have shown an improvement in the quality of life after PCI (2) and prognostic benefit has been indicated in observational studies (3). However, a recent meta-analysis of prospective randomized trials did not confirm an improvement in prognosis (4). The complexity of CTO lesions is leading to increasing procedural complication rates (5, 6). Due to an increasing burden of coronary heart disease worldwide (7), economic considerations need to be taken into account when selecting a treatment strategy. In the ORBITA trial, the investigators found that the cost per gained quality-adjusted life-years for a cohort of 1,000 patients was £ 90,218 (8). In a CTO population, the cost-effectiveness of PCI treatment is of particular interest due to more and longer procedures with the usage of several dedicated utensils (9). However, patients with untreated CTO lesions often have more symptoms and a more complex disease profile (10, 11) and therefore probably more hospital admissions. The current study aimed to investigate the difference in cost for the index procedure and subsequent admissions due to heart disease in patients who had been successful or unsuccessfully treated for their CTO lesions 3 years after the index procedure. The hypothesis was that patients who were successfully treated for their CTO had a more cost-effective treatment at follow-up. The following article is reported according to Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.

MATERIALS AND METHODS

Design and Study Population

The current study was conducted as an observational cohort study. The exposure of interest was successful vs. unsuccessful revascularization of all CTO lesions. Patients were eligible for enrollment if they were registered in the EUROCTO database, underwent CTO PCI at Aarhus University Hospital, and were citizens of the Central Region of Denmark at the time of event audit. All consecutive patients enrolled in the EUROCTO database who were treated at Aarhus University Hospital from 1 January 2009 to 31 December 2019 were entered into the study registry and merged with follow-up data on cardiac events. All patients who had completed 3 years follow-up were enrolled in the present study. During the enrollment period, Aarhus University Hospital was the only PCI center in the entire Central Region of Denmark (1.3 million inhabitants) performing approximately 100–120 CTO PCI cases a year. Non-CTO lesions were treated according to guidelines if technically feasible and safe, before treating CTO-lesions.

Exposure

Successful treatment was defined as no persisting CTO-lesions after an attempt to open all CTO's. An attempt to open a CTO could include one or more staged procedures at the operator's discretion. Unsuccessful was defined as failure to open index CTO and/or other bystander CTO-lesions after the final attempt. Bystander CTO-lesions were left untreated by the decision of the treating heart team or physician.

Outcome

All major adverse cardio- and cerebrovascular events (MACCE) during the index hospitalization or requiring hospital admission were registered through the entire follow-up period of 3 years. MACCE included all-cause death, myocardial infarction, stroke, target vessel failure, and decompensated chronic heart failure. Furthermore, all subsequent acute admissions where patients were discharged with an ICD-diagnosis describing that they had been admitted to observation for acute coronary syndrome (ACS) were registered. Outcome data were collected through medical record audits and from the Western Denmark Heart Registry (WDH) (12). All entries into the EUROCTO database, WDH, and medical records are performed consecutively in clinical practice at the time of procedure or event, meaning that data entry was prospective for all admissions and out-patient visits at all five acute hospitals in the Central Region of Denmark. Event audit was performed between 1 February 2020 and 1 December 2020. Events were adjudicated by Naja Stausholm Winther and Emil Nielsen Holck.

The primary endpoint in the current study was cumulative cost (net benefit (NB)) at patient-level 3 years after index CTO treatment between the successful (no remaining CTO's) and unsuccessful (one or more remaining CTO's) revascularization. The secondary endpoints were the difference in procedural cost and the cost per patient-year of follow-up. Furthermore, the incremental cost-effectiveness ratio (ICER) was calculated to assess the cost-effectiveness and plotted in a cost-effectiveness plane (CE-plane). The CE-planes were made with three effectiveness parameters: risk difference at 3 years for (1) death, (2) MACCE, and (3) suspected ACS. Cost calculation in the primary analysis was calculated using a Danish nationwide tool to group patients in 958 (In 2021) different cost categories (DRG) that have been used since 2004 to financially manage the entire public and private healthcare sector. The "DRG-rate" includes the average total cost for an admission in a specific disease category that year. The grouping for a complex PCI procedure was 05MP38 in 2021, with an average cost of EUR 5,037.72. The cost for index CTO treatment was calculated as the number of procedures multiplied by the 2021 DRG-rate added to the total cost of dedicated CTO equipment used at the index procedures and the DRG-rate of in-hospital complications, in case of complications. After discharge, the cumulative cost of all admissions due to cardiac disease or cardiac symptoms was calculated by adding the DRG-rate of these admissions. The primary analysis used the cumulation of costs from index procedure and event costs.

Statistics

Continuous variables are given as means ± SD or medians [interquartile range, IQR] depending on distribution, while frequencies are represented by *n* (%). No statistical testing is performed for descriptive statistics due to adherence to the

STROBE statement (13). The confidence interval (*CI*) of the main endpoint, NB, is calculated by non-parametric bootstrapping of the observed values. Survival curves for cumulative incidence of death, MACCE, and suspected ACS are plotted using Kaplan–Meier estimates for death and Nielson-Aalen estimates accounting for multiple events for MACCE and suspected ACS. ICER was calculated with both the mean and median cost difference in the numerator and the risk difference at 3 years in the denominator. In addition, 5,000 non-parametric bootstrap estimates for cost-effectiveness pairs were calculated and plotted in the CE-plane and elliptic 95% *CI*s were calculated using the lower 2.5% and upper 97.5% limits of the bootstrap estimates. Adjusted analysis of NB was performed with multiple linear regression, adjusting for age, sex, left ventricular ejection fraction (LVEF), three-vessel-disease, and chronic kidney disease since previous analysis have found these to be independent predictors of MACCE in the investigated cohort after performing a backward elimination model. A sensitivity analysis investigating bootstrapping of median values in the CE-plane and the difference in NB in successful vs. unsuccessful revascularization of the target CTO only was performed. The sample size was the total number of possible enrollments during the study period.

RESULTS

Baseline Characteristics

The main population in the current study consists of 441 patients with residence in the central region of Denmark. Of these, 342 patients had all CTOs opened (successful group) and 99 had one or more remaining CTO's (unsuccessful group). In total, 622 patients were identified in the EUROCTO database. The reasons for not being included in the primary analysis were mostly not residing in the Central Region of Denmark and < 3 years of follow-up (**Figure 1**). Patients with successful recanalization had an overall lower frequency of risk factors compared to patients with remaining CTOs. More patients had three-vessel disease, a lower LVEF, and a higher s-creatinine in the unsuccessful group. The Charlson comorbidity index was 3.3 ± 1.8 in the successful vs. 4.0 ± 1.7 in the unsuccessful group (**Table 1**).

Procedural Characteristics

The mean number of attempts were 1.4 ± 0.6 in the successful group vs. 1.5 ± 0.8 in the unsuccessful group, and the mean number of persisting CTO's were 1.1 ± 0.3 in the unsuccessful group. The overall technical success rate (i.e., successful index CTO-lesion treatment) for the entire cohort was 85.4%. Fewer balloons and stents were used in the unsuccessful group. **Table 2** shows the CTO equipment used for cost calculations. In the successful arm, 6.7% of patients had an in-hospital complication requiring additional treatment, and for the unsuccessful group this fraction was 7.1%, primarily driven by a large fraction of acute renal failure (3.8 vs. 4.0%) (**Supplementary Table 1**).

Events

In the successful group, 8.2% of the patients died within 3 years compared with 14.1% in the unsuccessful group. About 21.3 and 38.4% of patients had at least one MACCE in the successful vs. unsuccessful group. In total, 155 MACCE events occurred, and 184 admissions due to suspected ACS occurred in the follow-up period with 24.3% of the patients in the successful group and 24.2% in the unsuccessful group having at least one event (**Table 3**). The Kaplan–Meier and Nelson–Aalen cumulative estimates are shown in **Figure 2**.

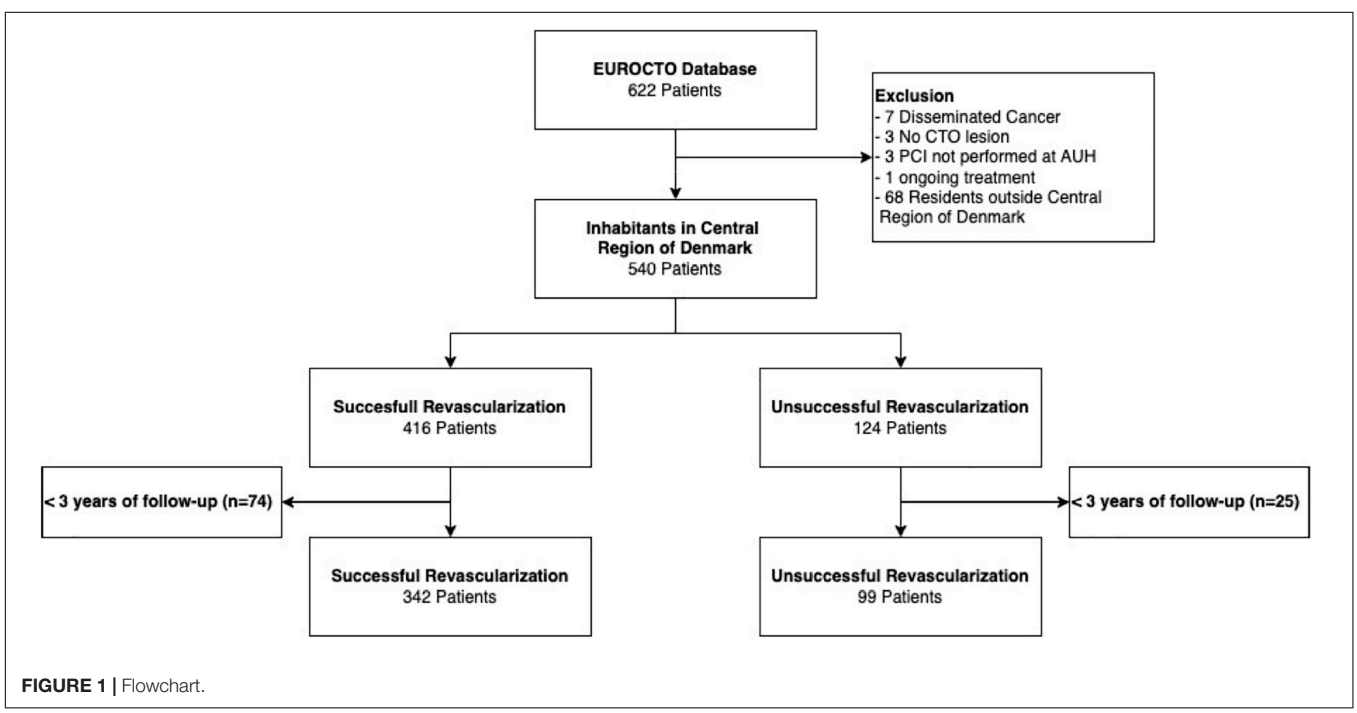

FIGURE 1 | Flowchart.

TABLE 1 | Baseline characteristics.

	Successful (*n* = 342)	Unsuccessful (*n* = 99)
Age	64.7 ± 10.8	67.8 ± 11.2
Sex	70 (20.5%)	19 (19.2%)
Familiar heart disease	147 (43.1%)	54 (54.5%)
Hypertension	209 (61.5%)	66 (67.3%)
Dyslipidemia	266 (78.0%)	82 (82.8%)
Peripheral disease	25 (7.4%)	11 (11.2%)
Diabetes mellitus		
Non-insulin dependent	60 (17.8%)	14 (14.4%)
Insulin dependent	22 (6.5%)	10 (10.3%)
BMI	28.4 ± 5.2	28.0 ± 4.6
Smoking		
Previous smoker	152 (46.8%)	54 (56.8%)
Active smoker	100 (30.8%)	17 (17.9%)
Previous CABG	51 (14.9%)	20 (20.2%)
Previous PCI	186 (54.4%)	63 (63.6%)
Previous MI	123 (36.0%)	39 (39.4%)
Left ventricular ejection fraction	52.8 ± 11.7	50.1 ± 12.3
Creatinine	93 ± 54	106 ± 92
Charlson comorbidity index	3.3 ± 1.8	4.0 ± 1.7
CCS class		
I	57 (16.7%)	24 (24.5%)
II	238 (69.6%)	50 (51.0%)
III	28 (8.2%)	15 (15.3%)
IV	4 (1.2%)	3 (3.1%)
Indication		
Chronic coronary syndrome	293 (85.7%)	81 (81.2%)
Acute coronary syndrome	39 (11.4%)	14 (14.1%)
Number of diseased vessels (including CTO)		
One-vessel	159 (46.5%)	20 (20.4%)
Two-vessel	112 (32.7%)	37 (37.8%)
Three-vessel	71 (20.8%)	41 (41.8%)
CTO vessel		
RCA	198 (57.9%)	46 (46.5%)
LAD	94 (27.5%)	25 (25.3%)
LCx	48 (14.0%)	28 (28.3%)
LM	2 (0.6%)	0 (0.0%)
JCTO score	3.1 ± 1.2	3.4 ± 1.0
Residual syntax	2.4 ± 9.3	15.5 ± 12.2

BMI, body mass index; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention, MI, myocardial infarction, CCS, Canadian cardiovascular society; CTO, chronic total occlusion; RCA, right coronary artery; LAD, left anterior descending; LCx, left circumflex; LM, left main. Numbers are given as n (%) or mean ± SD.

TABLE 2 | Procedural utensils and baseline medication.

	Successful (*n* = 342)	Unsuccessful (*n* = 99)
Procedural data		
Attempts	1.4 ± 0.6	1.5 ± 0.8
Number of persisting CTO's	NA	1.1 ± 0.3
Number of guidewires used	5.2 ± 3.8	5.8 ± 2.9
Number of balloons used	4.5 ± 2.8	3.1 ± 2.8
Numbers of stents placed	2.3 ± 4.3	1.2 ± 1.5
Total stent length	58.2 ± 33.9	30.3 ± 41.8
IVUS used	54 (15.8%)	8 (8.1%)
Number of microcatheters used	1.3 ± 0.9	1.2 ± 0.9
Rotablation used	9 (2.6%)	1 (1.0%)
Guide extension used	44 (12.9%)	11 (11.1%)
Procedure length (minutes)	83.2 ± 52.8	87.0 ± 50.5
Contrast used (mL)	182.6 ± 90.4	192.5 ± 92.8
Cumulative Air Kerma (mGy)	1,359 ± 1,413	1,552 ± 1,326
Dose area product (CGY*cm^2)	6,582 ± 8839.9	6,370 ± 9,005
Successful strategy		
Antegrade wiring	219 (64.0%)	NA
Antegrade dissection and re-entry	49 (14.3%)	NA
Retrograde wiring	15 (4.4%)	NA
Retrograde dissection and re-entry	56 (16.4%)	NA
Medication use		
Statins	319 (93.3%)	89 (89.9%)
Other lipid lowering drugs	14 (4.1%)	8 (8.1%)
B-receptor antagonists	248 (72.5%)	75 (75.8%)
ACE-inhibitors	132 (38.6%)	51 (51.5%)
ANG-II-antagonists	54 (15.8%)	13 (13.1%)
Ca^{2+}-receptor antagonists	96 (28.1%)	36 (36.4%)
Short-acting nitrates	134 (39.2%)	43 (43.4%)
Long-acting nitrates	116 (33.9%)	52 (52.5%)
Aspirine	331 (96.8%)	90 (90.9%)
P2Y12-inhibitors	339 (99.1%)	81 (81.8%)

CTO, chronic total occlusion; IVUS, intravascular ultrasound, ACE, angiotensin converting enzyme; ANG, angiotensine. Numbers are given as n (%) or mean ± SD.

Cost Analysis

The mean total cost was EUR 11.719 (11.034; 12.406) in the successful group vs. EUR 13.565 (11.899; 15,231) (p = 0.02) in the unsuccessful group, after 3 years of treatment. The primary endpoint of NB was EUR 1.846 (64; 3,627) (p = 0.02) after successful revascularization. Multiple linear regression adjusting for age, sex, LVEF, three-vessel-disease, and chronic kidney disease, which we have previously found to be possible confounders in the registry, found an adjusted estimate of NB to EUR 1,481 (–118; 3,079). The mean ICER for MACCE was –10.831 at 3 years (**Table 4**). Cost distribution in the two groups is plotted in **Figure 3**. CE-planes showed favorable cost with most bootstrap estimates lying in the south east (SE) quadrant for MACCE and death, and in the SE and south west (SW) quadrant for admission due to ACS (**Figure 2**). Furthermore, favorable effectiveness estimates were observed for death and MACCE in CE-plane analysis. For a cohort of 1,000 patients, annual event costs were EUR 226.635 [0; 1.00–1.586] in the successful group and EUR 395.730 [0; 1.16–3.942] in the unsuccessful group (p = 0.16).

Sensitivity Analysis

Procedural success is defined as successful revascularization of the index. CTO showed similar CE-plane results (**Supplementary Figure 1**). The CE-planes derived from median costs showed similar results as those reported in the study (**Supplementary Figure 2**).

DISCUSSION

The present cohort study investigating cost-effectiveness after PCI of patients with CTO found that patients who were fully revascularized for all CTO lesions had both a more effective but less expensive treatment. Adjusted analysis found a small reduction in NB after adjustment for age, sex, LVEF, three-vessel-disease, and chronic kidney disease. Improvement in NB was persistent for symptomatic admissions and deaths but not statistically significant. The main findings underline the importance of having a high success rate when embarking on a CTO program, since this may lead to a more efficient but also less costly outcome for the patients.

The mean index cost was EUR 9.429 ± 4.006 and 10.015 ± 4.538, respectively, in the two groups. These numbers are comparable, yet a bit lower, than those previously found in the OPEN-CTO registry, where the overall index hospitalization cost was EUR 15.091 (converted from 17.048 USD in the original article) (9). Additionally, when considering the findings in the current study cover 1.4 ± 0.6 and 1.5 ± 0.8 procedures. This is probably due to the fact that the costs in the current study are based on average costs for PCI in Denmark, as well as the fact that healthcare cost rates are more expensive in the United States than in Denmark (14). The lower costs are also supported by a *post hoc* analysis using Markov modeling of the FACTOR trial where the index CTO treatment was EUR 6,639 ± 3,249 (15). In the present study, the increased cost of CTO PCI compared with non-CTO PCI were corrected by adding the cost of the utensils used at the procedure, since these are not incorporated into the national "DRG" rate. This is supported by the findings of Karmpaliotis and colleagues who found that the total cost is higher in patients treated with PCI for a CTO lesion compared with non-CTO lesions (16).

TABLE 3 | Events 3 years after inclusion.

	Successful *n* = 342		Unsuccessful *n* = 99	
	Events	**Patients with atleast one event**	**Events**	**Patients with atleast one event**
MACCE	103	73 (21.3%)	52	38 (38.4%)
Death		28 (8.2%)		14 (14.1%)
Myocardial infarction	15	14 (4.1%)	7	7 (7.1%)
Stroke	5	5 (1.5%)	3	2 (2.0%)
Hospitalization for heart failure	22	16 (4.7%)	9	8 (8.1%)
Target vessel revascularization	33	27 (7.9%)	19	16 (16.1%)
Symptomatic admission				
Observation for MI	145	83 (24.3%)	39	24 (24.2%)
In hospital complications	30	23 (6.7%)	10	7 (7.1%)

MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction. Numbers are given as n (%).

The present study is the first study to investigate the long-term cost-efficiency of patients with CTO undergoing PCI. However, it is important to underline that the findings do not support if revascularization is preferable compared with optimal medical therapy as investigated in the ORBITA cost benefit sub study (8). All patients enrolled in the current analysis had clinical indication for revascularization. Therefore, the results indicate that to improve the cost-effectiveness of revascularization, it is important to have high success rate to both improve prognosis and lower average costs. This underlines the importance of having a dedicated CTO program with high volume operators to increase the success rate as observed by Young and colleagues (17). However, as we have seen with several prediction models, operator expertise is not always sufficient in highly complex lesions (18), and therefore, it is also important to point out that preprocedural planning and especially abstaining from or referral of a complex CTO case is important for both to decrease the expenses on the healthcare system and also improve the success rate for complex cases. In low volume sites, very low success rates of < 50% are observed (19). Therefore, we argue that the interpretation of the data in the present study underlines the global consensus reached by CTO-operators from 50 countries that CTO-operators must be able to handle many different techniques and scenarios to optimize the success rate (20). A collection of CTO procedures at fewer sites will probably facilitate a higher success rate without an increase in complication rate (17, 19). The present study did not investigate if a more aggressive technique was beneficial, and the treating physicians must always outweigh the potential complications and benefits. Therefore, it is important to assure the indication (OMT resistant symptoms and reversible ischemia) before embarking on CTO-PCI. By extrapolating the NB in the current study, an increase in success rate of 10% in a cohort of 1,000 patients would decrease the cost of EUR 198.465. However, these data are merely hypothesis generating and must be confirmed in a prospective randomized trial. Success rate in the current registry is comparable with other similar registries, such as PROGRESS-CTO, OPEN-CTO, RECHARGE registry, EUROCTO-registry, and jCTO registry with success rates ranging from 85 to 89% (20). Furthermore, a high jCTO score was observed in the current study (3.1 ± 1.2 and 3.4 ± 1.0). A recent external validation of the jCTO score found that lesions with jCTO scores of 3 have a predicted success rate of 73.3% and an observed success rate of 72.0% (18). We acknowledge that even higher success rates may be attainable by selecting cases with less severe complexity and by future improvement of techniques.

Patients in the current study are true all-comers since we investigated all patients who underwent CTO PCI at AUH and registered in the EUROCTO database in a 10-year period. Patient characteristics are comparable to *all* patients diagnosed with a CTO in Sweden between 2005 and 2012, though a lower frequency of patients with three vessel disease was observed in the successful arm (11). It is worth mentioning that patients enrolled in prospective trials are less diseased than what was observed in our cohort (2, 21). Despite being comparable, differences between the groups in the study exists, and therefore, adjusting for clinical

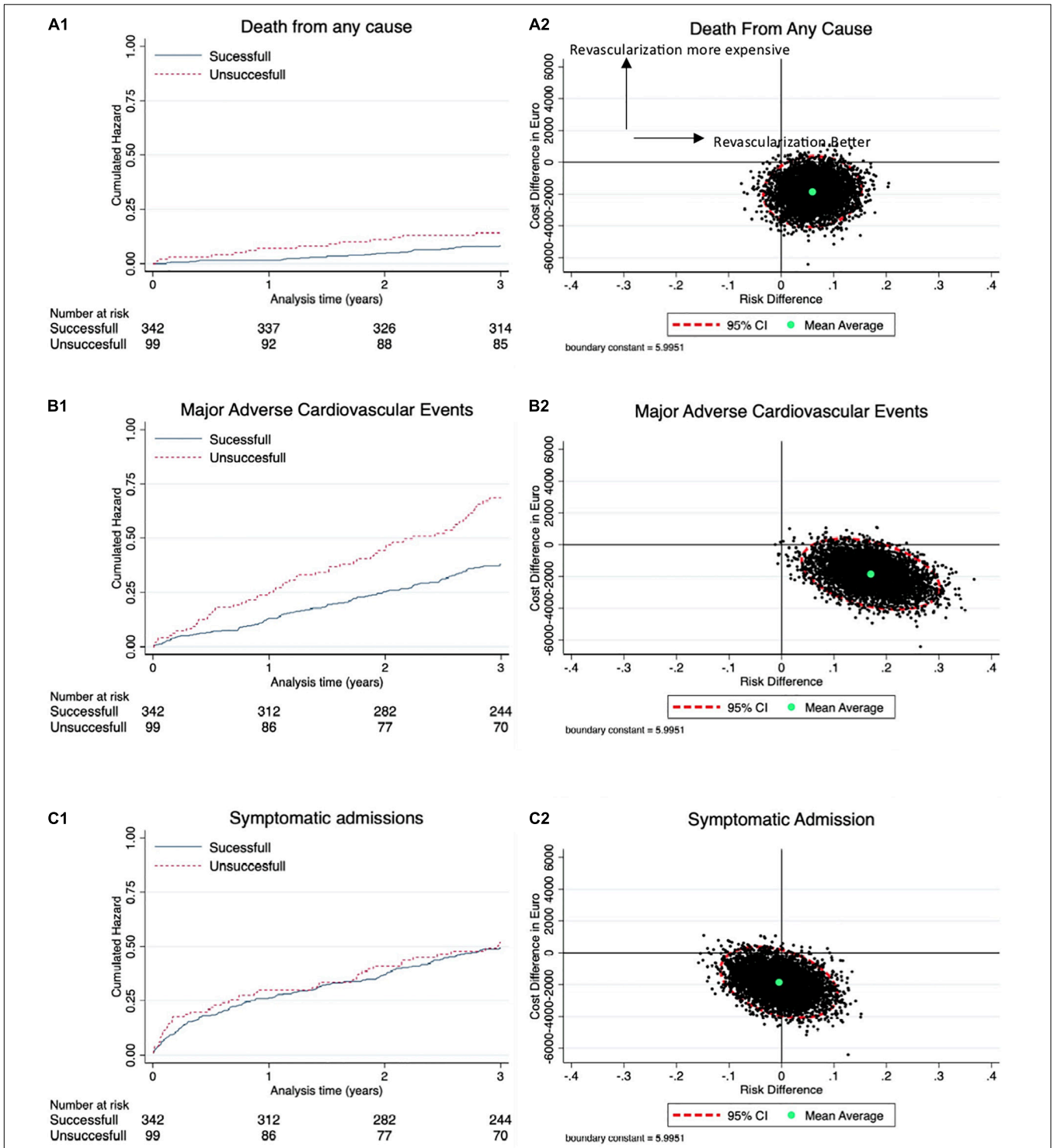

FIGURE 2 | Cost effectiveness. **(A1)** Kaplan–Meier curves showing difference in all-cause death with corresponding cost-effectiveness (CE) plane in **(A2)**. **(B1)** Nelson–Aalen estimates of difference in the major adverse cardio- and cerebrovascular events (MACCE) with corresponding CE-plane in **(B2)**. **(C1)** Nelson–Aalen estimates of difference in symptomatic admissions with corresponding CE-plane in **(C2)**.

important factors found to be of statistical significance in a backward selection model was performed. The model included age, sex, LVEF, chronic kidney disease, and three-vessel-disease. A reduction in NB of EUR 365 was found. This indicates that only minor differences between the groups were confounding the results, however, residual confound may still be present.

TABLE 4 | Index and event cost.

	Successful (*n* = 342)	Unsuccessful (*n* = 99)	Net benefit
Procedural cost in Euro			
Total cost			
Mean	9.429 ± 4.006	10.015 ± 4.538	584 (–423; 1,592)
Median	7.887 [6.496; 11.827]	8.164 [6,287; 11,579]	
Utensil's cost	2.528 ± 1.925	2.355 ± 1.736	
Hospital cost	6,749 ± 2.973	7.477 ± 3.955	
Complication cost*	1,672 ± 3,669	2,502 ± 4,194	
Event cost in Euro			
Mean	2.289 ± 4.966	3.550 ± 7.230	1,260 (–253; 2,775)
Median	0 [0; 2.399]	0 [0; 4.854]	
Total cost at 3 years in Euro			
Mean	11.719 (11.034; 12.406)	13.565 (11.899; 15,231)	1,845 (64; 3,627)
Median	10.617 [6.769; 13,803]	11.191 [7.322; 17.587]	

*ICER, incremental cost effectiveness ratio. All estimates are given as price in Euro per patient in mean (95% CI), mean ± SD or median [interquartile range, IQR]. *Complication costs are only calculated for patients with one or more complication(s).*

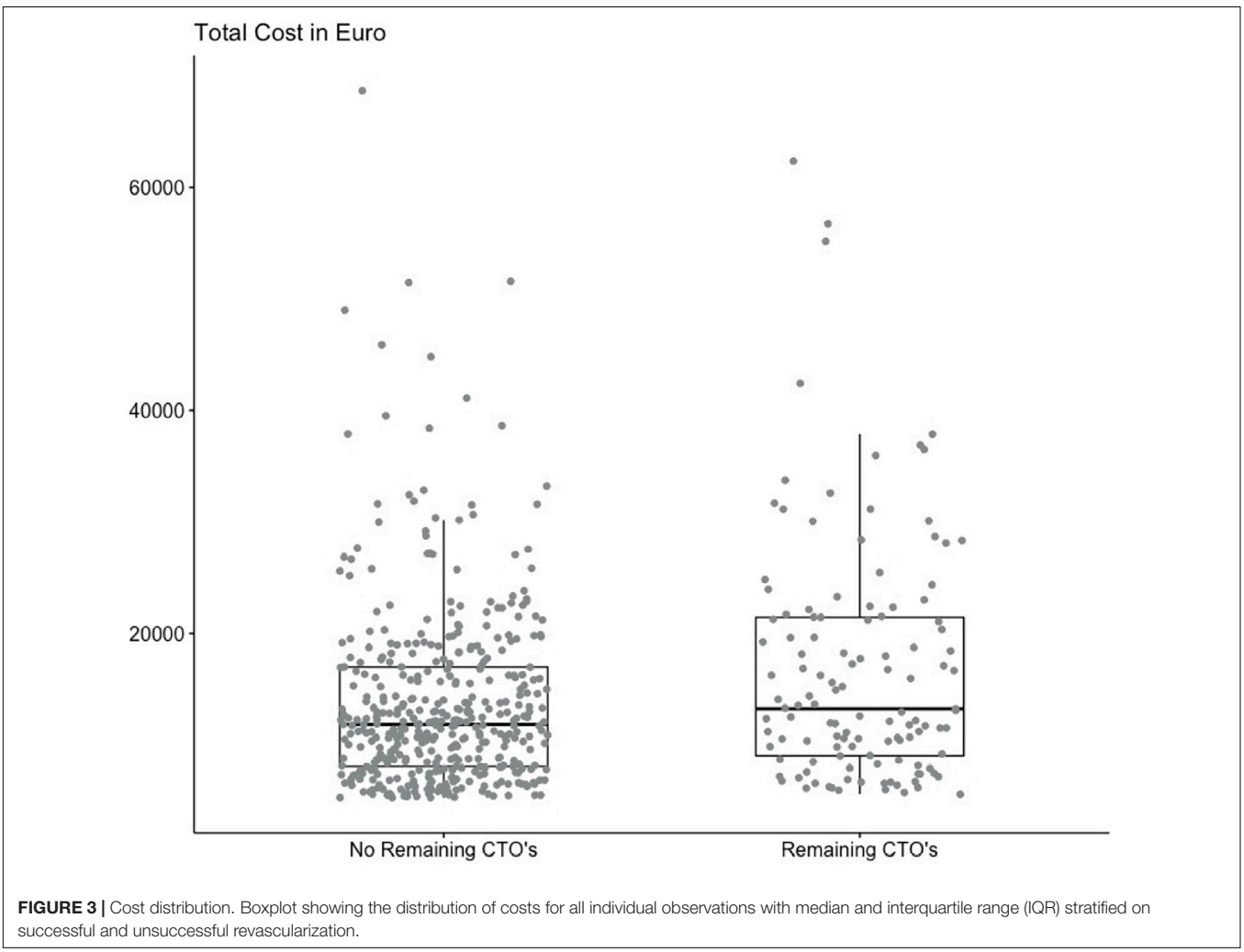

FIGURE 3 | Cost distribution. Boxplot showing the distribution of costs for all individual observations with median and interquartile range (IQR) stratified on successful and unsuccessful revascularization.

The majority of studies looking into outcomes following CTO PCI investigates the primary exposure as successful vs. unsuccessful index procedure defined as the success of opening the CTO of interest during one procedure. In the present trial, we choose that the patients should be fully revascularized in all their CTO lesions because we hypothesize that this will lower the

myocardium at risk. However, we performed a sensitivity analysis to investigate this matter and found a lower NB (NB = 821 [−1,124; 2,766]) (**Supplementary Figure 1**).

Limitations

The current study is a retrospective analysis of prospectively collected data. Therefore, the data were collected for another intent than what was used in the current study, which may lead to a selection bias. Ischemic testing was not performed in routine clinical practice in the first part of the study period and these data are therefore not included. Only patients at one single center were included, compromising the external validity, however, the center is the only center performing PCI within the central region of Denmark, inhabiting 1.3 million citizens and covering all layers of society. Furthermore, 100–120 CTO cases are performed at the center each year, which may be a bit low compared with other very high-volume centers. However, Young et al. and Zein et al. observed that superior outcomes were found if operators had performed > 60 and 35 cases in total, respectively. In the study by Zein et al. only 4 sites (8.7%) performed > 50 CTO PCIs' per year, however, we acknowledge that other very high-volume sites may be performing more procedures per year. We only evaluated events requiring hospital admissions, and therefore, the cost may have been underestimated in both groups. Furthermore, only events that occurred within the central region of Denmark were collected, and therefore a risk of underestimating event rate in both groups is present. We used DRG rates for the discharge diagnosis, and therefore, an underestimation of the cost may be present; however, this is consistent in both groups. No control group being treated with OMT alone was included. Patients treated with OMT alone for a CTO may have a significantly lower cost compared with PCI. This is supported by the findings in this study where two-thirds of the total cost at patient-level was contributed by the procedure(s). On the other hand, CTO-PCI may decrease the amount of anti-ischemic drugs used and therefore further lower costs in the successful arm, but the cost of medications was not captured in this trial. The findings in the present trial does not support the notion that successful revascularization of patients with CTO is more cost-efficient than OMT alone.

CONCLUSION

We found that patients fully revascularized for all their chronic total occluded coronary artery lesion(s) compared with patients where the procedure failed had a more cost-efficient treatment. Fully revascularized patients both experienced a lower event rate and NB, confirming that the treatment is neither harmful nor more expensive. However, future prospective trials investigating outcomes after CTO PCI should focus on selecting the right patients for revascularization and thereby further increasing cost-effectiveness.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because according to Danish law we are not able to share data unless a data processor/exchange agreement is made. Requests to access the datasets should be directed to EH, eh@clin.au.dk.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

EH and NW were responsible for data collection, data management, and analysis. EH and LM were responsible for statistical analysis. EH, LM, and EC were responsible for conceptualization and design of the study. EH drafted the manuscript. All authors critically revised the manuscript and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.849942/full#supplementary-material

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ORIGINAL RESEARCH
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Safety and Feasibility of Rotational Atherectomy for Retrograde Recanalization of Chronically Occluded Coronary Arteries

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Objective: To evaluate the safety and feasibility of rotational atherectomy (RA) in retrograde chronic total occlusion percutaneous coronary intervention (CTO-PCI) by analyzing immediate and long-term outcomes.

Background: Recent evidence supports the safety and feasibility of RA in CTO-PCI. However, few studies have focused on the use of RA in a retrograde approach to percutaneous revascularization of chronic total occlusion (CTO) lesions and information on long-term outcomes is lacking.

Methods: A total of 329 patients who underwent retrograde CTO-PCI, out of 1496 consecutive CTO-PCI patients from April 2017 to July 2020, were retrospectively recruited from the 2nd Cardiology Department of the Guangdong Provincial People's Hospital. 16 patients underwent RA (RA group) whilst 313 did not (non-RA group).

Results: Technical (87.5% vs. 87.5) and procedural (85.9% vs. 87.5) success rates were similar between both groups. There was no difference concerning major procedural complications between groups (12.5% vs. 19.2%; $p > 0.75$). No in-hospital MACCEs was recorded in the RA group while there were eight MACCEs in the non-RA group ($p > 0.99$). In the RA group, 2 cases recorded perforation (1 target vessel perforation case and 1 branch vessel perforation), and 55 cases of vessel perforations/dissections were recorded in non-RA group including 18 target vessel perforations, 2 branch vessel perforations, 35 collateral vessel perforations (one patient died from cardiac tamponade). No difference was found in terms of the perforation rate between the two groups ($p > 0.99$). Over a mean follow-up period of 26.47 ± 14.46 months, use of RA in retrograde CTO-PCI did not result in an increased mortality rate [hazard ratio (HR) 1.58, 95% confidence interval (CI), 0.31–8.21, $p = 0.65$], major adverse cardiac and cerebral events (HR 0.99, 95% CI 0.35–2.79, $p = 0.99$) or overall rehospitalization rate (HR 1.27, 95% CI 0.44–3.67, $p = 0.67$). Adjusted Kaplan–Meier curves according to Cox regression model suggested several predictors influencing the all-cause mortality, cardiovascular mortality, MACCEs, stroke rate, non-fatal myocardial infarction, target vessel recanalization rate and rehospitalization rate in the comparison.

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Conclusions: Our study demonstrates that the in-hospital outcomes and long-term follow up events were the same between RA and non-RA retrograde CTO-PCI patients. RA offered an option for skillful operators in difficult cases when the lesion was severely calcified in retrograde CTO-PCI.

Keywords: chronic total occlusion, percutaneous coronary intervention, in-hospital outcomes, long-term outcomes, retrograde, rotational atherectomy

INTRODUCTION

With advancements in technique and equipment, the success rate of chronic total occlusion percutaneous coronary intervention (CTO-PCI) has greatly improved over the years (1). Despite this, severely calcified coronary artery lesions remain a common cause of failure of equipment delivery and balloon expansion during chronic total occlusion (CTO) recanalization (2–6). Evidence of the viability and safety of CTO-PCI for calcified lesions using the antegrade approach abounds (7–9). Reverse controlled antegrade and retrograde subintimal tracking (reverse CART) is the most common retrograde CTO crossing technique in most contemporary series (66% in a multicenter U.S. registry) (10). The use of retrograde crossing techniques, particularly reverse CART, in severely calcified lesions during retrograde CTO-PCI has been considered to confer a relatively high risk of dissection and perforation following subsequent rotational atherectomy (RA) in these lesions. Azzalini et al. proposed the concept of vessel architecture, which sought to distinguish coronary structures (occlusive plaque and adventitia) from the extravascular space, and suggested that CTO-PCI can be carried out safely and effectively as long as one remains within the subadventitial space (11). The feasibility of RA in the subadventitial space during CTO-PCI has been suggested (12, 13). The present study sought to further evaluate the safety and feasibility of RA during CTO-PCI using the retrograde approach.

METHODS

Study Population

In this single-center, retrospective, cohort study, the records of patients who underwent CTO-PCI using the retrograde approach from April 2017 to July 2020 in the 2nd Cardiology Department of Guangdong Provincial People's Hospital were reviewed. The operators performed more than 200 CTO cases per year and with a success rate of about 90%. CTO-PCI was performed on 1496 consecutive patients, of which 329 patients matched the eligibility criteria and were included in our study. RA was used in 16 of the 329 patients because of failure of equipment crossing or balloon undilation in severely calcified stenotic lesions. **Figure 1** shows the flow chart of the study population. The eligibility criteria for the study were: (1) age of 18 years or older; (2) an indication for CTO-PCI, including angina symptoms and/or evidence of reversible myocardial ischemia by perfusion imaging or stress testing; and (3) All cases had failed antegrade wire escalation. Patients were excluded if they were older than 85 years or were not the suitable candidates because of severe hemorrhagic disease or intolerance to dual antiplatelet therapy. Demographic, angiographic, procedural, and in-hospital data were obtained from the catheterization laboratory database and hospital charts. **Figure 2** demonstrates a case of retrograde CTO-PCI using RA.

Definitions

A coronary CTO was defined as total occlusion of a coronary artery segment with Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 and an estimated duration of more than 3 months, with angiographic evidence. The duration of occlusion was estimated according to the onset of clinical symptoms or previous myocardial infarction (MI) with angiographic evidence. The Japanese-CTO (J-CTO) score and PROGRESS-CTO score were used to assess CTO lesions. Werner classification was used to assess collateralization (14–16). Technical success of retrograde CTO-PCI was defined as residual stenosis <30% and antegrade TIMI flow grade 3. Procedural success was regarded as technical success with no in-hospital major adverse cardiac and cerebral events (MACCEs). In-hospital events were defined as death, periprocedural MI, urgent target vessel revascularization (including repeat PCI or coronary artery bypass graft), pericardiocentesis, cardiac tamponade requiring surgery and stroke. During follow-up, MACCE was defined as cardiovascular death, non-fatal MI, ischemia-driven target vessel recanalization and stroke. The criteria for MI were based on the new Fourth Universal Definition of MI (17). Stent thrombosis was defined in accordance with the Academic Research Council criteria (18).

Interventional Procedures

Before and after CTO-PCI, all patients received optimal dual antiplatelet therapy (aspirin 100 mg once daily and clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily). Patients received an initial bolus of intravenous unfractionated heparin (150 IU/kg) during the procedure; additional boluses were given to maintain an activated clotting time (ACT) >300 s, which was monitored every 30 min. At the operator's discretion, additional doses of a glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitor were administered selectively. The choice of vascular access depended on the operator's personal preference as well as anatomical considerations. Retrograde recanalization techniques and equipment were used at the operator's discretion. RA was used following failure of balloon crossing or expansion, or after balloon rupture or failure of other equipment to cross after wire externalization. Rota wire® (Boston Scientific Corp) was exchanged after the extraction of wires *via* a Finecross® microcatheter (Terumo Company, Japan) or Corsair® (Asahi

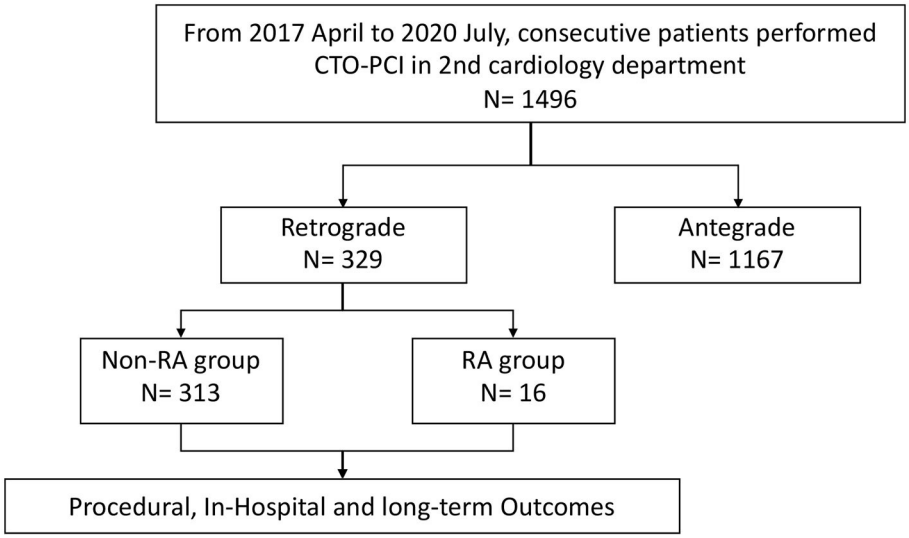

FIGURE 1 | Flow chart of the study population.

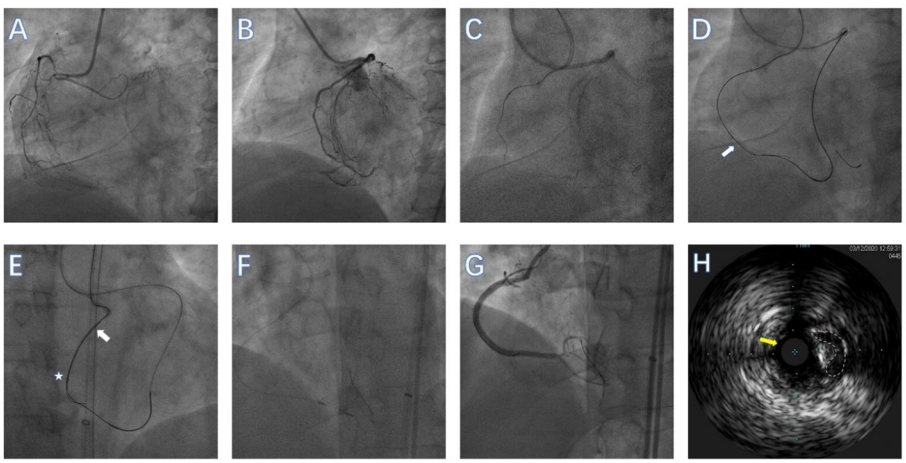

FIGURE 2 | Performing Guidezilla™ reverse controlled antegrade and retrograde subintimal tracking (CART) during rotational atherectomy (RA) in a right coronary artery (RCA) CTO lesion. **(A)** RCA in left anterior oblique view showing an ambiguous proximal cap without obvious calcification. **(B)** RCA in left anterior oblique view showing the distal cap of the RCA. **(C)** Antegrade wire in the subadventitial space of mid-RCA. **(D)** The CTO lesion was crossed over using the Guidezilla™ reverse CART technique (the white arrow represents the dilated balloon). **(E)** Retrograde wire (white arrow) was advanced into the Guidezilla™ (white star) of the RCA and externalized. **(F)** Rotational atherectomy was then performed using a 1.25-mm burr. **(G)** Angiography after successful CTO-PCI. **(H)** Intravascular ultrasound confirmed that the guidewire (yellow arrow) was in the subadventitial space (The white dotted line represents the true lumen of the vessel).

Intec, Japan) microcatheter. If the microcatheter failed to cross, Rota wire® was manipulated to primarily cross the CTO lesion (19). Retrograde angiography was performed to ensure that the Rota wire was in the true lumen. The size of the burr used was at the discretion of the operator. The rotational speed of RA was between 160000 and 200000 rotations per minute (RPM). Balloon pre-dilatation was performed after successful RA, followed by drug eluting stent implantation.

Follow-Up

Follow-up data was collected by telephonic interviews years after PCI as well as through the revision of clinical documentation when patients returned for further consultation. All data collection and use of patient data were done in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of Guangdong Provincial people's hospital and Guangdong Academy of Medical Sciences [No. GDREC2017196H(R1)] in July 2017.

Statistical Analysis

Quantitative data are reported as means ± SD and tested by the Student *t*-test. Pearson $\chi 2$ test or Fisher's exact test was used to analyze differences in qualitative data for discrete variables. The Kaplan–Meier method was used to calculate and graphically

TABLE 1 | Baseline clinical characteristics.

Variable	Non-RA ($n = 313$)	RA ($n = 16$)	*P*-value*
Age (years)	59.70 ± 10.52	60.87 ± 9.82	0.43
Male, *n* (%)	284 (90.7)	16 (100)	0.38
Diabetes mellitus, *n* (%)	95 (30.4)	8 (50)	0.10
Dyslipidemia, *n* (%)	89 (28.4)	5 (31.3)	0.81
Hypertension, *n* (%)	184 (58.8)	14 (87.5)	0.03
Current smoker, *n* (%)	70 (22.4)	3 (18.8)	>0.99
Prior MI, *n* (%)	79 (25.2)	4 (25)	>0.99
Prior PCI, *n* (%)	206 (65.8)	10 (62.5)	0.79
Prior CABG, *n* (%)	15 (4.8)	0 (0)	>0.99
LVEF (%)	54.34 ± 12.73	52.44 ± 11.50	0.38
LVEF <50%, *n* (%)	90 (28.8)	5 (31.3)	0.83
Serum creatinine, μmol/L	101.32 ± 89.76	98.14 ± 33.51	0.76

*MI, myocardial infarction; PCI, percutaneous coronary artery intervention; CABG, coronary artery bypass surgery; LVEF, left ventricular ejection fraction. *p < 0.05 is considered significant.*

TABLE 2 | Angiographic characteristics.

Variable	Non-RA ($n = 313$)	RA ($n = 16$)	*P*-value*
Target-vessel CTO			
LAD, *n* (%)	120 (38.3)	4 (25)	0.43
LCX, *n* (%)	7 (2.2)	0 (0)	>0.99
RCA, *n* (%)	185 (59.1)	12 (75)	0.30
LM, *n* (%)	1 (0.3)	0 (0)	>0.99
Multivessel, *n* (%)	263 (84)	16 (100)	0.14
Multiple CTO, *n* (%)	72 (23)	7 (43.8)	0.06
Blunt stump, *n* (%)	221 (70.6)	12 (75)	>0.99
Moderate/severe tortuosity	184 (58.8)	14 (87.5)	0.03<0.05
Moderate/severe calcification	157 (50.2)	16 (100)	<0.0001
Lesion length >20 mm	276 (88.2)	16 (100)	0.23
Prior failed CTO PCI, *n* (%)	97 (31)	4 (25)	0.78
J-CTO score	2.84 ± 1.03	3.88 ± 0.89	0.25
Progress CTO score	2.01 ± 0.81	2.19 ± 0.66	0.67
Werner score	1.41 ± 0.67	0.81 ± 0.75	0.95

*CTO, Chronic Total Occlusion; LAD, Left Anterior Descending; LCX, Left Circumflex; RCA, Right Coronary Artery; LM, Left Main. *p < 0.05 is considered significant.*

describe the free rates of MACCE, MI, stroke, survival, and rehospitalization of the two groups. The multivariable Cox regression analysis model was built by stepwise selection. All baseline and procedural patient variables in univariable analysis defined by $p < 0.1$ were entered into the stepwise model. Differences with a $p < 0.05$ were regarded as statistically significant. All statistical analyses were performed using the SPSS software package, version 20.0 (SPSS Inc, Chicago, IL) and GraphPad Prism version 9 (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

Baseline Clinical Characteristics

A total of 329 patients who fulfilled the inclusion criteria were included in the study. Clinical characteristics of the study population are shown in **Table 1**. Sixteen patients underwent RA during retrograde CTO-PCI while 313 patients had retrograde CTO-PCI without RA. The distribution of clinical characteristics between the two groups was not different. The mean age was 59.70 ± 10.52 years in the non-RA group and 60.87 ± 9.82 in the RA group, and more than 90% were male in both groups. There were no differences in the prevalence of hypertension, hyperlipidemia, smoking, diabetes mellitus or history of prior PCI or coronary artery bypass graft between the two groups. Renal function and ejection fraction did not differ significantly between the two groups.

Angiographic Characteristics

The angiographic characteristics of the patients' coronary lesions are described in **Table 2**. Compared to the non-RA group, RA patients had higher prevalence of moderate/severe calcifications (100% in RA vs. 50.2% in non-RA; $p < 0.0001$) and moderate/severe tortuosity (87.5% vs. 58.8%; $p = 0.03$) at the CTO lesions. There was no difference between the RA and non-RA groups with regards to the distribution of the CTO target vessel. Though most of the CTO lesions requiring retrograde PCI were in the right coronary artery, it did not suggest significant difference (75% and 59.1%, $p = 0.3$). J-CTO score (3.88 ± 0.89 vs. 2.84 ± 1.03, $p = 0.25$) and PROGRESS CTO score (2.19 ± 0.66 vs. 2.01 ± 0.81, $p = 0.67$) did not differ between the two groups, yet the scores were higher in the RA group. No difference was found in Werner score (0.81 ± 0.75 vs. 1.41 ± 0.67, $p = 0.95$) between the two groups.

Procedural Characteristics

Table 3 showed the procedural characteristics of the two groups. There was a higher trend toward use of reverse CART in successful crossing strategy (75% in RA vs. 59.4% in non-RA; $p = 0.29$), and retrograde wire escalation tended to be lower in RA patients (18.8% vs. 27.2%; $p = 0.57$). In the RA group guide catheter extension (Guidezilla™, Boston Scientific, Natick, USA) was more frequently applied, as compared with non-RA subjects (75% vs. 46%, $p = 0.04$). IVUS use was not different in cases of both cohorts. Septal collateral channel was the common interventional collateral channel in both retrograde PCI groups and showed no significant difference. Epicardial collateral channel tended to be applied more often in non-RA group (18.8% vs. 25.6%; $p = 0.77$). There was no significant difference in the number and length of stents implanted between the two groups. The main indications for RA during retrograde CTO-PCI were failure of equipment to cross the lesion (68.8%), followed by failure of balloon expansion in 25%, and balloon rupture in 6.3% of the procedures. In most cases, one burr was enough for RA (87.5%), and two burrs were used in 12.5%. The largest burr size was 1.25 mm in 37.5% and 1.50 mm in 62.5%. The mean rotational speed for RA was 186,363 ± 12,863 RPM. There was no Rota wire uncrossing in our center and rotational atherectomy

TABLE 3 | Procedural characteristics.

Variable	Non-RA ($n = 313$)	RA ($n = 16$)	*P*-value*
Successful crossing technique			
Reverse CART/ Guidezilla™ reverse CART, n (%)	186 (59.4)	12 (75)	0.29
Retrograde wire knuckle, *n* (%)	6 (1.9)	1 (6.3)	>0.99
Retrograde wire escalation, *n* (%)	85 (27.2)	3 (18.8)	0.57
Guidezilla™ use, *n* (%)	144 (46.0)	12 (75)	0.04
IVUS use, *n* (%)	61 (19.5)	5 (31.3)	0.33
Channel type			
Epicardial collateral channel, *n* (%)	80 (25.6)	3 (18.8)	0.77
Septal collateral channel, *n* (%)	238 (76.0)	13 (81.3)	0.77
Number of stents implanted	2.50 ± 1.17	3.14 ± 0.86	0.09
Total stent length (mm)	90.69 ± 30.67	105.5 ± 30.59	0.71
Indication of RA			
Equipment failure-to-cross, *n* (%)	/	11 (68.8)	
Balloon failure-to-expand, *n* (%)	/	4 (25)	
Balloon rupture, *n* (%)	/	1 (6.3)	
Number of burrs used			
One, *n* (%)	/	14 (87.5)	
Two, *n* (%)	/	2 (12.5)	
Largest burr used (mm)			
1.25, *n* (%)	/	6 (37.5)	
1.50, *n* (%)	/	10 (62.5)	
Rotational speed, RPM	/	186,363 ± 12,863	
Rotational atherectomy success, *n* (%)	/	16 (100)	
Technical success, *n* (%)	274 (87.5)	14 (87.5)	>0.99
Procedural success, *n* (%)	269 (85.9)	14 (87.5)	>0.99
Access site			
Bilateral/unilateral radical (%)	22 (7.0)	1 (6.3)	>0.99
Radical+femoral (%)	232 (74.1)	12 (75)	>0.99
Bilateral/unilateral femoral (%)	59 (18.8)	3 (18.8)	>0.99
Procedure time, minute	169.3 ± 71.30	188.3 ± 69.52	0.81
Contrast volume (ml)	211.1 ± 61.58	195.87 ± 63.76	0.77

*Reverse CART, Reverse Controlled Anterograde Retrograde Tracking; IVUS, intravascular ultrasound; RPM, revolutions per minute; *p < 0.05 is considered significant.*

during CTO-PCI was successful in all 16 cases. Almost 75% of the access site in both groups were radical plus femoral. Dual/single radical and dual/single femoral constituted a low percentage in two groups. Technical (87.5% vs. 87.5%; $p > 0.99$) and procedural (87.5% vs. 85.9%; $p > 0.99$) success rates were similar between the RA and non-RA group. Other procedural metrics were similar between the two groups.

Procedural Complications and In-hospital Outcomes

Procedural complications and in-hospital outcomes were shown in **Table 4**. There was no difference concerning major procedural

TABLE 4 | Procedural complications and in-hospital outcome.

Variable	Non-RA ($n = 313$)	RA ($n = 16$)	*P*-value
Procedural complications, *n* (%)	60 (19.2)	2(12.5)	0.75
Perforations/dissections, *n* (%)	55 (17.6)	2 (12.5)	>0.99
Target vessel, *n* (%)	18 (5.75)	1 (6.25)	>0.99
Branch vessel, *n* (%)	2 (0.6)	1 (6.25)	>0.99
Septal collateral vessel, *n* (%)	26 (8.3)	0 (0)	0.63
Epicardial collateral vessel, *n* (%)	15 (4.8)	0 (0)	>0.99
Covered stent implantation, *n* (%)	5 (1.6)	0 (0)	>0.99
Coiling, *n* (%)	9 (2.9)	2 (12.5)	0.09
Cardiac tamponade, *n* (%)	12 (3.8)	1 (6.25)	0.48
Stent thrombosis, *n* (%)	3 (1.0)	0 (0)	>0.99
Burr entrapment, *n* (%)	/	0 (0)	>0.99
Access complications, *n* (%)	2 (0.6)	0 (0)	>0.99
In-hospital MACCE, *n* (%)	8 (2.6)	0 (0)	>0.99
Death, *n* (%)	1 (0.3)	0 (0)	>0.99
Periprocedural MI, *n* (%)	0 (0)	0 (0)	>0.99
Target vessel recanalization, *n* (%)	0 (0)	0 (0)	>0.99
Stroke, *n* (%)	0 (0)	0 (0)	>0.99
Pericardiocentesis, *n* (%)	6 (1.9)	0 (0)	>0.99
Tamponade requiring surgery, *n* (%)	1 (0.3)	0 (0)	>0.99

MI, myocardial infarction; MACCE, major adverse cardiac and cerebral events.

complications between groups (12.5% vs. 19.2%; $p > 0.75$). In the RA group, there was one target vessel perforation with tamponade case, and one branch vessel perforation case identified by angiography after RA procedure. Spring coils were implanted in the perforated cases. No in-hospital MACCEs was recorded in the RA group while there were eight MACCEs in the non-RA group ($p > 0.99$). 55 cases of vessel perforations/dissections were recorded in non-RA group including 18 target vessel perforations, 2 branch vessel perforations, 26 septal collateral vessel perforations and 15 epicardial collateral vessel perforations (one patient died from cardiac tamponade).

Clinical Outcomes During Follow-Up

The overall follow-up rate was 93%. The duration of follow-up of non-RA group was 26.47 ± 14.46 months while the follow-up period of the RA group was 30.22 ± 15.07 months. **Table 5** demonstrated clinical outcomes during follow-up. No difference was found regarding MACCEs, reason of rehospitalization, all-cause mortality and so on. Details of the RA group patients were listed in **Supplementary Tables 1–3**.

In unadjusted analysis, there was no difference between the RA and non-RA groups in terms of survival (HR 1.58, 95% CI, 0.31–8.21, $p = 0.65$). Moreover, performing RA during retrograde CTO-PCI did not lead to an increase in the MACCE rate during follow-up (HR 0.99, 95% CI 0.35–2.79, $p = 0.99$). Neither the overall rehospitalization rate (HR 1.27, 95% CI 0.44–3.67, $p = 0.67$) or the heart failure symptom induced (HR 0.44, 95% CI 0.02–8.28, $p = 0.43$), angina induced ($p = 0.53$) or arrythmia induced ($p = 0.80$) rehospitalization rate

TABLE 5 | Clinical outcomes on follow-up.

	Non-RA ($n = 313$)	RA ($n = 16$)	*P*-value
Major adverse cardiac and cerebral events, *n* (%)	35 (11.2)	1 (6.3)	>0.99
Cardiac death, *n* (%)	12 (3.8)	1 (6.3)	0.48
Target-vessel revascularization, *n* (%)	10 (3.2)	0 (0)	>0.99
Myocardial infarction, *n* (%)	6 (1.9)	0 (0)	>0.99
Stroke, *n* (%)	7 (2.2)	0 (0)	>0.99
Reason of rehospitalization, *n* (%)	55 (17.6)	3 (18.8)	>0.99
Heart failure, *n* (%)	12 (3.8)	2 (12.5)	0.14
Angina, *n* (%)	17 (5.4)	0 (0)	>0.99
Stroke, *n* (%)	9 (2.9)	0 (0)	>0.99
kidney failure, *n* (%)	2 (0.6)	0 (0)	>0.99
Ventricular tachycardia, *n* (%)	1 (0.3)	0 (0)	>0.99
pacemaker implanting, *n* (%)	2 (0.6)	0 (0)	>0.99
Gastrointestinal Hemorrhage, *n* (%)	1 (0.3)	0 (0)	>0.99
Malignant tumor, *n* (%)	3(1.0)	0 (0)	>0.99
Surgery for other reasons, *n* (%)	3 (1.0)	0 (0)	>0.99
Routine health check, *n* (%)	5 (1.6)	1 (5.3)	0.26
All-cause mortality, *n* (%)	18 (5.8)	1 (6.3)	>0.99
Lost to follow-up, *n* (%)	23 (9.8)	0 (0)	0.62

RA, Rotational atheretomy.

was significantly different between the two groups. Of the three patients hospitalized in the RA group, one was asymptomatic according to our telephonic follow-up, hence, the observed difference between the two groups might be biased. No significant differences were observed between the two groups in terms of the non-fatal MI rate ($p = 0.54$), target vessel recanalization rate ($p = 0.46$) or the stroke rate ($p = 0.41$).

Details of multivariable stepwise Cox regression analysis adjusting for significant variables in univariable testing were listed in **Supplementary Tables 4**, **5**. Adjusted Kaplan–Meier survival curves following retrograde CTO-PCI, with and without RA, was illustrated in **Figure 3A**. Hypertension (HR 3.65, 95% CI, 1.21–11.04, $p = 0.02$), prior MI (HR 3.40, 95% CI, 1.13–10.30, $p = 0.03$), multivessel and moderate/severe calcification (HR 2.98, 95% CI, 1.05–8.50, $p = 0.04$) were independent predictors of survival. Prior MI (HR 7.39, 95% CI, 1.79–30.48, $p = 0.006$), multivessel (HR 0.13, 95% CI, 0.02–0.78, $p = 0.03$) and moderate/severe calcification (HR 5.02, 95% CI, 1.18–21.31, $p = 0.03$) were independent predictors of the cardiovascular mortality rate during follow-up (**Figure 3B**). Hypertension (HR 3.51, 95% CI, 1.59–7.72, $p = 0.002$) and prior MI (HR 2.53, 95% CI, 1.24–5.17, $p = 0.01$) were independent predictors of the MACCE rate during follow-up (**Figure 3C**). Multivessel (HR 0.21, 95% CI, 0.05–0.84, $p = 0.03$) was the independent predictor of stroke rate during follow-up (**Figure 3D**). Moderate/severe calcification (HR 7.77, 95% CI, 0.90–67.21, $p = 0.06$) was the independent predictor of non-fatal myocardial infarction rate during follow-up (**Figure 3E**). Prior failed PCI (HR 4.92, 95% CI, 1.05–22.97, $p = 0.04$) was the independent predictor target vessel recanalization rate (**Figure 3F**). **Figure 4** illustrated the Kaplan–Meier curves of adjusted overall rehospitalization rate (**Figure 4A**) and angina (**Figure 4B**), heart failure (**Figure 4C**) and arrhythmias (**Figure 4D**) caused rehospitalization rate. In the overall rehospitalization rate, moderate/severe calcification (HR 2.78, 95% CI, 1.33–5.82, $p = 0.007$) was an independent predictor.

DISCUSSION

To the best of our knowledge, this is the first study to compare the outcomes (in-hospital and long-term) of the use of RA in CTO-PCI using the retrograde approach. One of the main findings of our study was that the procedural success rate of retrograde CTO PCI was similar whether or not RA was performed. Additionally, we found that thought RA was used more often in patients with extreme vessel tortuosity and calcification, cases in both RA and non-RA groups performing retrograde CTO PCI were multivessel disease, multi-CTO lesions, and complex lesions (evidenced by J-CTO score and PROGRESS-CTO score) which can be regarded as CHIP (Complete Revascularization for High Risk Indicated Patients Session). We found similar rates of in-hospital complications as well as long-term survival, stroke, MI and MACCE rates with or without the use of RA during retrograde CTO-PCI despite similar rates of use of reverse-CART in the two groups. The rehospitalization rate was not higher when RA was used.

Balloon un-crossable or un-dilatable lesions account for 9 and 2% of CTO-PCI failure, respectively (20). Strategies such as the buddy wire technique, deep intubation of the guiding catheter, and the mother-and-child guide catheter techniques are frequently employed to facilitate device advancement during the procedure. RA can be very useful in this setting by debulking lesions with severe calcification to improve vascular compliance and device trafficability. A recent multicentral study suggested that excimer laser coronary atherectomy was effective in uncrossable CTO lesions (21). Although there is a lack of sufficient practice, we are optimistic about its prospects.

Recent randomized controlled trials have suggested that RA for complex calcified lesions was similar to that of plain old balloon angioplasty with regards to long-term clinical outcomes or reduction in lumen loss (4, 22, 23). Abdel-Wahab et al. have reported similar rates of immediate and 9-month lumen loss when modified balloons or RA were used in severely calcified coronary lesions (5). However, a recent *post hoc* analysis of the PREPARE-CALC (The Comparison of Strategies to PREPARE Severely CALCified Coronary Lesions) randomized trial found that RA had a higher procedural success rate compared with modified balloons in non-left anterior descending artery lesions (24). A retrospective review of 3540 patients in 21 centers (part of the PROGRESS-CTO registry) identified 116 patients in whom RA was performed and 3424 patients without RA, using both the antegrade and retrograde approaches to CTO-PCI (7). In this study, the technical and procedural success rates and MACCE rates were similar between the groups. RA

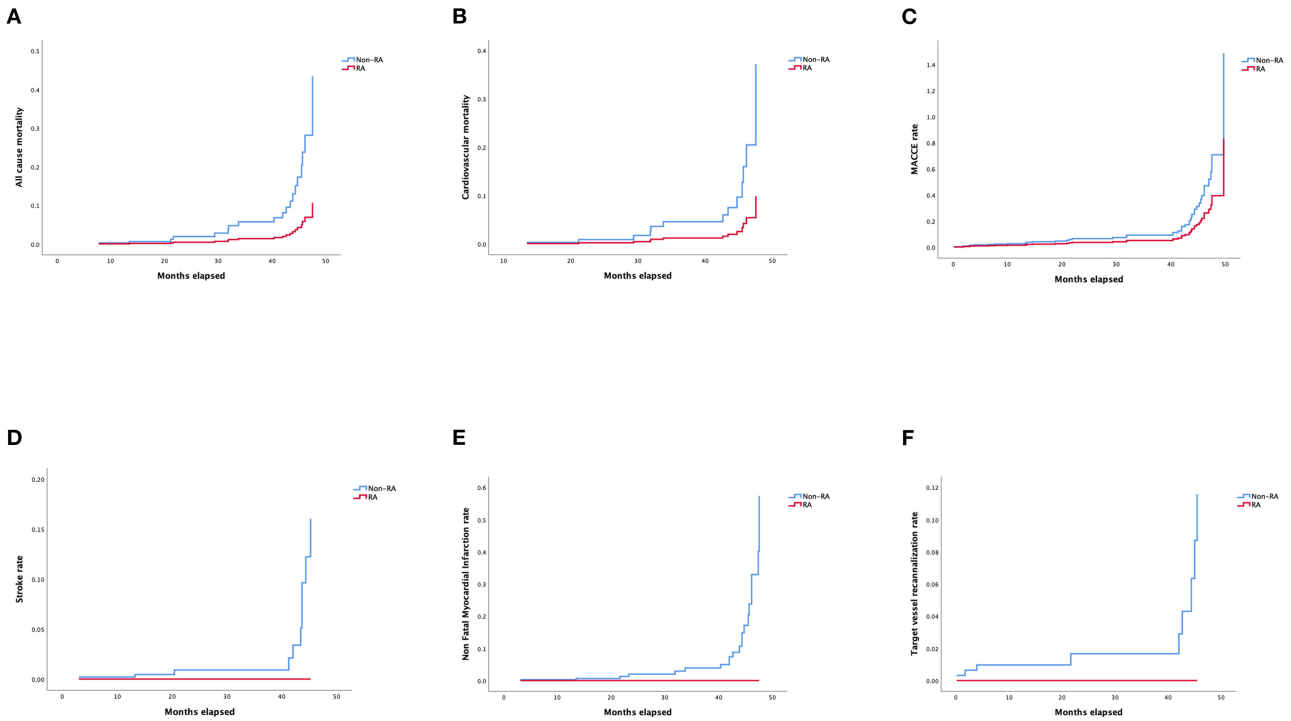

FIGURE 3 | (A) Adjusted Kaplan–Meier curves of all-cause mortality according to Cox regression model. **(B)** Adjusted Kaplan–Meier curves of cardiovascular mortality according to Cox regression model. **(C)** Adjusted Kaplan–Meier curves of MACCE rate according to Cox regression model. **(D)** Adjusted Kaplan–Meier curves of stroke rate according to Cox regression model. **(E)** Adjusted Kaplan–Meier curves of non-fatal myocardial infarction rate according to Cox regression model. **(F)** Kaplan–Meier curves of target vessel recanalization rate according to Cox regression model.

was used in only 4.9% of patients undergoing retrograde CTO-PCI in our center, similar to the rate in the PROGRESS-CTO registry. This indicates that whilst RA is not a necessity in CTO-PCI, it nevertheless remains an effective and useful option in the occasional resistant lesion. A small study ($n = 285$) suggested a trend toward a lower 1-year MACCE rate when RA was used in resistant CTO lesions, but this advantage was lost after adjusting for confounding variables on multivariate Cox regression analysis (HR 1.25, 95% CI, 0.33–1.94, $p = 0.242$) (9). Similar to our study, a single-center study in Germany that enrolled CTO ($n = 75$) and non-CTO ($n = 317$) PCI patients who had RA prior to stent implantation found no differences in in-hospital MACCE rates despite the occurrence of significantly more dissections when RA was employed (8). In an in-hospital cohort of 129 patients undergoing CTO-PCI with RA reported a higher incidence of dissection in the retrograde arm compared with the antegrade approach (25).

In this study, the technical success rate of RA procedural was 100%, which we attribute, amongst other things, to the good support afforded by 7F guiding catheters and guide catheter-extensions (Guidezilla^{TM}), as necessary, through unilateral radial and femoral artery or bilateral femoral artery vascular access sites. We analyzed the access site of the two groups and the result suggesting that in retrograde CTO-PCI surgery operators tended to apply right radial plus femoral artery. Comparing with bilateral radial artery and bilateral femoral artery, this method could provide a stronger support for catheters with less puncture complications and restriction after surgery (26). The right access is more feasible for the operators to stand a long time in the operation. For those lesions with severe tortuosity and calcification, the microcatheter often failed to cross in the antegrade approach (to facilitate wire exchange). In these cases, sophisticated operators would trace the track left by the stiff wire in the calcified lesion with Rotawire in the antegrade microcatheter and return to the distal true lumen. As the lesion was usually severely calcified, a track was usually left in the lesion without elastic recoil (19). During this procedure, retrograde angiography was performed once the Rotawire crossed the lesion to ensure that it was in the true lumen to reduce the risk of perforation (12). The smallest-sized burr (1.25 mm) was used at a speed of 160,000-180,000 RPM. In our study, reverse CART was used significantly more frequently in the RA group. As the lesions in the RA group were longer and more calcified, antegrade CTO wires were more prone to cross into the subadventitial space with inability to return to the true lumen (11). In this scenario, we switched over to the retrograde approach for recanalization, which likely accounted for the more frequent use of reverse CART in the RA group. Reverse CART allows the guide wire to travel through the subadventitial space and

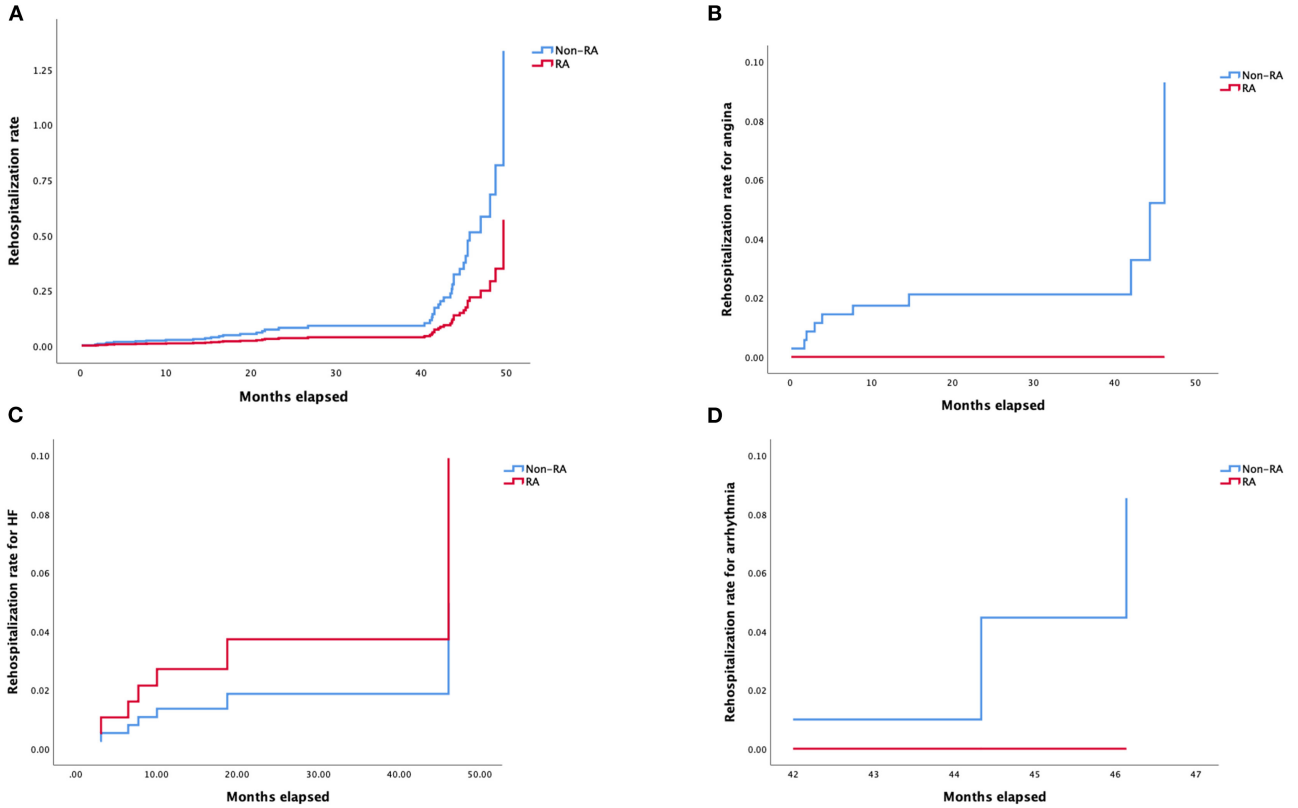

FIGURE 4 | (A) Kaplan–Meier curves of rehospitalization rate according to Cox regression model. **(B)** Kaplan–Meier curves of rehospitalization rate for angina according to Cox regression model. **(C)** Kaplan–Meier curves of rehospitalization rate for heart failure according to Cox regression model. **(D)** Kaplan–Meier curves of rehospitalization rate for arrhythmia according to Cox regression model.

could lead to extension of the dissection plane and predisposition to perforation. This was confirmed by the findings of our study. However, we also found that the technical success, long term MACCE, and survival rates were similar, independent of the use of RA (27). Guidezilla^{TM} usage was higher in the RA group due to more severe calcification and tortuosity of the target vessels. Deep intubation of the Guidezilla^{TM} helped to direct the retrograde guide wire following CTO crossing (28). After successful retrograde wire externalization, the burr was delivered for RA. During the procedure, the Guidezilla^{TM} provided stability, maintained coaxiality with the Rotawire, and protected proximal branches during RA in distal lesions.

We found two cases regarded as procedural failure. Both two cases were due to vessel perforation and needed endovascular coiling to arrest the bleed. One of the two cases of perforation developed into pericardial tamponade requiring pericardial drainage. None of the two patients experienced adverse cardiovascular or cerebral events. Historically, a feared complication of RA has been enlargement of a subintimal dissection. We used reverse CART and wire knuckle techniques for retrograde CTO lesion crossing. This study found two cases of dissection in the RA group, but was not significantly higher than the rate recorded in the non-RA group. Research suggests that low-speed (140,000 RPM) RA did not result in a reduction in the slow flow phenomenon compared with high-speed (190,000 RPM) RA (29). But one successful case in the RA group reported cardiac death during rehospitalization. Overall, procedural success and MACCE rates were not different between the two groups in-hospital and during follow up.

Our study had some limitations. First, as a single-center retrospective study, the lack of randomization and potential for selection bias during the procedure might have affected the study outcomes. Second, the operations were performed by skillful operators in a large center and may not applicable to those small centers. Additionally, the number of patients who underwent RA during retrograde CTO-PCI was relatively small. Follow-up angiography was not performed for our patients. In this retrospective study, economic considerations in the past may lower the usage rate of IVUS, but our practice suggested that IVUS was a vital approach in the RA procedure for e.g., the selection of burr and RA guidewire, prevention of coronary perforation, evaluation of RA, and selection of the stent (30). IVUS was applied in complicating CTO lesions if possible. As a result, the true benefits of RA in CTO-PCI using the retrograde approach need to be further assessed by larger studies or dedicated randomized trials.

CONCLUSION

In summary, our study demonstrates that the in-hospital outcomes and long-term follow up events were the same between RA and non-RA retrograde CTO-PCI patients. RA offered an option for skillful operators in difficult cases when the lesion was severely calcified in retrograde CTO-PCI.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committee of Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences [No. GDREC2017196H(R1)]. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW designed the topic and revised the manuscript. BZ were involved in the conception and design of this study. ZZ and HL provided data and gave advice to the design of the research. KW and ZH gave advice to the reversion of the manuscript. A-SY revised the manuscript. JH analyzed the data and wrote the draft. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.854757/full#supplementary-material

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Temporal Trends in Complex Percutaneous Coronary Interventions

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Background: Accumulated experience combined with technological advancements in percutaneous coronary interventions (PCI) over the past four decades, has led to a gradual increase in PCI utilization and complexity. We aimed to investigate the temporal trends in PCI complexity and the outcomes of complex PCI (C-PCI) in our institution.

Methods: We analyzed 20,301 consecutive PCI procedures performed over a 12-year period. C-PCI was defined as a procedure involving at least one of the following: Chronic total occlusion (CTO), left main (LM), bifurcation or saphenous vein graft (SVG) PCI. Four periods of 3-year time intervals were defined (2008–10, 2011–2013, 2014–2016, 2017–2019), and temporal trends in the rate and outcomes of C-PCI within these intervals were studied. Endpoints included mortality and major adverse cardiac events [MACE: death, acute myocardial infarction (MI), and target vessel revascularization (TVR)] at 1 year.

Results: A total of 5,647 (27.8%) C-PCI procedures were performed. The rate of C-PCI has risen significantly since 2,017 (31.2%, $p < 0.01$), driven mainly by bifurcation and LM interventions ($p < 0.01$). At 1-year, rates of death, acute MI, TVR and MACE, were all significantly higher in the C-PCI group (8.8 vs. 5.1%, 5.6 vs. 4.5%, 5.5 vs. 4.0%, 17.2 vs. 12.2%, $p < 0.001$ for all, respectively), as compared to the non-complex group. C-PCI preformed in the latter half of the study period (2014–2019) were associated with improved 1-year TVR (4.4% and 4.8% vs. 6.7% and 7.1%, $p = 0.01$, respectively) and MACE (13.8% and 13.5% vs. 17.3% and 18.2%, $p = 0.001$, respectively) rates compared to the earlier period (2007–2013). Death rate had not significantly declined with time.

Conclusion: In the current cohort, we have detected a temporal increase in PCI complexity coupled with improved 1-year clinical outcomes in C-PCI.

Keywords: trends, complexity, PCI—percutaneous coronary intervention, bifurcation, CTO (chronic total occlusion), left main, SVG = saphenous vein graft

INTRODUCTION

Complex percutaneous coronary intervention (C-PCI) is commonly defined as an elective or urgent PCI with any of the following characteristics: ≥ 3 drug eluting stents (DES) implanted, bifurcation PCI with 2 stents, left main (LM) coronary artery PCI, saphenous vein graft (SVG) PCI, total stent length > 60 mm, or chronic total occlusion (CTO) as target lesion (1). Patients who undergo C-PCI with DES in the setting of both stable coronary artery disease (CAD) and acute coronary syndrome (ACS), are at a substantially higher ischemic risk, in a graded fashion, with increased procedural complexity (1, 2). As clinical and angiographic characteristics of patients undergoing PCI with DES have evolved substantially over the last 20 years, current trends indicate that approximately 30% of all PCI procedures may be considered complex according to lesion or anatomic factors (3). Owing to technical and methodological advancements, patients who were previously treated medically or surgically, are now often offered PCI with an emphasis on unprotected left main disease (ULMD) (4–6) and CTO (7). In order to successfully predict and identify patients who are prone to increased residual ischemic risk, these intricate procedures require interventional cardiologists to use both clinical (8) and angiographic (9) risk scores, and implement treatment accordingly. The aim of the current study was to evaluate the trends of complex PCI procedures throughout the last decade, with their subsequent outcomes. Specifically, we sought to compare trends in a large prospective registry of patients treated at an academic medical center institution which encompasses 2 hospitals.

MATERIALS AND METHODS

Patients and Setting

All consecutive patients who underwent PCI at the Rabin Medical Center (RMC), Petach Tikva, Israel ("Hasharon" and "Beilinson" campuses) between January 2008 and December 2019 were included in the current analysis. Data regarding clinical diagnoses were collected from the institutional electronic medical record system, in keeping with the ICD-9 system. Laboratory data were retrieved from the RMC central laboratory database. Demographic data, including death dates, were obtained from the institutional demographic information system, which is linked to the state of Israel Ministry of Interior data, and was thereafter verified with the Israel Central Bureau of Statistics. Patients' follow-up was performed using a detailed registry, collected from the institutional electronic medical records system.

Clinical and Procedural Data

All follow-up data were collected up to June 2021. Data collection was approved by the institutional ethics committee in compliance with the Declaration of Helsinki, with a waiver for the need of individual informed consent. We initially compared C-PCI and non-C-PCI patients. C-PCI was defined as a procedure involving at least one of the following: CTO, LM, bifurcation or SVG PCI. Four periods of 3-year time intervals were defined (2008–2010, 2011–2013, 2014–2016, 2017–2019), and temporal trends in the rate and outcomes of C-PCI within these intervals were studied.

Clinical Endpoints

Endpoints included mortality and major adverse cardiac events [MACE: death, acute myocardial infarction (MI), and target vessel revascularization (TVR)] at 1 year. In accordance with the "fourth universal definition of myocardial infarction" (10), MI was defined as acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischemia.
- New ischemic ECG changes.
- Development of pathological Q waves.
- Imaging evidence of new loss of viable myocardium or new regional wall motion. abnormality in a pattern consistent with an ischemic etiology.
- Identification of a coronary occlusion or significant stenosis by angiography.

To evaluate the interaction between complexity and temporal trends in outcomes (i.e., death and MACE) additional multivariate cox models were constructed with time period as a continuous variable and a complexity: time period interaction term.

Statistical Analysis

Categorical data are reported as frequency and percentages and compared using the χ^2-test or the Fisher exact test, as appropriate. Continuous variables are presented as mean ± *SD* or median and interquartile range and compared using the 2-sample *t*-test or the 2-sample Wilcoxon rank-sum (Mann-Whitney) test. All tests were two-tailed, and $p < 0.05$ was considered significant. Analysis of between period trends were performed using the Cochran-Armitage trend test or linear regression as appropriate.

Time-to-event curves were constructed using the Kaplan–Meier method and compared using the log-rank test. Given competing risks, cumulative incidence functions were used to plot 1 year risk of TVR and acute MI. Univariate and multivariate Cox regression models were conducted to evaluate the association between complexity and outcomes, and the association between time period and outcomes within the complex PCI group. The following covariates were included in the multivariable model: age, hypertension, diabetes mellitus (DM) congestive heart failure (CHF), severe left ventricular (LV) systolic function, prior myocardial infarction (MI) or ACS, cardiogenic shock and renal failure. Covariate were selected owing to uneven distribution between study groups. All analyses were performed using R (R-studio, V.4.0.0, Vienna, Austria).

RESULTS

Patients and Procedural Characteristics

Of 20,301 procedures performed over a period of 12 years (2008–2020), 5,647 (27.8%) were identified as complex. Baseline

TABLE 1 | Baseline characteristics, complex vs. non-complex PCI.

Variable	Non-complex 14,654 (72.2%)	complex 5,647 (27.8%)	*P*-value
Age (years)	65.6 ± 11.9	66.3 ± 12.6	<0.001
Female gender	3,194 (21.8)	1,208 (21.4)	0.56
Hypertension	11,312 (77.2)	4,218 (74.7)	<0.001
Smoking Hx	5,305 (36.2)	2,010 (35.6)	0.37
Diabetes mellitus	7,239 (49.4)	2,677 (47.4)	0.01
Dementia	278 (1.9)	136 (2.4)	0.02
CHF	1,553 (10.6)	700 (12.4)	<0.001
Prior CABG	1,597 (10.9)	1,124 (19.9)	<0.001
Anticoagulation	1,246 (8.5)	587 (10.4)	<0.001
Hemoglobin	13.3 ± 1.8	13.2 ± 1.8	0.12
eGFR	82.1 ± 28.6	79.8 ± 29.0	<0.001
Prior MI or ACS	8,133 (55.5)	3,569 (63.2)	<0.001
Proximal LAD	2,696 (18.4)	1,383 (24.5)	<0.001
Radial access	7,415 (50.6)	2,541 (45)	<0.001
Severe LV function	2,330 (15.9)	1,207 (21.4)	<0.001
IIbIIIa inhibitor administration	1,099 (7.5)	672 (11.9)	<0.001
Cardiogenic shock	117 (0.8)	141 (2.5)	<0.001

Values are expressed as n (%) or mean ± SD.
PCI, percutaneous coronary intervention; CHF, congestive heart failure; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; ACS, acute coronary syndrome; LAD, left anterior descending; LV, left ventricle.

characteristics of complex vs. non-complex PCIs are shown in **Table 1**. There was no difference in gender distribution or smoking between the groups (p = NS for both). Patients in the C-PCI group were older (66.3 ± 12.6 vs. 65.6 ± 11.9, $p < 0.001$), had lower estimated glomerular filtration rate (eGFR) (79.8 ± 29.0 vs. 82.1 ± 28.6, $p < 0.001$), were more likely to have CHF (12.4 vs. 10.6%, $p < 0.001$) and severe LV systolic function (21.4 vs. 15.9%, $p < 0.001$), were more likely to present as ST-elevation myocardial infarction (STEMI) (20.9 vs. 11.2%, $p < 0.001$) or cardiogenic shock (2.5 vs. 0.8%, $p < 0.001$), were more likely to be treated using anti-coagulation therapy (10.4 vs. 8.5%, $p < 0.001$), had a higher rate of significant proximal left anterior descending (LAD) disease (24.5 vs. 18.4%, $p < 0.001$), were less likely to be catheterized *via* transradial approach (45.0 vs. 50.6%, $p < 0.001$), and were treated with a IIbIIIa inhibitors more frequently (11.9 vs. 7.5%, $p < 0.001$), as compared to the non-complex PCI group. Baseline characteristics of patients who underwent C-PCI procedures, grouped to 4 periods (2008–2010, 2011–2013, 2014–2016, 2017–2019), are shown in **Table 2**. There was no difference between the groups in gender distribution, smoking rate, DM rate or eGFR (p = NS for all). A positive temporal trend was observed in patient age (65.1 ± 12.7 vs. 66.5 ± 12.9 vs. 67.3 ± 12.4 vs. 66.3 ± 12.5, respectively, $p = 0.01$), rate of hypertension (79.3% vs. 76.4% vs. 74.8% vs. 70.2%, respectively, $p < 0.001$), significant proximal LAD disease (20.2% vs. 20.8% vs. 24.4% vs. 30.3%, respectively, $p < 0.001$), and transradial approach rate (3.4% vs. 31.0% vs. 64.7% vs. 69.7%, respectively, $p < 0.001$), while a negative temporal trend was detected in the rate of CHF (18.3% vs. 16.1% vs. 10.7% vs. 6.9%, respectively, $p < 0.001$), previous CABG (25.8% vs. 22.3% vs. 18.7% vs. 14.8%, respectively, $p < 0.001$), cardiogenic shock on presentation (3.2% vs. 3.0% vs. 2.1% vs. 2%, respectively, $p < 0.05$) and IIbIIIa inhibitor administration (26.9% vs. 15.8% vs. 6.8% vs. 5.3%, respectively, $p < 0.001$).

Temporal Trends of Clinical Outcomes

The rate of C-PCI procedures has risen significantly since 2017 ($p < 0.01$) (**Figure 1**), mainly driven by bifurcation and LM

TABLE 2 | Baseline characteristics of complex PCI per period.

Variable	2008–2010 1,263 (22.4%)	2011–2013 1,232 (21.8%)	2014–2016 1,387 (24.6%)	2017–2019 1,765 (31.2%)	*P*-value
Age (years)	65.1 ± 12.7	66.5 ± 12.9	67.3 ± 12.4	66.3 ± 12.5	0.01
Female gender	251 (19.9)	278 (22.6)	301 (21.7)	379 (21.5)	0.50
Hypertension	1,002 (79.3)	941 (76.4)	1,037 (74.8)	1,239 (70.2)	<0.001
Smoking Hx	462 (36.6)	400 (32.5)	456 (32.9)	688 (39)	0.12
Diabetes mellitus	623 (49.3)	580 (47.1)	642 (46.3)	830 (47.0)	0.28
Dementia	33 (2.6)	25 (2.0)	33 (2.4)	44 (2.5)	0.89
CHF	231 (18.3)	198 (16.1)	148 (10.7)	122 (6.9)	<0.001
Prior CABG	326 (25.8)	275 (22.3)	259 (18.7)	261 (14.8)	<0.001
Anticoagulation	130 (10.3)	136 (11.0)	122 (8.8)	199 (11.3)	0.73
Hemoglobin	13.2 ± 1.8	13.2 ± 1.9	13.3 ± 1.8	13.3 ± 1.8	0.92
eGFR	82.2 ± 28.1	81.6 ± 30.5	77.6 ± 27.7	78.6 ± 29.3	0.59
Prior MI or ACS	820 (64.9)	777 (64.9)	859 (61.9)	1,114 (63.1)	0.36
Proximal LAD	255 (20.2)	256 (20.8)	338 (24.4)	535 (30.3)	<0.001
Radial access	43 (3.4)	382 (31.0)	897 (64.7)	1,220 (69.1)	<0.001
Severe LV function	259 (20.5)	269 (21.8)	275 (19.8)	408 (23.1)	0.23
IIbIIIa inhibitor administration	340 (26.9)	195 (15.8)	94 (6.8)	94 (5.3)	<0.01
Cardiogenic shock	40 (3.2)	37 (3.0)	29 (2.1)	35 (2)	0.04

Values are expressed as n (%) or mean ± SD.
PCI, percutaneous coronary intervention; CHF, congestive heart failure; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; ACS, acute coronary syndrome; LAD, left anterior descending; LV, left ventricle.

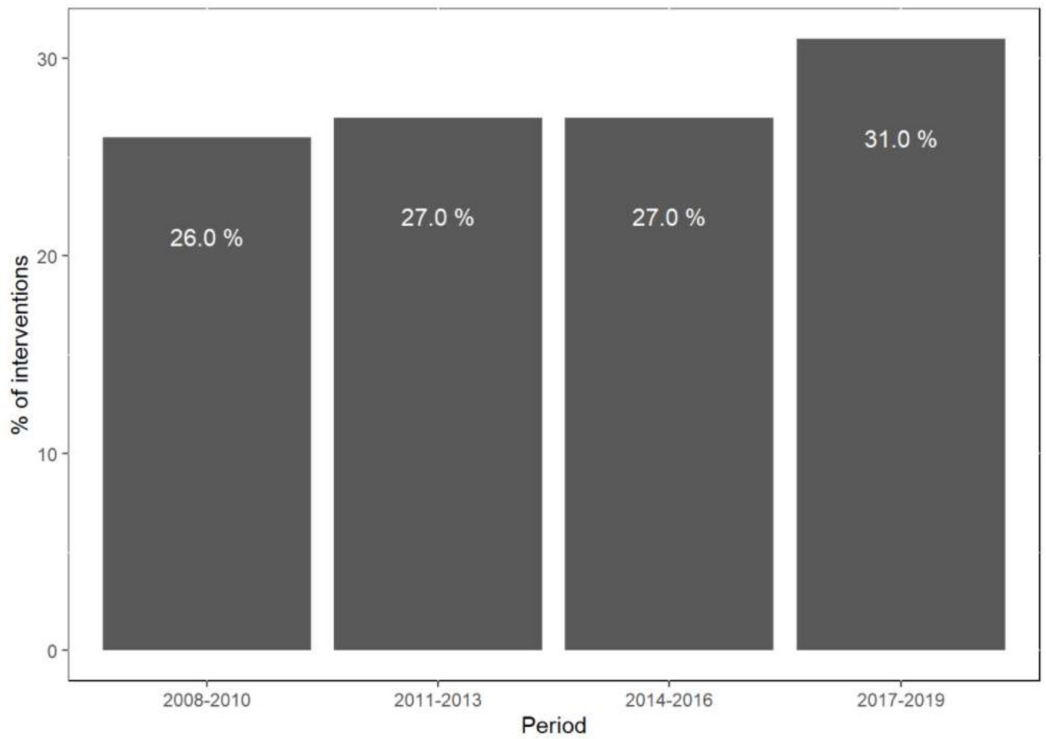

FIGURE 1 | Rate of complex PCI (percent of total interventions) per time period.

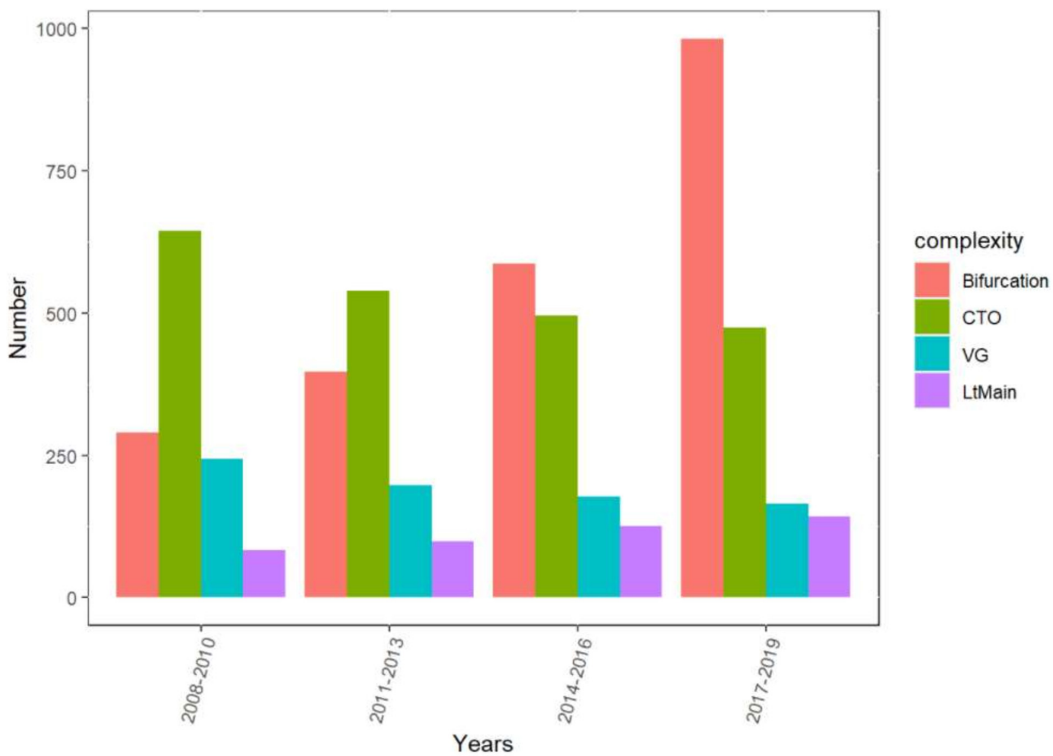

FIGURE 2 | Interventions grouped by time period and complexity definition.

TABLE 3 | Complex vs. non-complex outcomes.

Variable	Non-complex 14,654 (72.2%)	Complex 5,647 (27.8%)	*P*-value
Death	746 (5.1)	474 (8.4)	<0.001
TVR	654 (4.5)	317 (5.6)	<0.001
Acute MI	580 (4.0)	311 (5.5)	<0.001
MACE	1,515 (10.3)	872 (15.4)	<0.001

Values are expressed as n (%) or mean ± SD.
PCI, percutaneous coronary intervention; TVR, Target vessel revascularization MI, myocardial infarction; MACE, major adverse cardiovascular event.

interventions ($p < 0.01$), whereas the amount of SVG and CTO procedures has steadily declined ($p < 0.01$) (**Figure 2**).

Outcomes of complex vs. non-complex PCIs are shown in **Table 3**. At 1-year, rates of death (8.4 vs. 5.1%, $p < 0.001$), acute MI (5.5 vs. 4.0%, $p < 0.001$), TVR (5.6 vs. 4.5%, $p = 0.001$) and MACE (15.4 vs. 10.3%, $p < 0.001$), were all significantly higher in the C-PCI group, as compared to the non-complex group (**Figures 3**, **4**). Notably, even though MACE was significantly lower in the later periods in both complex and non-complex groups (**Figure 5**), overall all-cause mortality did not change during the study period, regardless of complexity (**Figure 6**). Interaction between C-PCI and MACE (HR: 0.88, 95% CI 0.84–0.92, $p < 0.001$) was found to be significant. In contrast, interaction between C-PCI and death (HR: 1.02, 95% CI 0.96–1.09, $p = 0.444$) was not significant.

Temporal outcomes of patients who underwent C-PCIs are shown in **Table 4**. Rates of MACE at 1-year were significantly lower in both the 2014–2016 and 2017–2019 groups, as compared to the 2008–2010 and 2011–2013 groups (13.8% and 13.5% vs. 17.3% and 18.2%, $p = 0.001$, respectively). This was driven by lower rates of TVR at 1-year (4.4% and 4.8% vs. 6.7% and 7.1%, $p = 0.01$, respectively). There was no difference in rates of acute MI (4.6% vs. 5.9% vs. 5.2% vs. 6.2%, $p = 0.76$, respectively) or death (8.2% vs. 8.3% vs. 8.3% vs. 8.8%, $p = 0.83$, respectively) at 1-year between the groups. Cumulative incidence of TVR and acute-MI at 1 year, grouped by time periods, are shown in **Figures 7**, **8**, respectively.

The results of the COX regression analyses are shown in **Tables 5**, **6**. After adjustment for possible confounders, C-PCI was an independent risk factor for both death (HR: 1.34, 95%CI 1.19–1.51, $P < 0.001$) and MACE (HR- 1.30, 95%CI 1.19–1.42, $P < 0.001$). As to the effect of time periods on outcomes of C-PCI: only the most recent time period (2017–2019) emerged as an independent prognostic variable of lower MACE rate (compared to 2008–2011, HR: 0.79, 95% CI 0.66–0.96, $p = 0.015$). Notably, a trend toward lower 1-year MACE was observed throughout the study period (HR: 0.91, 95%CI 0.86–0.97, p for trend = 0.02).

DISCUSSION

In the current study, from a large cohort of 20,301 consecutive patients, we observed an increased incidence of C-PCI procedures, with a trend toward reduced 1-yaer MACE rate following complex PCI. One-year mortality rates remained unchanged. To our knowledge, the current research represents the largest single center C-PCI registry, comparing trends over a 12-year period.

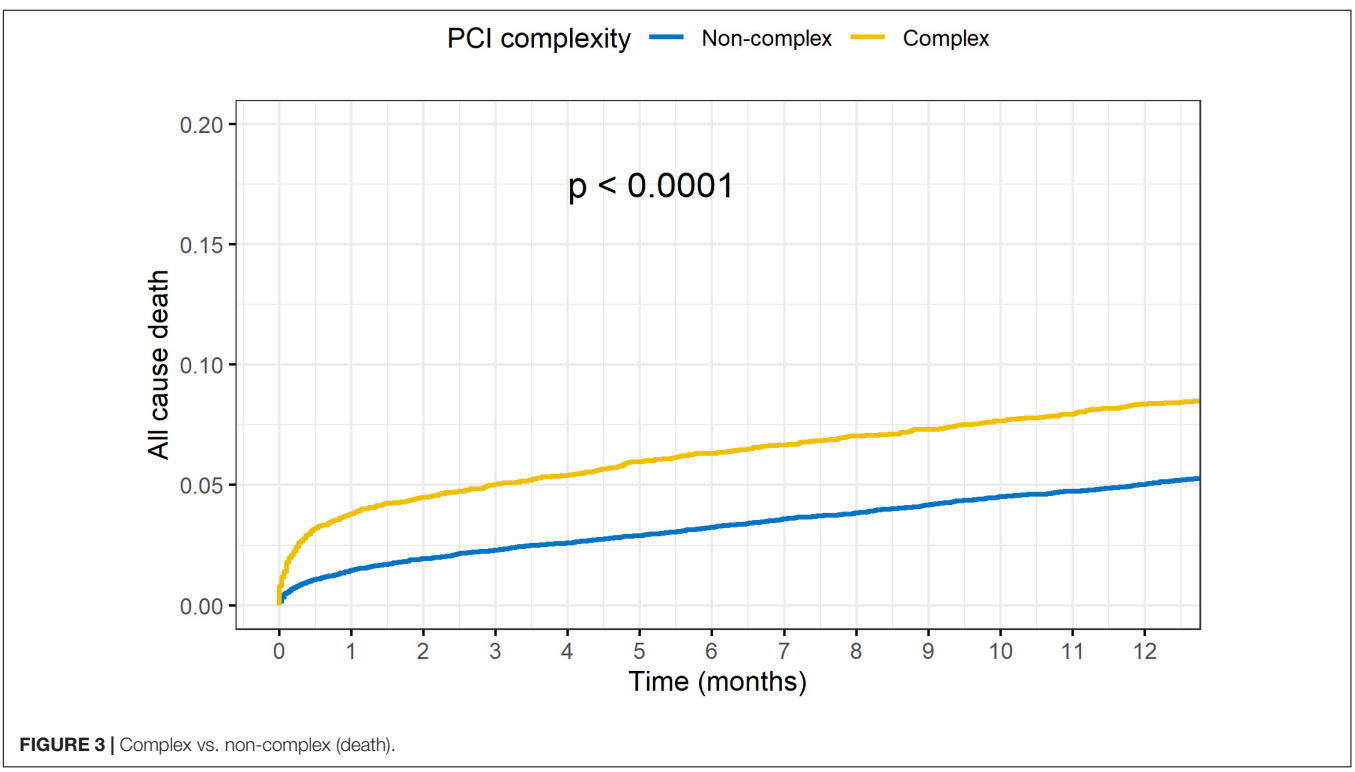

FIGURE 3 | Complex vs. non-complex (death).

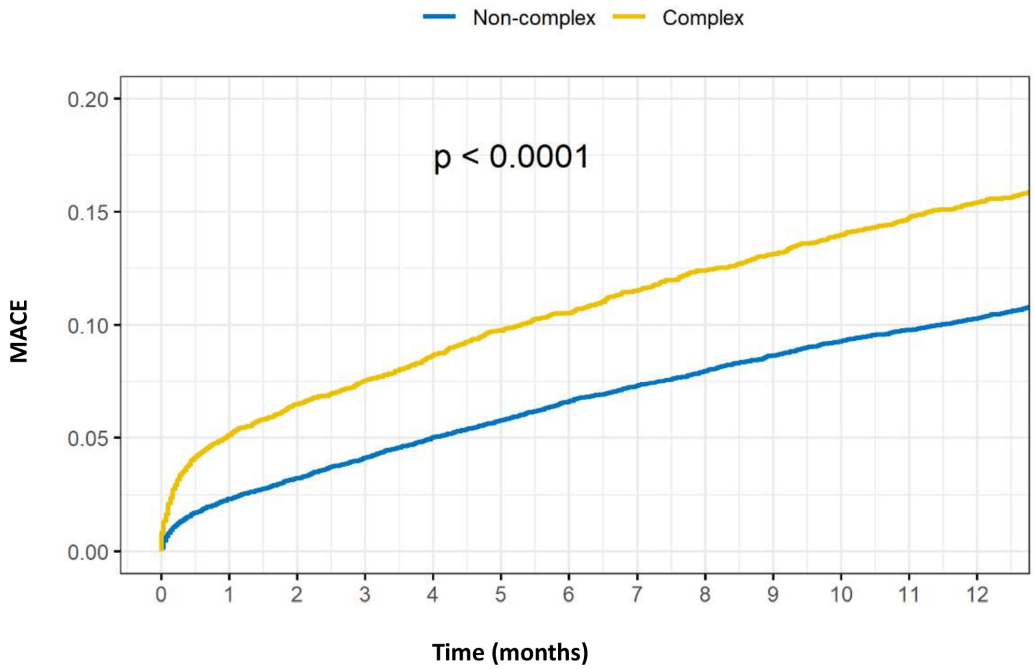

FIGURE 4 | Complex vs. non-complex (MACE).

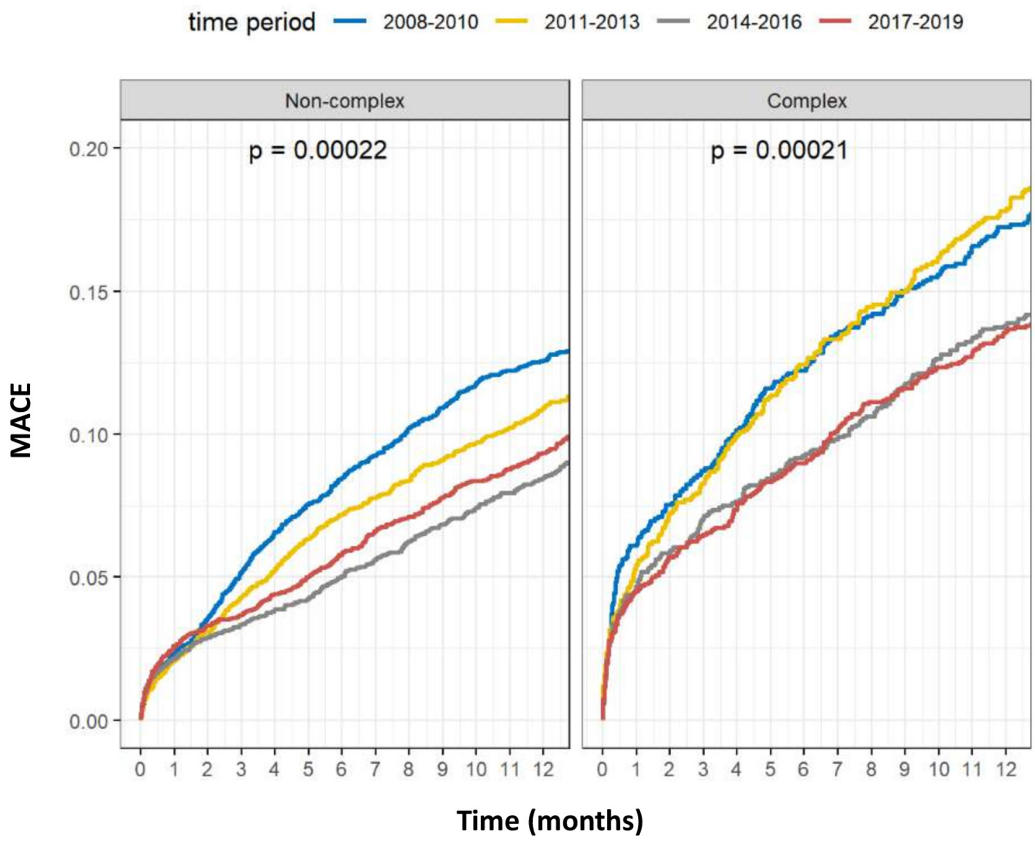

FIGURE 5 | Complex vs. non-complex (per time period MACE).

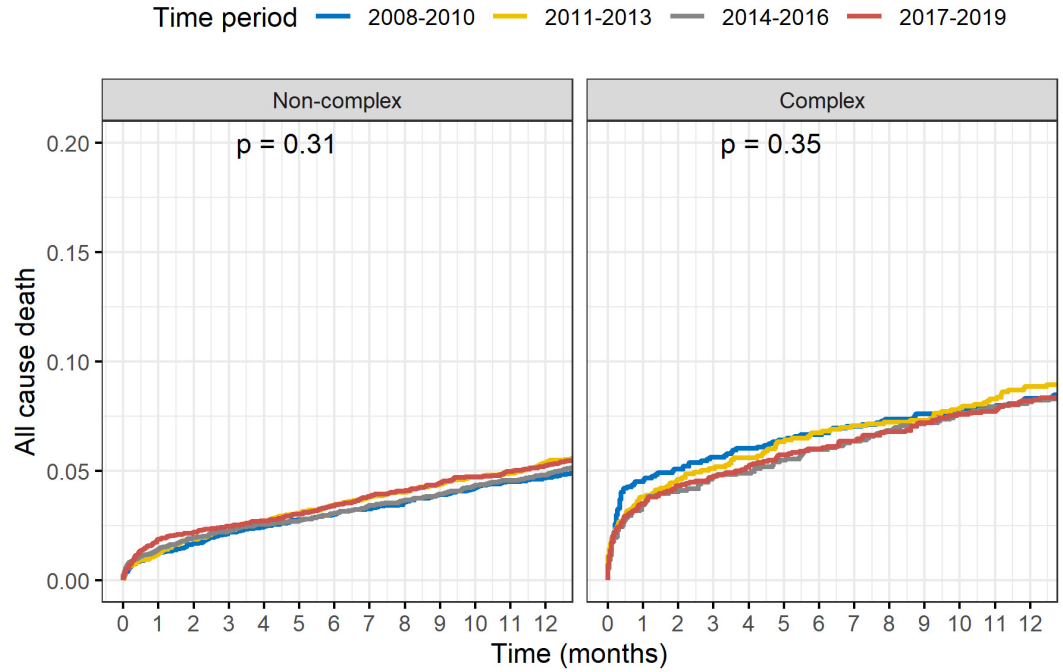

FIGURE 6 | Complex vs. non-complex (per time period death).

TABLE 4 | Complex PCI—temporal outcomes.

Variable	2008–2010 1,263 (22.4%)	2011–2013 1,232 (21.8%)	2014–2016 1,387 (24.6%)	2017–2019 1,765 (31.2%)	*P*-value
Death	105 (8.3)	109 (8.8)	114 (8.2)	146 (8.3)	0.83
TVR	84 (6.7)	87 (7.1)	61 (4.4)	85 (4.8)	0.01
Acute MI	66 (5.2)	76 (6.2)	64 (4.6)	105 (5.9)	0.76
MACE	218 (17.3)	224 (18.2)	192 (13.8)	238 (13.5)	0.001

Values are expressed as n (%) or mean ± SD.
PCI, percutaneous coronary intervention; TVR, Target vessel revascularization MI, myocardial infarction; MACE, major adverse cardiovascular event.

Our study demonstrates a gradual rise in the rate of C-PCI procedures over the last decade. This observation could be explained by the evolution of PCI over that time period, coupled with the rising age and increasing comorbidity profile of our patient population (11). Indeed, more patients are offered PCI in lieu of CABG owing to the progressively narrowing gap in treatment effect between PCI and CABG (4). On the other end, more people who would have been treated conservatively previously are now offered revascularization with PCI. Analyzing the data, the following patterns emerged—a gradual increase in LM and bifurcation interventions, and significant decrease in SVG and CTO intervention procedures. Several explanations apply: First, PCI for left main disease of low or intermediate anatomic complexity has been studied extensively in the past decade and was shown to have comparable outcomes with CABG (12, 13). Second, both scientific data and clinical expertise, which accumulated during the past decade, has dramatically increased the number of bifurcation procedures. The recent NORDIC-BALTIC (14) trial reinforced the findings of earlier BBC (15) and CACTUS (16) trials, favoring provisional side branch stenting, without the routine stenting of both main and side branches in true bifurcations.

We hypothesize that the simplification of bifurcation stenting has led to a wider application of PCI in bifurcation lesions, previously treated conservatively. Additionally, contemporary bifurcation stenting technique emphasize side-branch wire protection and preservation which may lead to a more "inclusive" definition of bifurcation lesion. While provisional stenting is favored in non-LM disease, some evidence supports the upfront 2-stent DK-crush technique in LM disease. The evolution of bifurcation stenting: classic crush—classic crush with kissing balloon inflation (KBI)—mini crush—DK crush—nano crush (17), could by itself lead to increased rates of C-PCI procedures as it offers new solution for complex coronary anatomy. In keeping with the findings of these trials, our research shows a gradual increase in the amount of bifurcation procedures over the last decade.

In contrast, CTO and SVG interventions have been steadily declining over that period of time. Despite the FREEDOM (18) trial which demonstrated CABG superiority over PCI for

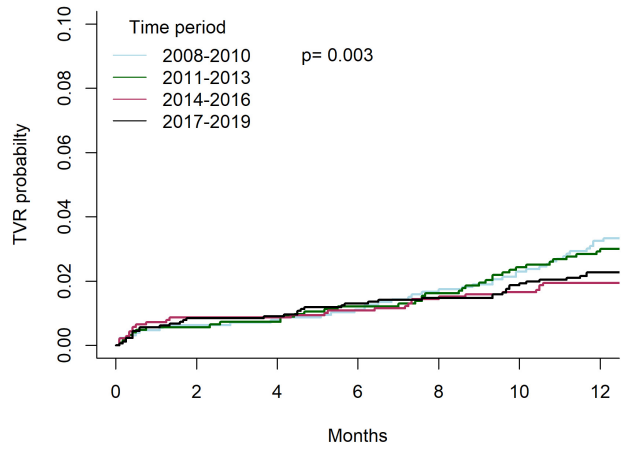

FIGURE 7 | Cumulative incidence of TVR at 1 year, grouped by time period.

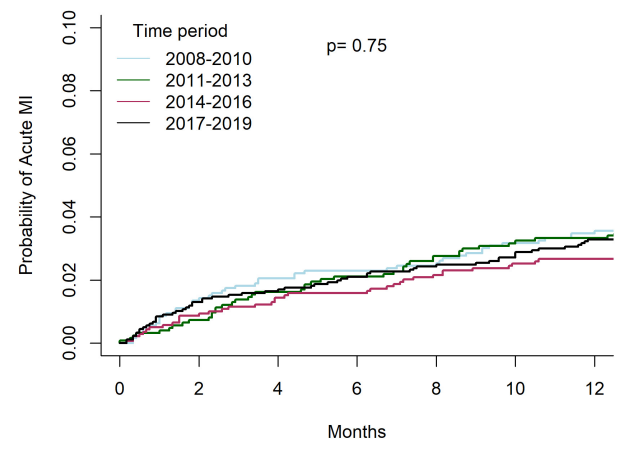

FIGURE 8 | Cumulative incidence of acute-MI at 1 year, grouped by time period.

TABLE 5 | Cox regressions models—complex vs. non-complex PCI.

Outcome	HR (95% CI)	*P*-value
Death univariate	1.69 (1.50–1.89)	<0.001
Death multivariate*	1.34 (1.19–1.51)	<0.001
MACE univariate	1.55 (1.42–1.68)	<0.001
MACE multivariate*	1.30 (1.19–1.42)	<0.001

**Adjusted to—age, hypertension, diabetes mellitus, congestive heart failure, severe left ventricular systolic function, previous myocardial injury or acute coronary syndrome, cardiogenic shock and renal failure.*
MACE, major adverse cardiac events.

TABLE 6 | Cox regressions models—advanced time periods compared to the reference time period (2008–2010).

Outcome	HR (95% CI)	*P*-value	*P* for trend
1 year death univariate			0.778
2011–2013	1.06 (0.81–1.39)	0.662	
2014–2016	0.98 (0.75–1.28)	0.892	
2017–2019	0.99 (0.77–1.27)	0.933	
1-year death multivariate*			0.572
2011–2013	0.92 (0.70–1.21)	0.578	
2014–2016	0.98 (0.75–1.28)	0.901	
2017–2019	0.90 (0.70–1.16)	0.417	
1-year MACE univariate			< 0.001
2011–2013	1.05 (0.87–1.26)	0.609	
2014–2016	0.78 (0.64–0.95)	0.014	
2017–2019	0.77 (0.64–0.92)	0.005	
1-year MACE multivariate*			0.002
2011–2013	1.02 (0.85–1.24)	0.776	
2014–2016	0.83 (0.69–1.02)	0.073	
2017–2019	0.79 (0.66–0.96)	0.015	

**Adjusted to—age, hypertension, diabetes mellitus, congestive heart failure, severe left ventricular systolic function, previous myocardial injury or acute coronary syndrome, cardiogenic shock and renal failure.*
MACE, major adverse cardiac events.

patients with multivessel CAD and DM, the total amount of PCIs is on the rise with a parallel decline in CABG (19). As described earlier, this phenomenon might be explained by the combination of worsening risk profile in patient eligible for revascularization combined with practical advances in C-PCIs in the form of cumulative experience, new techniques and more efficient devices. Moreover, the revolution of transcatheter aortic valve replacement (TAVR) over the last decade has diminished the role of CABG even further. CAD and aortic stenosis frequently coexist; hence PCI is frequently pursued pre-TAVR after discussions between the patient and the Heart Team (20). As to SVGs in particular, their use has been declining steadily over the past decade due to their worse outcomes as compared to arterial grafts (21, 22). Moreover, when comparing PCI of a diseased native artery with PCI of an SVG in patients with previous CABG who require PCI, SVG PCI has worse outcomes as shown by Redfors et al. (23), patient who underwent SVG PCI had higher rates of cardiac death, stent thrombosis, ischemia-driven target-vessel revascularization, and overall MACE at 2 years than did those who underwent PCI of the native vessel, whenever it is feasible. Furthermore, as was shown by Brilakis et al. (24), SVG PCI had higher rates of in hospital death, no-reflow, periprocedural MI, and cardiogenic shock as compared with PCI of the native vessel in patient with prior CABG. Hence, decrease in the number of CABGs, combined with the decreased use of SVGs during these surgeries, and the worse outcomes as compared to native vessel intervention, may explain the gradual decline in SVG intervention during our follow up.

The principal rational of CTO-PCI is to improve symptoms (25). It is defined as a total occlusion in a coronary artery with non-collateral Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 of at least 3-month duration. CTO-PCI has evolved dramatically in both effectiveness and safety over the last decade and is now a standard complex procedure with a success rate over 90%, in highly experienced centers (26). Contrary to recently published data, our study shows a gradual decrease in CTO procedures. This decline may represent a more selective utilization of CTO-PCI in our institution owing to the absence

of evidence supporting survival benefit (27). Lastly, is should be mentioned that *ad hoc* PCI of CTOs is not uncommon practice in our institution. Some lesions which could have been considered CTOs requiring planned prolonged procedures in the early time periods, may have been easily crossable with the more contemporary equipment and hence not classified as CTO.

LIMITATIONS

This study has several limitations. First, although all data were collected prospectively, we used a single-center observational design which has the inherent limitations associated with a non-randomized comparison. Second, we decided to focus selectively on several important domains of C-PCI: LM, CTO, SVG or bifurcation intervention, and follow their temporal trends. Third, our data did not include either Medina classification for bifurcation lesions nor J-CTO scores for CTOs.

CONCLUSION

Rates of C-PCIs are on the rise, with worse overall outcomes, including higher mortality, as compared to non-complex procedures. Although MACE and TVR decreased significantly throughout the years, acute MI and death remained unchanged. As the complexity of procedures increases, so does the need for a deeper understanding of its pathophysiology, and the need to synergize between complex invasive intervention and secondary prevention during follow up.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Rabin Medical Center, in compliance with the Declaration of Helsinki. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MK wrote the first and final draft of the manuscript. SV, HV-A, and GG collected data and contributed to the analysis. TB organized the database. AS, PC, GW, and YT wrote sections of the manuscript. LP and RK contributed to the design of the study. AL conceived and designed the analysis and reviewed the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Impact of concomitant COVID-19 on the outcome of patients with acute myocardial infarction undergoing coronary artery angiography

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Background: The impact of COVID-19 on the outcome of patients with MI has not been studied widely. We aimed to evaluate the relationship between concomitant COVID-19 and the clinical course of patients admitted due to acute myocardial infarction (MI).

Methods: There was a comparison of retrospective data between patients with MI who were qualified for coronary angiography with concomitant COVID-19 and control group of patients treated for MI in the preceding year before the onset of the pandemic. In-hospital clinical data and the incidence of death from any cause on 30 days were obtained.

Results: Data of 39 MI patients with concomitant COVID-19 (COVID-19 MI) and 196 MI patients without COVID-19 in pre-pandemic era (non-COVID-19 MI) were assessed. Compared with non-COVID-19 MI, COVID-19 MI was in a more severe clinical state on admission (lower systolic blood pressure: 128.51 ± 19.76 vs. 141.11 ± 32.47 mmHg, $p = 0.024$), higher: respiratory rate [median (interquartile range), 16 (14–18) vs. 12 (12–14)/min, $p < 0.001$], GRACE score (178.50 ± 46.46 vs. 161.23 ± 49.74, $p = 0.041$), percentage of prolonged (>24 h) time since MI symptoms onset to coronary intervention (35.9 vs. 15.3%; $p = 0.004$), and cardiovascular drugs were prescribed less frequently (beta-blockers: 64.1 vs. 92.8%, $p = 0.009$), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers: 61.5 vs. 81.1%, $p < 0.001$, statins: 71.8 vs. 94.4%, $p < 0.001$). Concomitant COVID-19 was associated with seven-fold increased risk of 30-day mortality (HR 7.117; 95% CI: 2.79–18.14; $p < 0.001$).

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Conclusion: Patients admitted due to MI with COVID-19 have an increased 30-day mortality. Efforts should be focused on infection prevention and implementation of optimal management to improve the outcomes in those patients.

KEYWORDS

novel coronavirus, COVID-19, myocardial infarction, revascularization, comorbidity

Introduction

Since the beginning of the global pandemic, over 425 million people worldwide and nearly 6 million people in Poland have contracted coronavirus disease (COVID-19) with associated reported deaths exceeding 6 million and 100 thousand worldwide and in Poland, respectively (1, 2). COVID-19 has now become one of the leading causes of death globally, with death number comparable to those from cardiovascular disease (CVD) or cancer (1, 2). Although there is currently a declining trend in infection rates, it is expected that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection will likely remain at least as a dangerous, periodically recurring disease at an endemic level.

The pandemic has significantly impacted the behavior of patients suffering from myocardial infarction (MI). Due to increased levels of anxiety associated with interactions with healthcare workers as well at least partially limited access to in- and out-patient setting, an overall decrease in the number of invasive procedures and number of patients admitted due to ST elevation myocardial infarction (STEMI) and an increased amount of time from the first symptoms of MI to intervention have been observed in comparison with the pre-pandemic period (3–5).

Furthermore, an increasing amount of data suggests that during COVID-19, not only is the respiratory system involved but data also demonstrate that the cardiovascular system may be affected which can lead to myocardial injury. These patients tend to have a significantly worse prognosis than those without the myocardial injury (6–8). So far, it has been proven that the inflammatory and immune response due to viral infection has also had a role in the pathogenesis of an acute MI (9, 10). However, there are only a few studies that have assessed the impact of the COVID-19 infection on the outcome in the setting of patients with acute MI requiring revascularization (11, 12).

Even though it intuitively appears to be obvious that the patients with signs of a viral infection and MI even when optimally treated [including percutaneous coronary interventions (PCIs)] have a worse prognosis than patients with MI but without a viral infection, there is still a profound need to quantify this difference in the form of a mortality risk which up to this point has not been quantified. This, in turn, will allow for the implementation of adequate strategies aiming to reduce the risk of an undesirable prognosis in patients suffering from MI complicated with a concomitant COVID-19. Moreover, there is less to no data about the differences in the clinical course, comorbidities, and other factors influencing the outcome in patients with myocardial infarction depending on the presence/absence of COVID-19. Thus, we decided to compare the groups of patients admitted to our hospital due to MI and qualified for coronary angiography with concomitant SARS-CoV-2 infection against a control group consisting of patients treated for MI in our hospital in the preceding year before the onset of the pandemic.

Materials and methods

We retrospectively studied the medical records of all consecutive patients who were admitted due to MI with concomitant SARS-CoV-2 infection to the University Hospital in Krakow between 6 March 2020 and 15 May 2021. In this described period, all patients admitted to our hospital, including those with MI on admission were diagnosed with SARS-CoV-2 infection according to the WHO and Polish guidelines using the reverse transcription polymerase chain reaction (RT-PCR) method (rhino-oropharyngeal swab positivity for SARS-CoV-2 RNA) (13–15). Patients with COVID-19 were treated according to the treatment algorithm recommended by the Polish Association of Epidemiologists and Infectiologists (13, 14). All patients in our study were diagnosed with MI and received the standard medical therapy according to the European Society of Cardiology (ESC) guidelines, and all were ultimately qualified for coronary angiography (16, 17).

For the control group, we retrospectively studied the medical records of all consecutive patients who were admitted due to MI and qualified for coronary angiography to the University Hospital in Krakow between the period of 15 April 2019 and 15 September 2019. The time period for the non-COVID-19 MI group of patients chosen for analysis was selected to minimize the possible impact of other viral infections on the clinical course of MI (in our country, a peak incidence of respiratory viral infections has regularly been noticed between the months of January–March each epidemic season and nearly

no incidences of these aforementioned infections during the mid-Spring to Summer seasons) (18). Additionally, this enabled us to avoid the possibility of inclusion in control group patients with undiagnosed SARS-CoV-2 infection or inclusion of patients with MI which occurred after SARS-CoV-2 infection (either diagnosed or undiagnosed) which could have had an impact on the outcome during MI. Cardiovascular risk factors and cardiovascular diseases were identified based on the previous medical history of diagnosis and/or treatment and defined according to the current ESC guidelines (19). All clinical data including demographics, medical history, inpatient clinical course, laboratory results, treatments, and in-hospital outcomes were obtained from the electronic medical records used by the University Hospital in Krakow. The estimated glomerular filtration rate (eGFR) was calculated from the Modification of Diet in Renal Disease (MDRD) formula (20). Heart rate, arterial blood pressure, Killip class, and Global Registry of Acute Coronary Events (GRACE) risk score were assessed in all patients based on their clinical condition (21). Thrombolysis in myocardial infarction (TIMI) coronary flow grade scores was evaluated before and after PCI (22). The primary percutaneous coronary intervention was defined as the strategy of taking a patient with MI directly to the cardiac catheterization laboratory to undergo mechanical revascularization. Transthoracic two-dimensional echocardiography was performed in patients during the admission to the Cardiology Department to measure left ventricular ejection fraction (LVEF). Based on the data obtained from the Universal Electronic System for Registration of the Population in Poland, the occurrence of death from any cause at 30 days was evaluated for all study participants. Our study was an observational retrospective analysis of anonymized electronic medical records of patients hospitalized in our hospital. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Bioethics Committee of the Jagiellonian University (no. 1072.6120.278.2020 and no. 1072.6120.333.2020).

Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables were expressed as means and standard deviation (SD) or medians and interquartile range (IQR). Normality was assessed by the Shapiro–Wilk test. We divided the study population into two groups according to their diagnosis of COVID-19. Differences between groups were compared using the Student's or Welch's *t*-test depending on the equality of variances for normally distributed variables. The Mann–Whitney U test was used for non-normally distributed continuous variables. Cox-proportional hazards models were fit to determine the adjusted associations between cofounders (including COVID-19 status) and mortality. Variables that were associated with the occurrence of 30-day mortality with a significance level of $p < 0.2$ in the bivariable models as well as other variables judged to be of clinical importance were selected for possible inclusion in the multivariable logistic regression model to predict the occurrence of the outcome. Adjusted hazard ratios (HRs), along with 95% confidence intervals (CIs), were computed for all covariates. The proportional hazards model assumptions were checked using the Schoenfeld test and graphical diagnostics. Furthermore, to analyze event-free survival in 30-day follow-up after hospital admission due to MI, Kaplan–Meier curves were drawn for all patients stratified by COVID-19 status. In all analyses, a *p*-value of 0.05 or less was considered statistically significant. The statistical analysis was performed with the IBM SPSS 24.0 software package, STATA software, version 15 and R Core Team (2020).

Results

Study population and clinical characteristics

A total of 235 patients [94 women (40.0%)] with MI were reviewed. The mean age ± standard deviation (SD) was 68.46 ± 12.21 years. There were 79 (33.61%) patients with STEMI and 156 (66.38%) with no ST elevation myocardial infarction (NSTEMI). Arterial hypertension (82.55%) and diabetes (41.28%) were the predominant coexisting diseases. There were 58 patients (24.68%) with Killip class 3 or 4. Multivessel disease (MVD) was found in 85 subjects (36.17%). Median (interquartile range) time from the onset of symptoms to coronary angiography was 480.9 (240–1,200) min. Half of the study group was qualified for PCI (124 patients, 52.77%). Among patients who underwent PCI, STEMI was diagnosed in 44 patients (35.5%), left main coronary artery (LMCA) was infarct-related artery (IRA) in 3 patients (2.4%), and total occlusion of an IRA was seen in 36 patients (29.0%). TIMI 3 after PCI was achieved in 113 patients (93.4%).

There were 39 patients with MI and concomitant COVID-19 (COVID-19 MI group) and 196 patients with MI and without COVID-19 (non-COVID-19 MI group). There were no significant differences concerning age, gender, body mass index (BMI), and comorbidities (i.e., arterial hypertension, heart failure, chronic kidney disease, diabetes, atrial fibrillation, chronic obstructive pulmonary disease, history of previous myocardial infarction, and history of previous coronary artery bypass graft) observed between study groups (Table 1).

In-hospital course, angiographic findings, drugs therapy, and predictors of 30-day mortality

Patients with COVID-19 MI presented a more severe clinical state on admission (assessed by a lower systolic blood pressure, higher respiratory rate, higher GRACE score) in

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TABLE 1 Basic characteristics of participants.

Characteristics	Non-COVID-19 MI *N* = 196 (83.4%)	COVID-19 MI *N* = 39 (16.6%)	*p* value[$]
Age, years, mean (SD)	68.03 (12.31)	70.64 (11.60)	0.233
Female sex, *n* (%)	79 (40.3)	15 (38.5)	0.489
BMI*, kg/m^2, mean (SD)	26.66 (5.01)	27.01 (3.90)	0.324
Pre-existing conditions, *n* (%)			
Arterial hypertension	161 (82.1)	33 (84.6)	0.458
Diabetes mellitus	84 (42.9)	13 (33.3)	0.178
History of previous MI	52 (26.5)	12 (30.8)	0.358
History of CABG	7 (3.6)	3 (7.7)	0.220
Heart failure	55 (28.1)	11 (28.2)	0.563
Atrial fibrillation	28 (14.3)	10 (25.6)	0.069
Malignant disease	14 (7.1)	3 (7.7)	0.560
COPD	4 (2.0)	2 (5.1)	0.261
Chronic kidney disease	22 (11.2)	5 (12.8)	0.476

Data are presented as mean (SD), median (Q1–Q3), or number (%).
*Data available for 43 patients (35 for non-COVID-19 MI and 8 for COVID-19 MI).
[$]For between non-COVID-19 MI group and COVID-19 MI group difference.
BMI, body mass index; CABG, coronary artery bypass graft, COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; MI, myocardial infarction.

comparison with the non-COVID-19 MI group; however, there were no significant differences in the frequency of STEMI/NSTEMI, admission values of high sensitivity cardiac troponin (hs cTn), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and LVEF between groups (Table 2). The frequency rate of PCI and non-obstructive coronary artery disease were similar between study groups, and no significant differences were found in the IRA, the percentage of reaching TIMI 3 after PCI, the frequency rate of primary PCI or MVD, and the amount of contrast used during coronary invasive procedure. In patients with COVID-19 MI (in comparison with patients with non-COVID-19 MI), there was a significantly higher percentage of patients with prolonged time (>24 h) from the initial onset of MI symptoms to coronary intervention. Patients with MI and COVID-19 had significantly higher levels of peak NT-proBNP, but there were no differences in peak hs cTn and peak creatinine during the hospital stay when compared to patients with non-COVID-19 MI. In comparison with patients with non-COVID-19 MI, COVID-19 MI subjects received less frequently cardiovascular drugs (beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and statins). Even though there were no differences between the study groups in the frequency rate of need for mechanical ventilation and catecholamine use during a hospital stay, there was a significantly higher 30-day mortality rate in patients with MI and COVID-19 (Table 3).

The Kaplan–Meier curves in Figure 1 display that patients with non-COVID-MI had higher survival rate, than patients with COVID-19 MI based on a 30-day observation period (Figure 1).

In the Cox-proportional hazards model advanced age, STEMI, reduced LVEF, and COVID-19 were associated with an increased risk of 30-day mortality (Figure 2).

Discussion

The main finding of our study is that the patients who have suffered from both acute MI and have contracted the COVID-19 have a significantly higher 30-day risk of mortality compared to those patients with MI who did not have COVID-19. Despite no significant differences in demographics or comorbidities, patients with COVID-19 in our analysis had a worse clinical state at the admission, less frequently received guidelines-recommended medication and coronary intervention that was delayed.

Due to the relatively short observational period of pandemic, the comprehensive reports on the effect of concomitant COVID-19 on the diagnosis, treatment, and outcomes in patients with MI are still being carried out. In North American registry (NACMI), patients with STEMI and COVID-19 were compared to a control group of patients with STEMI treated 5 years before the pandemic (23). This enabled researchers to study both the impact of infection itself on the outcome and to analyze the effect of pandemic on the management of patients with MI (23). In NACMI registry, patients with COVID-positive STEMI were found to have more severe clinical condition before PCI (higher rates of cardiac arrest and cardiogenic shock) in comparison with control group (23). In this registry, the in-hospital mortality rate in COVID-19 group of patients was significantly higher (33%) than in the control group (4%) (23). Additionally, delayed coronary intervention was also observed in this registry among patients with COVID-19 (23). In contrast to our study, the NACMI registry included only patients with STEMI (23) but in another international registry of acute coronary syndromes in patients with COVID-19, Kite et al. (24) included patients with both STEMI and NSTEMI COVID-19-positive and highly suspicious for COVID-19 who underwent invasive coronary angiography and compared them with pre-COVID-19 cohort. It has been observed that in-hospital mortality in patients with COVID-19 was significantly higher than in control subjects in both STEMI and NSTEMI groups (reaching 22 and 6% in STEMI and NSTEMI, respectively) (24). Both the NACMI registry and study of Kite et al. did not assess the possible effect of the frequency of cardiac guidelines-recommended medication in patients with MI according to their COVID-19 status (23, 24). In our study, we included only confirmed by RT-PCR tests COVID-19 cases and additionally, the data about cardiac medication therapy were also assessed.

Both the findings from the above-mentioned registries (23, 24) and the results of our study prompt a deeper consideration

TABLE 2 Clinical characteristics on admission among non-COVID-19 MI and COVID-19 MI group.

Parameters on admission	Non-COVID-19 MI $n = 196$ (83.4%)	COVID-19 MI $n = 39$ (16.6%)	p value[$]
SBP*, mmHg, mean (SD)	141.11 (32.47)	128.51 (19.76)	0.024
DBP*, mmHg, mean (SD)	81.26 (17.92)	79.16 (13.37)	0.499
Heart rate*, /min, mean (SD)	80.23 (18.04)	84.27 (19.58)	0.221
Respiratory rate*, /min, median (IQR)	12 (12; 14)	16 (14; 18)	<0.001
GRACE score*, mean (SD)	161.23 (49.74)	178.50 (46.46)	0.041
Killip 4 class, n (%)	28 (14.3)	5 (12.8)	0.521
STEMI, n (%)	62 (31.6)	17 (43.6)	0.105
Ejection fraction*, mean (SD)	45.25 (14.52)	43.00 (15.19)	0.400
NT-proBNP*, pg/ml, median (IQR)	2,866.00 (767.00; 8,570.50)	6,192.00 (1,071.00; 18,263.00)	0.076
hs cTn*, ng/ml, median (IQR)	2,449.55 (560.60; 11,440.29)	7,503.89 (1,154.93; 21,844.29)	0.063
Creatinine*, μmol/l, median (IQR)	87.00 (70.00; 114.00)	112.00 (71.45; 155.00)	0.022

Data are presented as mean (SD), median (Q1–Q3), or number (%).
[$]for the difference between non-COVID-19 MI group and COVID-19 MI group.
*Data available in: 229 patients for SBP and DBP; 152 patients for NT-pro BNP; 235 patients for hs cTn—high-sensitivity cardiac troponin; 224 patients for creatinine; 235 patients for heart rate; 228 patients for respiratory rate; 235 patients for GRACE score; 231 patients for EF.
COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction; hs cTn, high-sensitivity cardiac troponin; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction.

of to what extent a COVID-19 itself, and to what pandemic-related side factors (delays in patients admission to hospital, logistical challenges related to health systems reorganization, etc.) influenced the higher mortality observed in our study among patients with MI and COVID-19 in comparison with pre-pandemic MI control group. It has been proven that patients with cardiovascular diseases including MI have limited cardiac, renal, and/or pulmonary reserve, making them more susceptible to complications arising from SARS-CoV-2 infection leading to a more severe clinical course (25, 26). In our study, patients with MI and COVID-19 had higher scores on the GRACE scale, lower systolic blood pressure values, and higher respiratory rates compared to patients with non-COVID-19 MI. Those observations may be due to the fact that COVID-19 does not solely affect the respiratory system but also often causes multi-organ failure that can present itself as myocardial injury or aggravation of kidney disease which negatively affects the prognosis of patients suffering from COVID-19 (27). Our observations of significantly different levels of heart and renal failure laboratory markers (higher baseline creatinine and peak NT-proBNP in patients with COVID-19 MI) between study groups support the thesis of cardiac and/or renal involvement in patients with COVID-19. The results of NACMI registry and study of Kite et al. also confirm both respiratory and cardiac involvement in patients with COVID-19 MI (23, 24). Kite et al. (24) reported that among patients with cardiogenic shock, one of the dominant cause of death (31% of cases) was respiratory (despite severe conditions due to cardiogenic shock). In NACMI registry, patients with COVID-19 were reported to have frequently pulmonary infiltrates on chest X-ray (23). Having in mind that it has been proven previously that viral infections (i.e., influenza, SARS, and MERS) have been proven to exacerbate MI (28, 29), we postulate that results of our study and above-mentioned registries confirm that COVID-19 should be considered as the dominant cause of increased mortality in this group of patients.

Since the beginning of pandemic in our hospital, over 5,000 patients with COVID-19 have been hospitalized and precise correlations between cardiovascular diseases and their prognosis have been thoroughly described in our other publication (30). We observed that significant number of patients with COVID-19 present with increased myocardial injury markers (more than 40% for hs cTn and more than 80% for NT-proBNP) which agrees with other published findings (31–34). This might suggest that the process of differentiating myocardial injury from MI in patients with concurrent COVID-19 remains challenging. Additionally, the diagnosis of MI with indications for coronary innervation might be time-consuming in those patients. This may also attribute to the significantly longer time delay since onset of symptoms to intervention. There are numerous studies confirming that time delay to treatment is a significant factor associated with an increased risk of heart failure and mortality in patients with MI (35–37). Scholz et al. (35) demonstrated that every 10-min treatment delay resulted in 3.31 additional deaths in 100 PCI-treated patients with STEMI patients with cardiogenic shock. In the study of Terkelsen et al. (36), system delay was an independent risk factor of increased 30-day mortality; however, it was confirmed only for STEMI of anterior

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TABLE 3 Angiography results, in-hospital drug therapy and patient's outcome among non-COVID-19 MI and COVID-19 MI group.

Parameter	Non-COVID-19 MI $N = 196$ (83.4%)	COVID-19 MI $N = 39$ (16.6%)	*p*-value
Multivessel disease, *n* (%)	66 (33.7)	19 (48.7)	0.056
Time from onset of symptoms to cardiac intervention >24 h, *n* (%)	30 (15.3)	14 (35.9)	0.004
PCI, *n* (%)	105 (53.6)	19 (48.7)	0.352
Non-obstructive coronary arteries, *n* (%)	39 (19.9)	10 (25.6)	0.272
Primary PCI, *n* (%)*	92 (87.6)	18 (94.7)	0.328
Acute total occlusion of IRA, *n* (%)*	32 (30.5)	4 (21.1)	0.296
STEMI, *n* (%)*	36 (34.3)	8 (42.1)	0.341
Infarct related artery*			
LAD, *n* (%)*	43 (41.0)	8 (42.1)	0.559
LMCA, *n* (%)*	3 (2.9)	0 (0.0)	0.604
Cx, *n* (%)*	29 (27.6)	6 (31.6)	0.459
RCA, *n* (%)*	28 (26.7)	5 (26.3)	0.610
TIMI 3 after PCI, *n* (%)*	97 (95.1)	16 (84.2)	0.110
Time from onset of symptoms to PCI > 24 hours, *n* (%)*	17 (16.19)	8 (42.11)	**0.010**
Contrast, ml, median (IQR)*	200 (150; 250)	220 (200; 300)	0.408
Peak hs cTn, ng/ml, median (IQR)	9,559.71 (2,542.90; 25,000.00)	11,899.43 (2,764.94; 25,000.10)	0.730
Peak NTproBNP, pg/ml, median (IQR)	2,984.00 (796.00; 10,246.00)	6,329.00 (1,733.00; 18,263.00)	**0.034**
Peak creatinine, μmol/l, median (IQR)	103.00 (80.00; 136.00)	134.00 (86.05; 189.00)	0.071
ACEI/ARB, *n* (%)	159 (81.1)	24 (61.5)	**0.009**
Beta blockers, *n* (%)	180 (91.8)	25 (64.1)	**<0.001**
Statins, *n* (%)	185 (94.4)	28 (71.8)	**<0.001**
Catecholamines, *n* (%)	28 (14.3)	5 (12.8)	0.521
Mechanical ventilation, *n* (%)	23 (11.7)	5 (16.6)	0.513
Death in 30-day follow-up	17 (9.4)	12 (38.7)	**<0.001**

*Percentages and median calculated only among patients who underwent PCI.

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; COVID-19, coronavirus disease 2019; Cx, left circumflex artery; hs cTn, high-sensitivity cardiac troponin; IRA, infarct-related artery; IQR, interquartile range; LAD, left anterior descending artery; LMCA, left main coronary artery; MI, myocardial infarction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OMT, optimal medical treatment; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial Infarction; PCI, percutaneous coronary intervention.

wall. The delay in revascularization treatment in patients with MI and COVID-19 has also been reported (3, 23, 38). Our findings show that 35.9% of patients with MI and COVID-19 underwent the cardiovascular intervention after more than 24 h from the onset of symptoms; however, we did not confirm that time since onset of symptoms to coronary angiography was an independent factor of increased risk of 30-day mortality, which can be explained by the fact that in our study, in contrast to above-mentioned studies, we included patients with both STEMI and NSTEMI and there was a significant number of patients who did not require PCI. Additionally, we must acknowledge that the cause for the treatment delay for patients with COVID-19 MI is multifactorial (including patient's delayed presentation and healthcare re-organization during pandemic).

It has been suggested that MI with non-obstructive coronary artery (MINOCA) is being frequently observed in patients with COVID-19 (11, 23, 39). MINOCA is a heterogeneous group of disorders including Takotsubo syndrome, myocarditis, transient thrombosis, or type 2 MI which must be taken into consideration in diagnostic process in patients with MI and concomitant COVID-19. The incidence of MINOCA varied across the studies of patients with MI and COVID-19 from 26 up to 56% (11, 23, 39). In our study, the frequency rate of MINOCA reached 25% in COVID-19 group of patients, but there were no significant differences in comparison with patients with non-COVID-19 MI. We must admit that in our daily practice (including both pre-pandemic and pandemic periods), advanced non-invasive diagnostic tools such cardiac magnetic resonance imaging should be used more frequently to determine the underlying causes of myocardial infarction with non-obstructive coronary arteries and to reduce the number of coronary angiography not requiring PCI.

It is recommended that patients with MI should be treated with beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin-receptor blocker and statins as it has been proven that these drugs improve the prognosis of patients

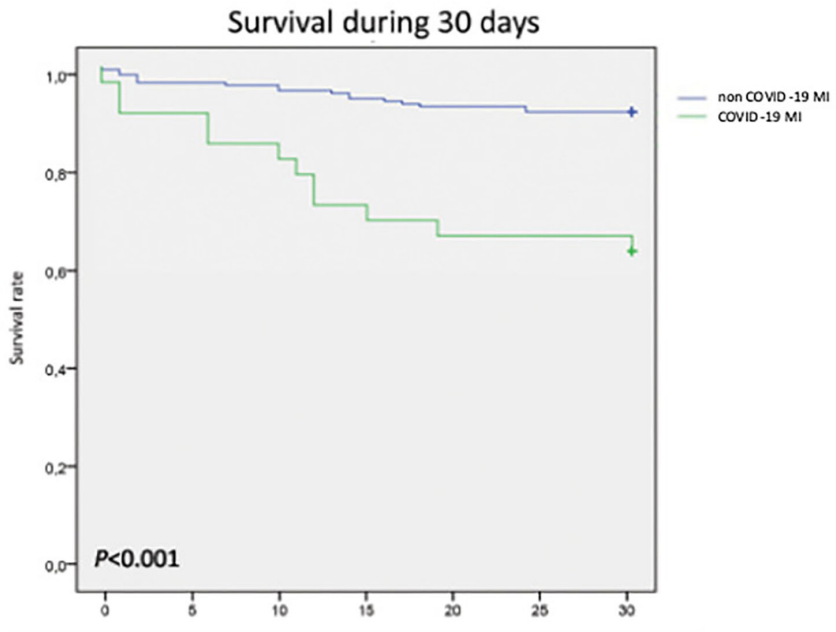

FIGURE 1
The Kaplan–Meier curve displaying proportional 30-day mortality from any cause stratified by COVID-19 status; $p < 0.001$. COVID-19, coronavirus disease 2019; MI, myocardial infarction.

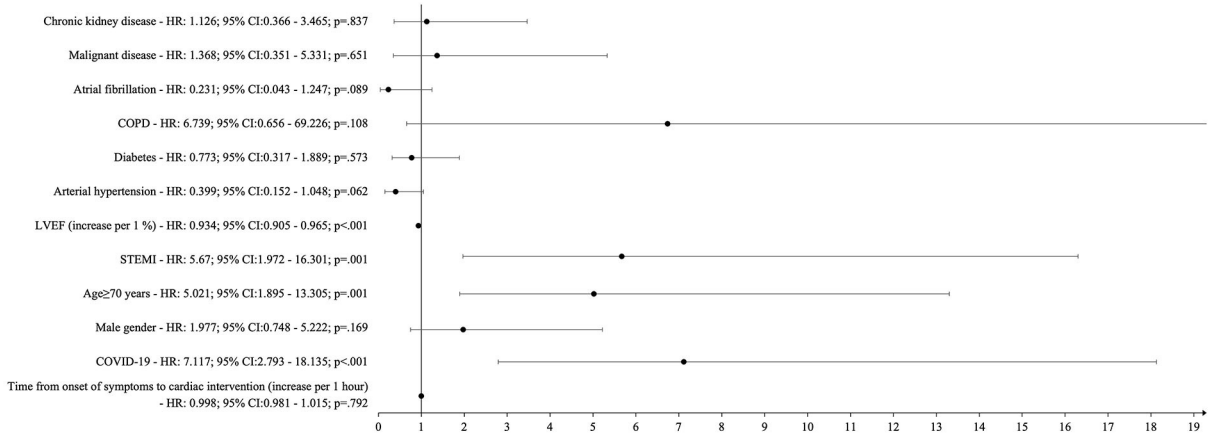

FIGURE 2
Cox regression analysis: independent predictors of 30-day mortality. CI, confidence Interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; LVEF, left ventricular ejection fraction; STEMI, ST-elevation myocardial infarction.

after MI (16, 17). In our research, the aforementioned drugs have been prescribed at a much lower rate in patients with MI and COVID-19 compared to patients with non-COVID-19 MI. Due to the retrospective character of our work, we can only speculate on the causes of this discrepancy. It should be assumed that there were clinical contraindications that may have influenced the decision to use these medications in the COVID-19 MI group. Such contradictions may include renal failure or tendencies for hypotension and might have had an impact on poor outcome.

When analyzing the mortality risk of patients with COVID-19 MI, we must take into consideration a possible contribution of pandemic-related collateral factors on final outcome (patients' need for self-isolation or fear of catching the infection, delays in patients' admission to hospital, logistical challenges related to health systems reorganization, etc.). High mortality risk of patients with COVID-19 observed in NACMI registry (23) in a study of Kite et al. (24) or reported by us shows sevenfold increased risk of 30-day mortality in patients with COVID-19 in comparison with pre-pandemic MI control group which may at least be partially explained by above-mentioned non-infectious factors. Thus, efforts toward the reduction of the mortality risk in this group of patients should be focused not only on the prevention of SARS-CoV-2 infection and implementation of COVID-19 effective treatment but also on the improvement in diagnosis of MI, optimization of both interventional and medical treatment, and efficient health system organization.

Our study has several limitations. First, the retrospective study design limits the ability to obtain complete data for patients' characteristics; second, we could not distinguish between type I (plaque rupture/erosion) and type 2 MI (supply demand mismatch alone). In our hospital, inflammatory markers were not typically drawn during routine blood testing for patients with MI before the COVID-19 pandemic; thus, we could not test the association between inflammatory marker levels and the prognosis in both groups of patients. It is also important to underline that in MI patients with COVID-19, GRACE score results should be interpreted with caution because there may be several factors that could have contributed to the altered heart rate or blood pressure in patients with COVID-19 (i.e., fever, hypovolemia, etc.). Additionally, it is worth to underline that pandemic has greatly impacted the healthcare system and modified the management strategies in patients with MI. The possible impact of pandemic itself (i.e., delay in hospital admission due to fear of COVID-19 infection, temporary lockdown, temporarily shifting resources to the treatment of only acute cases, shortage of ambulance transport, and shortage of staff) must be taken into consideration as a possible additional factors responsible for poor outcomes of COVID-19 MI group of patients in comparison with control group (patients with non-COVID-19 MI in pre-pandemic era).

Conclusion

Patients admitted due to acute MI with COVID-19 have increased 30-day mortality in comparison with patients with MI in the pre-pandemic era. Efforts should be focused on the infection prevention and the implementation of optimal management to improve outcome in those patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Bioethics Committee of the Jagiellonian University (No. 1072.6120.278.2020 and No. 1072.6120.333.2020). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MT, WW, AB, TD, CP, PL, MZ, JR, and MR contributed to the conception and design or analysis and interpretation of data, or both. MT, WW, MK, AO, AB, TD, CP, PL, MZ, JR, ZS, SB, and MR drafted the manuscript or revised it critically for important intellectual content. All authors approved the submitted manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The novel bio-SYNTAX scoring system for predicting the prognosis of patients undergoing percutaneous coronary intervention with left main coronary artery disease

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Background: Simple and effective risk models incorporating biomarkers associated with left main coronary artery (LMCA) stenosis are limited. This study aimed to validate the novel Bio-Clinical SYNTAX score (Bio-CSS) incorporating N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients with LMCA stenosis.

Methods: Patients who underwent percutaneous coronary intervention (PCI) for LMCA stenosis using a drug-eluting stent ($n = 275$) were included in the study. We developed the Bio-CSS incorporating NT-proBNP and validated the ability of the Bio-CSS to predict major adverse cardiac events (MACEs) and compared its performance to that of the SYNTAX score (SS) and SS II. The MACEs were defined as death, non-fatal myocardial infarction (MI), and repeat revascularizations.

Results: The Bio-CSS (34.7 ± 18.3 vs. 51.9 ± 28.4, $p < 0.001$), as well as SS (23.6 ± 7.3 vs. 26.7 ± 8.1, $p = 0.003$) and SS II (29.4 ± 9.9 vs. 36.1 ± 12.8, $p < 0.001$), was significantly higher in patients with MACEs. In the Cox proportional hazards model, the log Bio-CSS (hazard ratio 8.31, 95% CI 1.84–37.55) was an independent prognostic factor for MACEs after adjusting for confounding variables. In the receiver operating characteristic curves, the area under the curve of the Bio-CSS was significantly higher compared to those of SS (0.608 vs. 0.706, $p = 0.001$) and SS II (0.655 vs. 0.706, $p = 0.026$). Patients were categorized into the three groups based on the tertiles of the Bio-CSS. Patients in the highest tertile of the Bio-CSS had significantly higher MACEs compared to those in the lower two tertiles (log-rank $p < 0.001$).

Conclusion: In patients who underwent PCI for LMCA stenosis, the novel Bio-CSS improved the discrimination accuracy of established combined

scores, such as SS and SS II. The addition of NT-proBNP to the clinical and angiographic findings in the Bio-CSS could potentially provide useful long-term prognostic information in these patients.

KEYWORDS

risk stratification, N-terminal pro-B type natriuretic peptide, left main coronary artery disease, percutaneous coronary intervention, drug eluting stent

Introduction

The advances in percutaneous coronary intervention (PCI) techniques have improved the clinical outcomes of unprotected left main coronary artery (LMCA) stenosis (1–5). However, it is still uncertain whether PCI with the current drug-eluting stent (DES) is non-inferior to coronary artery bypass graft (CABG) surgery for a clinical outcome or not (6, 7). Therefore, risk stratification is crucial for the improvement of clinical outcomes in patients with LMCA stenosis undergoing PCI. The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score (SS) system was developed to predict the risk of major adverse cardiac events (MACEs) after PCI (8–10). However, the ability of SS to ascertain 1-year MACEs was insufficient for patients with LMCA stenosis who underwent PCI due to insufficient clinical information. Therefore, effective risk models, which improve the performance of SS in these patient subsets, are essential.

Biomarkers such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) could provide useful prognostic information in patients with coronary artery disease (11–13). However, simple and effective risk models incorporating relevant biomarkers in patients with LMCA are limited. Therefore, we developed the Bio-Clinical SS (Bio-CSS), which incorporates NT-proBNP and validated the ability of the Bio-CSS to predict MACEs, especially compared to that of SS and SS II in patients with LMCA stenosis who underwent PCI.

Materials and methods

Study design and patient population

This observational study included 374 consecutive patients with *de-novo* unprotected LMCA stenosis who were admitted for coronary angiography between June 2006 and December 2012. Patients with significant *de-novo* unprotected LMCA stenosis were enrolled in this study. Significant unprotected LMCA stenosis was defined as severe LMCA diameter stenosis (>70%) as determined by angiography, or intermediate LMCA stenosis (50–69%) as determined by angiography with intravascular ultrasound (IVUS)-derived minimal luminal area of < 6 mm^2. Patients with cardiogenic shock, cardiac arrest during hospitalization, protected LMCA stenosis, and bare-metal stent were excluded from this study. The choice of revascularization modality was mainly determined by attending physicians based on contemporary guidelines. As a rule, patients with significant LMCA stenosis and complex anatomy were recommended CABG as the first revascularization modality. If they declined CABG, PCI was performed as an alternative therapy. PCI was performed for LMCA stenosis in 315 patients. Overall, 40 patients were excluded from this study, including 23 patients with inadequate data, 10 patients with cardiogenic shock, and 7 patients with bare-metal stent implantation. Finally, 275 patients who underwent PCI for LMCA stenosis with DES were analyzed in this study. The flowchart of the study is given in Figure 1. The study protocols were approved by the Institutional Review Boards of Kyungpook National University Hospital (No. KNUH 2020-06-006). Informed consent was waived by the board.

We analyzed the baseline demographic and clinical characteristics, including age, sex, cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, and family history of coronary heart disease), and comorbidities. ECG was recorded and analyzed in all the patients by attending cardiologists. Venous blood specimens were obtained on admission. The serum creatinine was determined using standard methods. The NT-proBNP level was quantified using an electrochemiluminescence immunoassay method (Modular Analytics E170, Roche Diagnostics, Germany). The left ventricular ejection fraction (LVEF) was determined using two-dimensional echocardiography at the index hospitalization.

Standard interventional techniques were used for all the procedures. The main treatment principles of the PCI procedure were as follows: wiring of the LMCA to the left anterior descending (LAD) and/or left circumflex (LCX) artery, predilatation of stenosed areas of the LMCA before IVUS examination if the passage of IVUS catheter is not possible, IVUS examination at the operator's discretion, implantation of the stent from LMCA to LAD or LCx, postdilatation with the single or final kissing balloon technique at the operator's discretion, and IVUS examination after stenting. The IVUS images were obtained using a manual or automatic fullback system *via* commercially available imaging systems (40 MHz IVUS catheter, Boston Scientific: 20 MHz IVUS

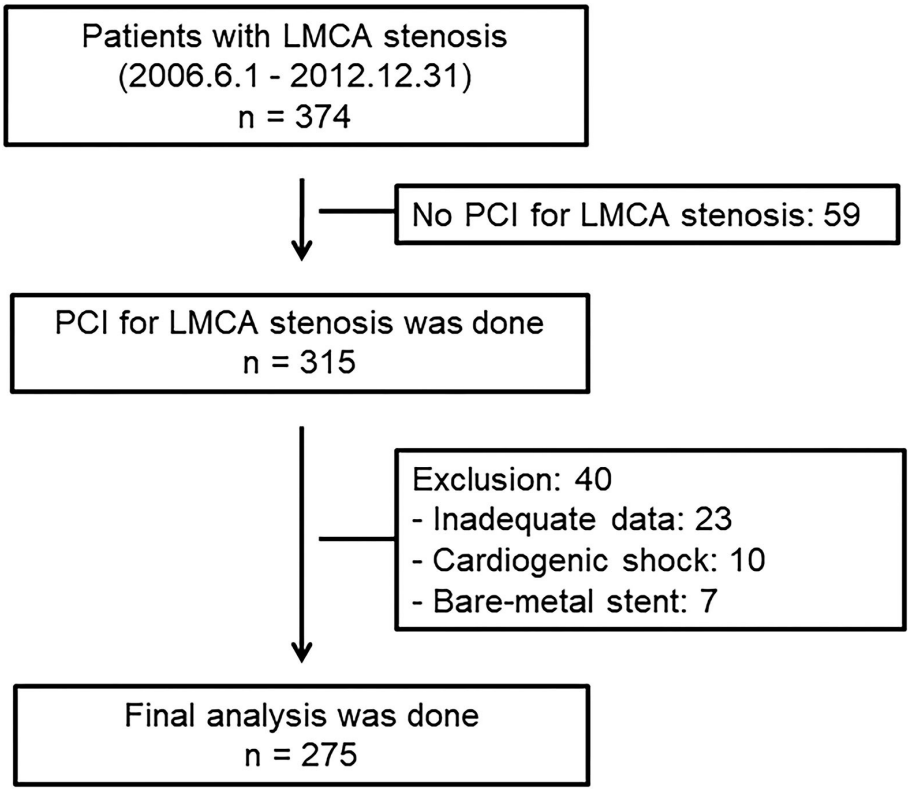

FIGURE 1
Flowchart of the study patients. LMCA, left main coronary artery; PCI, percutaneous coronary intervention.

catheter, Volcano, Rancho Cordova, California, USA). A preinterventional IVUS examination provided information about the characterization of plaque and guided treatment strategy, including the selection of appropriate diameter for balloons and stents. The poststenting IVUS examination enables the evaluation of stent expansion and apposition and aids in deciding on additional procedures.

Antiplatelet therapy and periprocedural anticoagulation were performed using standardized regimens. Before the procedure, all the patients received a loading dose of aspirin (300 mg) and clopidogrel (300 or 600 mg). In the catheterization laboratory, a bolus of unfractionated heparin (75–100 U/kg) was administered for anticoagulation, to achieve an activated clotting time $>$ 300 s. The routine use of postprocedure unfractionated heparin was not recommended unless the patients required intra-aortic balloon pumps. The use of glycoprotein IIb/IIIa receptor inhibitors was left to the attending interventional cardiologist's judgment. Postprocedure, the patients were prescribed aspirin (100 mg) and clopidogrel (75 mg) for at least 12 months, potentially longer, based on the operator's discretion.

Bio-clinical synergy between PCI with taxus and cardiac surgery score

The SS and SS II scores for each patient were calculated by scoring all the coronary lesions with diameter stenosis $\geq$ 50%, in vessels $\geq$ 1.5 mm, using the SS algorithm and are available on the SS website (www.syntaxscore.org) (8, 9). The age, creatinine, and ejection fraction (ACEF) score was calculated using the following formula: ACEF = Age/LVEF + 1 (if creatinine was $>$ 2.0 mg/dl) (14). The clinical SS (CSS) was calculated retrospectively for every patient using the formula CSS = (SS) $\times$ (ACEF score). The Bio-CSS was calculated by adding the log-transformed NT-proBNP levels to CSS (CSS + log NT-proBNP).

Clinical outcomes

The mean follow-up duration was 1,625 $\pm$ 931 days. The patients were followed-up for more than 1 year. The MACEs were defined as death, non-fatal myocardial infarction, and

repeat revascularization, including PCI and CABG. During the follow-up period, the follow-up data were obtained by reviewing medical records and telephone interviews with patients.

Statistical analyses

Data are expressed as mean ± SD for continuous variables and percentages for categorical variables. All the comparisons between the baseline variables were assessed using Student's *t*-test for continuous variables and Pearson's chi-squared test for categorical variables. The patients were categorized into the three groups based on the tertiles of the Bio-CSS: Bio-CSS_{LOW} < 28 ($n = 84$), 28 ≤ Bio-CSS_{MID} < 39 ($n = 95$), and Bio-CSS_{HIGH} ≥ 39 ($n = 96$). The cumulative incidence rates of MACE and the mortality based on the Bio-CSS tertiles were estimated using the Kaplan–Meier method, and further compared by using the log-rank test. Univariate analyses were performed to determine the predictors for MACEs. The Cox proportional-hazards model was used to calculate the hazard ratios (HRs) and the CIs for the independent predictors of MACEs. The variables with *p*-values ≤ 0.05 on the univariate analysis were entered into the Cox proportional-hazards model. The Hosmer–Lemeshow chi-square—a measure of deviation between the observed and predicted outcomes in deciles of predicted risk—was used to evaluate the calibration of the model.

The increased discriminative value of the Bio-CSS compared to the SS and SS II was estimated using three measures (Harrell's C-index, net reclassification improvement, and integrated discrimination improvement). Harrell's C-index (c-statistic) was defined as the proportion of usable patient pairs, in which the predictions and outcomes were concordant (1). We estimated the receiver operating characteristic (ROC) curves and compared the areas under the ROC curves (AUC) for the SS, SS II, and Bio-CSS in corresponding logistic models (15). The net reclassification improvement and integrated discrimination improvement were calculated by analyzing the differences in the individual estimated probabilities for MACEs of the Bio-CSS to SS and SS II (16). Because no prior risk categories exist for MACEs, we calculated the category-free net reclassification improvement (16). For all the analyses, a two-sided $p < 0.05$ was considered statistically significant. The statistical analysis was

TABLE 1 Clinical characteristics of the study subjects.

Variables	Bio-CSS < 28 ($N = 84$)	28 ≤ Bio-CSS < 39($N = 95$)	Bio-CSS ≥ 39 ($N = 96$)	*p* value
Bio-CSS	22.1 ± 4.4	32.7 ± 3.4	61.9 ± 26.1	<0.001
Age (year)	57.0 ± 10.8	65.4 ± 7.8	70.2 ± 8.7	<0.001
Male, *n* (%)	61 (72.6)	74 (77.9)	69 (71.9)	0.589
Body mass index (Kg/m^2)	23.9 ± 2.3	23.9 ± 2.7	22.9 ± 2.7	0.058
Clinical presentation				<0.001
Chronic stable angina, *n* (%)	26 (31.0)	38 (40.0)	11 (11.5)	
Acute coronary syndrome, *n* (%)	58 (69.0)	57 (60.0)	85 (88.5)	
Medical history				
Coronary heart disease, *n* (%)	12 (14.8)	18 (20.5)	24 (27.3)	0.137
Hypertension, *n* (%)	35 (43.2)	54 (61.4)	48 (54.5)	0.059
Diabetes mellitus, *n* (%)	20 (24.7)	31 (35.2)	36 (40.9)	0.079
Hyperlipidemia, *n* (%)	22 (27.2)	34 (38.6)	24 (27.3)	0.172
Current smoker, *n* (%)	48 (59.3)	54 (61.4)	54 (61.4)	0.950
Left ventricular ejection fraction (%)	58.9 ± 7.1	57.7 ± 7.5	45.0 ± 13.1	<0.001
Serum creatinine (mg/dL)	0.80 ± 0.22	1.04 ± 0.78	1.45 ± 1.52	<0.001
Log NT-proBNP (pg/mL)	4.7 ± 1.2	5.5 ± 1.3	7.0 ± 1.7	<0.001
Discharge medication				
Aspirin, *n* (%)	83 (98.8)	95 (100.0)	95 (99.0)	0.584
Clopidogrel, *n* (%)	81 (96.4)	94 (98.9)	94 (97.9)	0.514
ACE-I/ARBs, *n* (%)	71 (84.5)	75 (78.9)	70 (72.9)	0.166
Beta-blockers, *n* (%)	74 (88.1)	88 (92.6)	78 (81.2)	0.06
Statins, *n* (%)	68 (81.0)	70 (73.7)	74 (77.1)	0.513
Diuretics, *n* (%)	6 (7.1)	16 (16.8)	34 (35.4)	<0.001

Data expressed as mean ± SD or number (percent).
SS, SYNTAX score; SS II, SYNTAX score II; Bio-CSS, Biomarker-Clinical SYNTAX score; NT-proBNP, N-terminal pro-B type natriuretic peptide; ACE-I/ARBs, Angiotensin-converting enzyme inhibitors/angiotensinogen type II receptor blockers.

performed using SAS software (version 9.3, SAS Institute, Cary, North Carolina, USA).

Results

The mean age of the participants was 64.5 ± 10.6 years, and 204 (74.2%) were men. The mean Bio-CSS was 39.7 ± 23.0 (median, 33.0; range, 12.1–182.3). The baseline characteristics of the study population are shown in Table 1. The age, prevalence of acute coronary syndrome, serum levels of creatinine, and NT-proBNP significantly increased as the Bio-CSS tertile increased, whereas the LVEF significantly decreased as the Bio-CSS tertile increased. The indicators of lesion complexity, such as the number of diseased vessels, presence of left main (LM) bifurcation, and small vessels with the long lesions, were significantly higher in the Bio-CSS_{HIGH} tertile compared to the other groups (Table 2).

During the follow-up, 80 (29.1%) MACEs, including 55 (20%) all-cause deaths, 23 (8.4%) non-fatal MIs, and 16 (5.8%) revascularizations, occurred (Table 3). Overall, the MACEs (49.0 Bio-CSS_{HIGH} vs. 23.2 Bio-CSS_{MID} vs. 13.1% Bio-CSS_{LOW}, $p < 0.001$) and mortality (41.7 Bio-CSS_{HIGH} vs. 12.6 Bio-CSS_{MID} vs. 3.6% Bio-CSS_{LOW}, $p < 0.001$) were significantly higher in the Bio-CSS_{HIGH} tertile as compared to the two lower tertiles.

In univariate analysis for MACEs, the Bio-CSS (34.6 ± 18.2 vs. 51.8 ± 28.3, $p < 0.001$), SS (23.6 ± 7.2 vs. 26.7 ± 8.0, $p = 0.002$), and SS II (29.4 ± 9.9 vs. 36.0 ± 12.8, $p < 0.001$) were significantly higher in patients with MACEs than in those patients without MACEs (Supplementary Table 1). The log-transformed NT-proBNP level was significantly higher in patients with MACEs than in those patients without MACEs

TABLE 2 Angiographic and procedural characteristics of the study subjects.

Variables	Bio-CSS <28 (*N* = 84)	28 ≤Bio-CSS <39(*N* = 95)	Bio-CSS≥39 (*N* = 96)	*p* value
LMCA status				<0.001
LMCA, isolated, *n* (%)	24 (28.6%)	1 (1.1%)	3 (3.1%)	
LMCA + 1-vessel disease, *n* (%)	17 (20.2%)	15 (15.8%)	5 (5.2%)	
LMCA + 2-vessel disease, *n* (%)	16 (19.0%)	31 (32.6%)	15 (15.6%)	
LMCA + 3-vessel disease, *n* (%)	27 (19.8%)	48 (50.5%)	73 (76.0%)	
LM bifurcation	55 (65.5%)	82 (86.3%)	85 (88.5%)	<0.001
LM Stent size (mm)	3.56 ± 0.34	3.57 ± 0.50	3.39 ± 0.32	0.003
LM Stent length (mm)	21.8 ± 5.95	23.98 ± 6.07	23.55 ± 6.29	0.049
Reference vessel diameter (mm)	3.58 ± 0.48	3.47 ± 0.41	3.40 ± 0.38	0.025
Minimal lumen diameter (mm)	1.73 ± 0.43	2.01 ± 2.45	1.73 ± 1.64	0.455
Drug-eluting stent type				0.815
Sirolimus eluting stent, *n* (%)	3 (3.6%)	5 (5.3%)	2 (2.1%)	
Paclitaxel eluting stent, *n* (%)	11 (13.1%)	14 (14.7%)	20 (20.8%)	
Zotarolimus eluting stent, *n* (%)	23 (27.4%)	24 (25.3%)	28 (29.2%)	
Everolimus eluting stent, *n* (%)	38 (45.2%)	45 (47.3%)	40 (41.7%)	
Biolimus eluting stent, *n* (%)	9 (10.7%)	7 (7.4%)	6 (6.2%)	
LM stenting strategy				0.981
1 stent strategy, *n* (%)	75 (89.3%)	84 (88.4%)	85 (88.5%)	
2 stent strategy, *n* (%)	9 (10.7%)	11 (11.6%)	11 (11.5%)	

Data expressed as mean ± SD or number (percent).
LMCA, left main coronary artery; LM, left main.

TABLE 3 Clinical outcomes during the follow-up.

Variables	Bio-CSS < 28 (*N* = 84)	28 ≤ Bio-CSS < 39(*N* = 95)	Bio-CSS ≥ 39 (*N* = 96)	*p* value
Major adverse cardiac events, *n* (%)	11 (13.1)	22 (23.2)	47 (49.0)	<0.001
Death, *n* (%)	3 (3.6)	12 (12.6)	40 (41.7)	<0.001
Non-fatal MI, *n* (%)	5 (6.0)	6 (6.3)	12 (12.5)	0.192
Revascularizations, *n* (%)	5 (6.0)	6 (6.3)	5 (5.2)	0.946

Data expressed as number (percent).
Bio-CSS, Biomarker-Clinical SYNTAX score; MI, myocardial infarction.

TABLE 4 Multivariate predictors of major adverse cardiac events during the follow-up.

Variables	HR	95% CI	*p* value
Male	1.99	0.93–4.23	0.075
Acute coronary syndrome	1.27	0.67–2.39	0.460
Beta-blockers	0.69	0.37–1.31	0.256
Statins	0.49	0.28–0.86	0.012
Diuretics	1.44	0.78–2.66	0.239
Log Bio-CSS	8.31	1.84–37.55	0.006

HR, hazard ratio; CI, confidence interval; Bio-CSS, Biomarker-Clinical SYNTAX score.

(5.45 ± 1.52 vs. 6.51 ± 2.04, $p < 0.001$). Patients with MACEs were more likely to be male and had acute coronary syndromes. The use of beta-blockers and statins was significantly higher, and the use of diuretics was significantly lower in patients with MACEs. As per the Cox proportional-hazards model (Table 4), the log Bio-CSS (HR 8.31, 95% CI 1.84–37.55; $p = 0.006$) and statin therapy (HR 0.49, 95% CI 0.28–0.86; $p = 0.012$) were independent prognostic factors for MACEs after adjusting for confounding variables. The Kaplan–Meier survival curve analysis indicated that patients in the Bio-CSS_{HIGH} tertile had significantly higher rates of MACEs when compared with the lower 2 tertiles (log-rank $p < 0.001$; Figure 2A). Additionally, the mortality rate was significantly higher for the Bio-CSS_{HIGH} tertile compared to the lower two tertiles (log-rank $p < 0.001$; Figure 2B).

The AUC for the ROC analysis of the Bio-CSS for predicting MACEs was 0.706 (Figure 3) and significantly higher compared to SS (0.608, $p = 0.001$) and SS II (0.655, $p = 0.026$) (Table 5). The Bio-CSS significantly improved the reclassification (0.617; $p < 0.001$) and integrated discrimination (0.084; $p < 0.001$) of the patients compared to SS. No improvements were seen in SS II for the AUC for the prediction of MACEs of patients compared to SS ($p = 0.345$). The Bio-CSS also significantly improved the reclassification (0.273; $p = 0.043$) and integrated discrimination (0.045; $p = 0.003$) of the patients compared to SS II.

Discussion

The main findings from this study are as follows. First, patients with the higher Bio-CSS have high-risk clinical and angiographic characteristics. Second, the novel Bio-CSS is an independent predictor of MACEs in patients who underwent PCI with LMCA stenosis. Third, the patients with the highest Bio-CSS tertiles have worse clinical outcomes. Fourth, the novel Bio-CSS was found to be superior to both the SS and SS II in the prediction of MACEs in patients who underwent PCI with LMCA stenosis.

There are two significant findings in our study. First, to the best of our knowledge, this is the first risk prediction model incorporating the NT-proBNP levels of patients who underwent PCI with LMCA stenosis. NT-proBNP is a well-known predictor of clinical outcomes in patients with coronary artery disease (17). The variables included in the CSS score—age, creatinine, and LVEF—are well-known contributors to the risk of LMCA stenosis (18, 19). In patients with chronic heart failure, the plasma levels of NT-proBNP are influenced by age, renal function, and LVEF (20–22). However, in patients with coronary artery disease, NT-proBNP was an independent predictor of all-cause mortality after adjustment for age and LVEF (17). Therefore, despite the close links among the NT-proBNP, age, creatinine level, and LVEF, the NT-proBNP can provide valuable additional prognostic information beyond the conventional risk factors.

Second, the Bio-CSS has a robust prognostic accuracy compared with the SS and SS II, and accurately stratifies the patients for long-term clinical outcomes in real-world patients who underwent PCI with LMCA stenosis. The original SS was developed based on coronary anatomy and lesion characteristics (9, 14). Although the SS was good at predicting the overall MACEs, the absence of any clinical characteristics in the SS calculation limited the scope for improvement of the predictive ability of risk scores in patients with LMCA stenosis (23). The SS II was developed to overcome these limitations. In the previous studies (DELTA and CREDO-Kyoto registry), the predictive ability of the SS II was superior for all-cause mortality compared to the anatomical SS in patients treated with PCI for LMCA stenosis and complex coronary artery disease (24, 25). However, it includes the two anatomical and six clinical factors for the prediction of 4-year mortality in the patients undergoing PCI or CABG. The incorporation of too many variables in the risk model—with the aim of creating an "optimal model"—may result in statistical overfitting and instability (26). A simple model may occasionally outperform a more complex model. The CSS is simple, practical, and easy to calculate by multiplying the SS with the ACEF score (using only the age, creatinine level, and LVEF) (10). Although the CSS had a better index of separation for most ischemic endpoints compared to the SS, the rate of MACEs was comparable between the SS and CSS in patients who underwent PCI with acute coronary syndrome (27). Therefore, in the previous study, we developed and validated the Bio-CSS for the first time to improve the prediction ability of the CSS for clinical outcomes in patients with acute myocardial infarction (28). Although the external validation of the Bio-CSS was not performed in the present study, we believe that the Bio-CSS could be applied to patients who underwent PCI with LMCA stenosis for the best risk prediction model.

This study has certain limitations. First, our study is not a randomized and controlled study. Therefore, we cannot completely exclude the possibility of residual confounding factors that were not available in our registry. Second, the ROC method of analysis may not be appropriate for the present study, as it is only suited for diagnostic purposes. Although the ROC

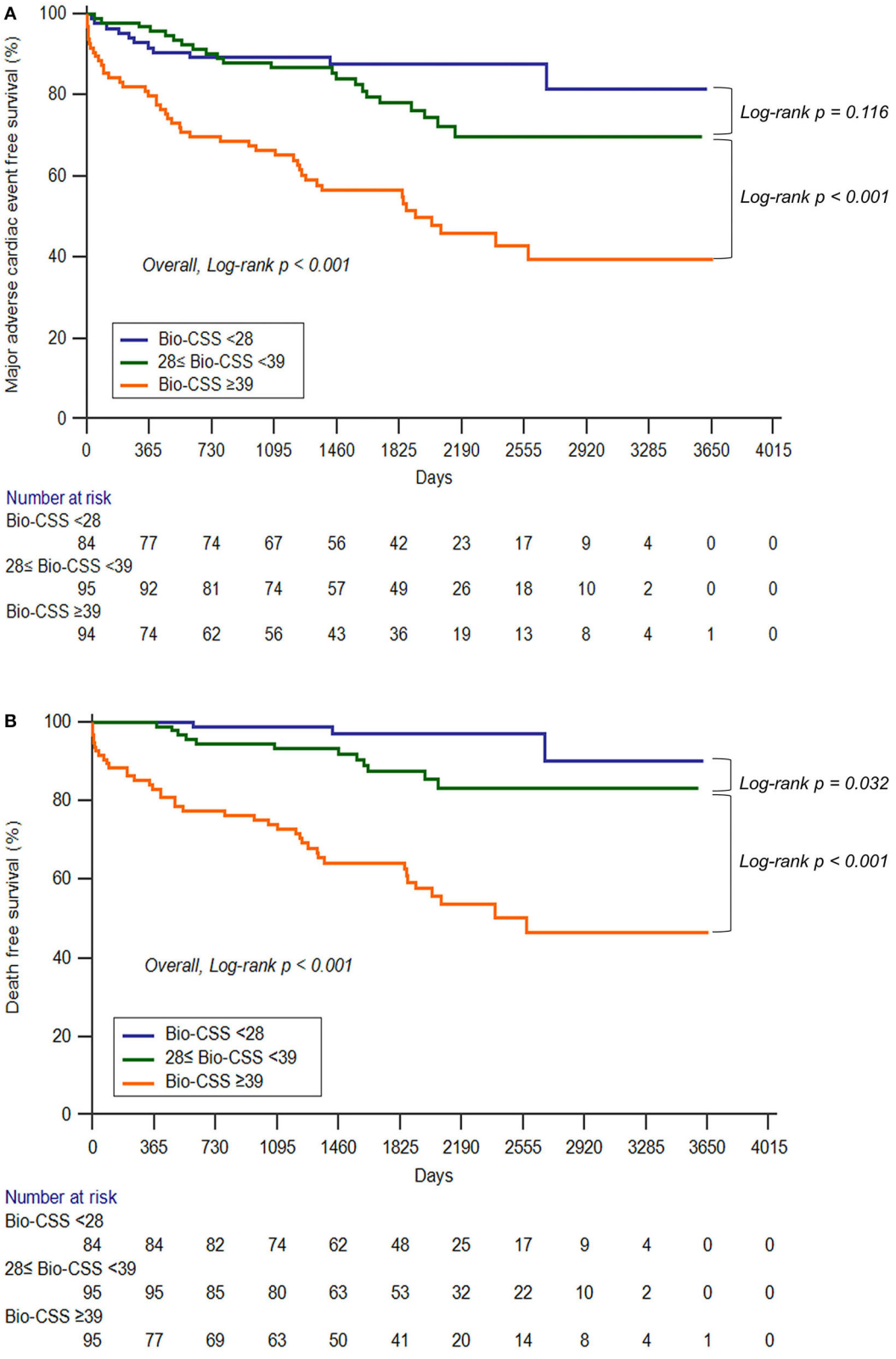

FIGURE 2
The Kaplan–Meier survival curves depict the major adverse cardiac events **(A)** and mortality **(B)** according to the Bio-CSS tertiles. Bio-CSS, Biomarker-clinical SYNTAX score.

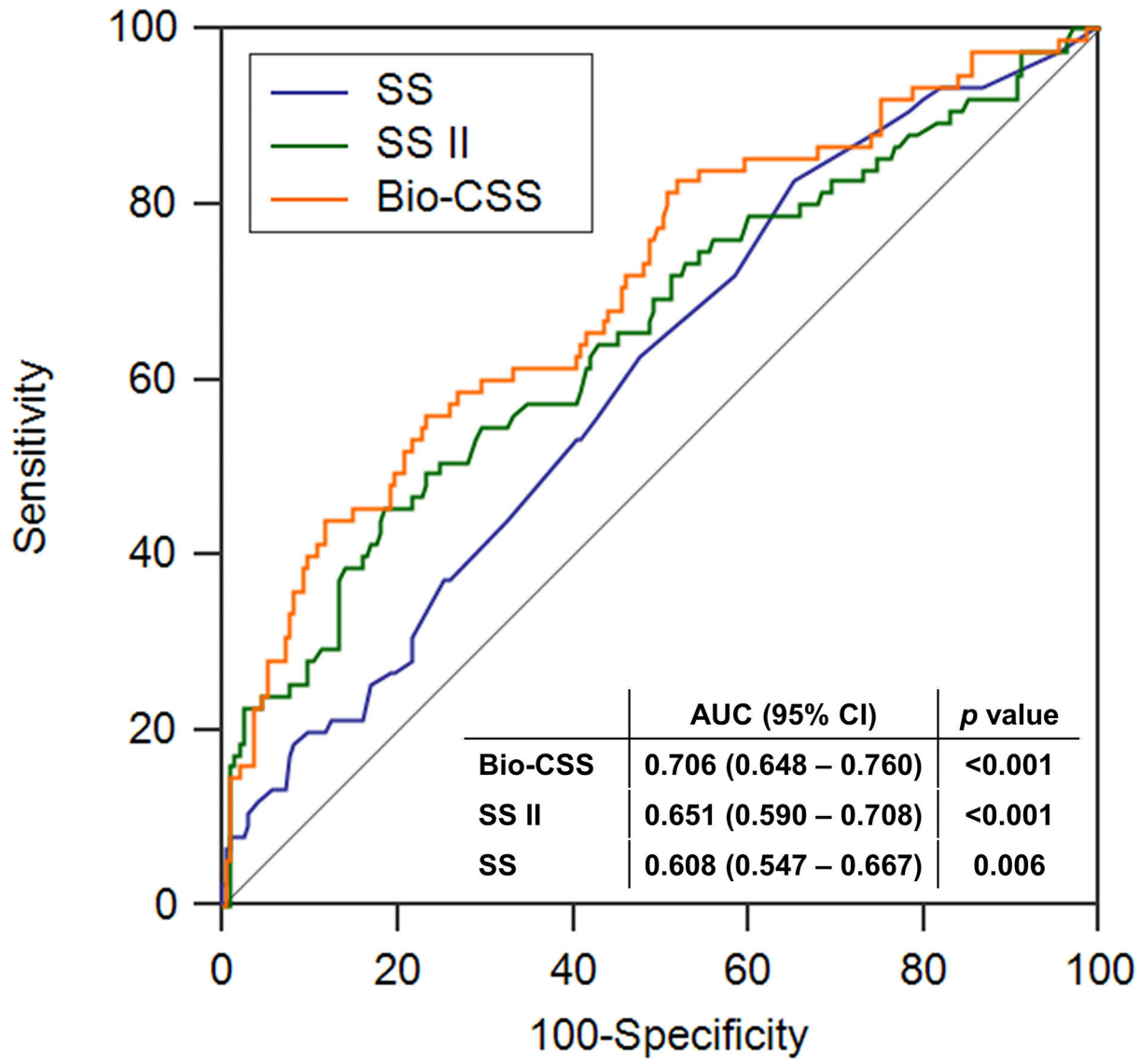

FIGURE 3
The receiver operating characteristics analysis of the SS, SS II, and Bio-CSS for major adverse cardiac events. SS, SYNTAX score; SS II, SYNTAX score II; Bio-CSS, Biomarker-clinical SYNTAX score; AUC, area under the curve; CI, confidence interval.

method has not been extensively validated for prognostic models because these models must incorporate time-censored data (29), the same method has been used in the previously published study (28). Despite these limitations, we believe that the Bio-CSS could provide the necessary clinical insight to determine the prognosis of patients who underwent PCI with LMCA stenosis.

In conclusion, an improvement in the ability of the SS and SS II for the prediction of long-term MACEs can be achieved by combining the CSS with the NT-proBNP level to formulate the Bio-CSS. The Bio-CSS is a novel valid model for the prediction of long-term MACEs in patients undergoing PCI with LMCA stenosis.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Boards of Kyungpook National University Hospital

TABLE 5 Discrimination of the SYNTAX score, the SYNTAX score II, and the Bio-Clinical SYNTAX score in predicting major adverse cardiac events.

Variables	Discrimination					
	C- index	*p* value	NRI	*p* value	IDI	*p* value
SS	0.608		Reference		Reference	
SS II	0.651	0.345	0.302	0.025	0.038	0.045
Bio-CSS	0.706	0.001	0.617	<0.001	0.084	<0.001
SS II	0.651		Reference		Reference	
Bio-CSS	0.706	0.026	0.273	0.043	0.045	0.003

SS, SYNTAX score; CSS, Clinical SYNTAX score; Bio-CSS, Biomarker-Clinical SYNTAX score; NRI, Net Reclassification Improvement; IDI, Integrated Discrimination Improvement. The NRI was defined as ($P_{\text{improved prediction among patients with major adverse cardiac events}} + P_{\text{improved prediction among patients without major adverse cardiac events}}$) ($P_{\text{worsened prediction among_patients with major adverse cardiac events}} + P_{\text{worsened prediction among patients without major adverse cardiac events}}$), where p = proportion of patients. The IDI was defined as ($\sum^{i}_{\text{major adverse cardiac events}}$ ($P_{new}(i)$ $P_{old}(i)$)/n (Patients with major adverse cardiac events)) ($\sum^{j}_{\text{no major adverse cardiac events}}$ ($P_{new}(j)$ $P_{old}(j)$)/n (Patients without major adverse cardiac events)), where p = predicted probability of major adverse cardiac events.

(No. KNUH 2020-06-006). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JY, JL, and HP contributed to the conception and design of this study. HK and NK conducted the investigations and organized the database. JL wrote the first draft of the manuscript. JY, MB, DY, and YC wrote sections of the manuscript. All authors have contributed to manuscript revision, reading, and approval of the submitted version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.912286/full#supplementary-material

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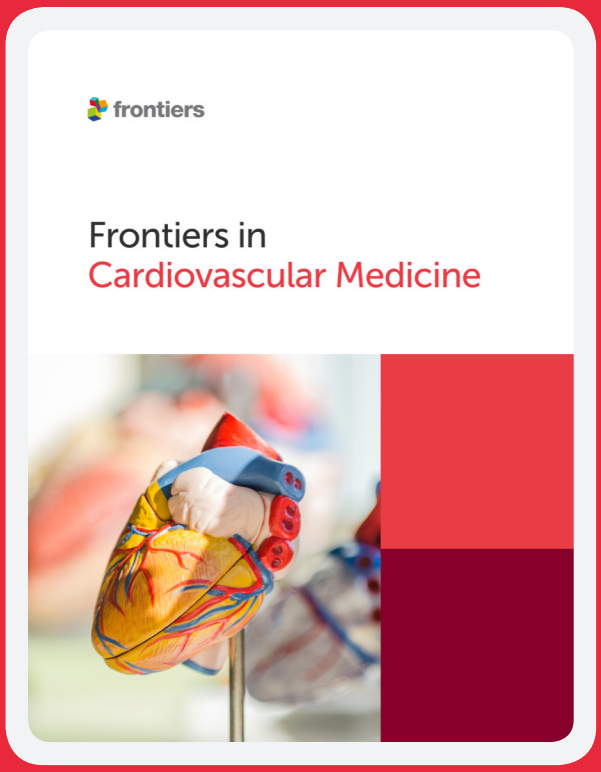

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