Acta Cardiol Sin 2023;39:277–286
Original Article
doi: 10.6515/ACS.202303_39(2).20220821A

Coronary Artery Disease

Management of Restenosis after Stenting in Left Main Coronary Artery Disease

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Background: The optimal alternative treatment strategy to coronary artery bypass graft surgery (CABG) for in-stent restenosis (ISR) in left main (LM) coronary artery disease remains uncertain.

Method: We retrospectively screened all intervention reports from an intervention database and extracted those mentioning an LM stent. We then manually confirmed reports involving LM ISR and divided them into two groups, those in which the patient received a new drug-eluting stent (new-DES) strategy, and those in which the patient received a drug-coated balloon (DCB) only. A composite endpoint of major adverse cardiovascular events (MACEs) and each individual endpoint were compared. We also performed a brief analysis of similar designed studies.

Results: Between the new-DES (n = 40) and DCB-only (n = 22) groups, during median respective follow-up times of 581.5 and 642.5 days, no significant statistical differences were detected in MACEs (50.0% vs. 50.0%, p = 0.974), cardiovascular death (27.5% vs. 13.6%, p = 0.214), nonfatal myocardial infarction (30.0% vs. 31.8%, p = 0.835), or target lesion revascularization (35.0% vs. 45.5%, p = 0.542). We analyzed four similar studies and found comparable MACE findings (odds ratio: 0.85, 95% CI: 0.44-1.67).

Conclusions: Our findings support both DCB angioplasty and repeat DES implantation for LMISR lesions in patients who were clinically judged to be unsuitable for CABG; the treatments achieved comparable clinical results in terms of MACEs in the medium term.

Key Words: Coronary artery bypass • Coronary restenosis • Percutaneous coronary intervention

INTRODUCTION

Coronary artery bypass graft (CABG) surgery is the gold standard therapy for left main coronary artery disease (LMCAD); nevertheless, cumulative evidence from large randomized and observational clinical trials has suggested that percutaneous coronary intervention (PCI) is a safe and feasible alternative.[1-3] European and

Abbreviations

CABG	Coronary artery bypass graft surgery
CIs	Confidence intervals
DCB	Drug-coated balloon
DES	Drug-eluting stent
ISR	In-stent restenosis
LAD	Left anterior descending
LCX	Left circumflex
LM	Left main
LMCA	Left main coronary artery
LMCAD	Left main coronary artery disease
MACEs	Major adverse cardiovascular events
MI	Myocardial infarction
MITO	Milan and New-Tokyo
ORs	Odds ratios
PCI	Percutaneous coronary intervention
SD	Standard deviation
TLR	Target lesion revascularization

Received: July 9, 2021 Accepted: August 21, 2022
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US guidelines recommend both CABG and PCI for LMCAD, depending on anatomical considerations.[4,5]

However, PCI for patients with LMCAD has been associated with a higher risk of restenosis and repeat revascularization than CABG. In the SYNTAX trial, compared with the CABG group, significantly more patients (23%) in the left main (LM)-PCI subgroup with SYNTAX scores < 33 and first-generation drug-eluting stents (DES) underwent target lesion revascularization (TLR).[6] The EXCEL trial randomly performed CABG or PCI with everolimus-eluting stents to 1905 patients with SYNTAX scores ≤ 32. At 3 years, the primary outcomes [death, stroke, and myocardial infarction (MI)] were similar between the PCI and CABG groups (15.4% vs. 14.7%, respectively; p = 0.018 for noninferiority, p = 0.98 for superiority), but the rates of ischemia-driven revascularization were 12.6% and 7.5%, respectively (p < 0.0001).[7]

Because the rates of LM-PCI have increased, treating restenosis of left main coronary artery (LMCA) stenting has become a new challenge, and data regarding the ideal PCI strategy for patients with LM in-stent restenosis (ISR) are lacking. Evidence from systematic reviews suggests that drug-coated balloon (DCB) angioplasty and repeat stenting with DESs are the most effective treatments for ISR, but most clinical trials have excluded patients with LM restenosis.[8,9] This study therefore compared the medium-term clinical outcomes of DCB angioplasty and DES implantation in patients with LM-ISR lesions.

METHODS

Ethical considerations

The study protocol was approved by the Institutional Review Board of National Cheng Kung University Hospital (A-ER-109-229).

Data source

We retrospectively screened all intervention medical reports between January 2009 and December 2019 from the cardiovascular electronic medical records database of National Cheng Kung University Hospital. We excluded reports not mentioning coronary intervention and selected patients with multiple reports only when an LM intervention was documented. LMCAD-ISR was defined as stent deployment involving the LMCA with over 50% restenosis and stenosis within 5 mm of the stent. Finally, we included patients who were documented to have a deployed LM stent with subsequent ISR confirmed by a coronary angiography report, which we selected as the index PCI report. Patients who were clinically judged to be unsuitable for CABG were defined as high operational risk by surgeons and the patients were not willing to accept CABG.

A comprehensive PubMed search was conducted, and all relevant studies identified were reviewed independently by two authors (CWH and MSH) to identify those comparing the clinical outcomes of coronary bifurcation restenosis. The following search terms were used: “coronary artery,” “bifurcation,” “restenosis,” and “in-stent restenosis.”

Clinical data

We retrospectively collected the patients’ clinical data, including medical chart records, laboratory data, and imaging reports, as well as all reports of clinical events occurring before and after the index report. Major adverse cardiac events (MACEs) were defined as a composite endpoint of cardiac death, nonfatal MI, or TLR. MI was defined as clinically suspicious symptoms or electrocardiogram abnormalities with elevated cardiac enzymes, and was classified as ST segment elevation or non-ST segment elevation MI. Stent thrombosis was defined in accordance with the Academic Research Consortium criteria.

Coronary angiography interpretation

Two independent cardiologists (CWH and MSH) manually reviewed all intervention images and reports. Intervention details, including the previous stent deployment site and indication, vessel size, image guidance (intravascular ultrasound or optical coherence tomography) used, and treatment modalities, were determined independently. For LM bifurcation, the main vessel was always considered the LMCA into the left anterior descending artery (LAD), and the side branch was considered the left circumflex (LCX) artery. LM bifurcation lesions were classified according to the Medina classification system; among the lesion types, (1,1,1), (1,0,1), and (0,1,1) lesions were considered true bifurcation lesions. An ISR pattern was defined based on Mehran’s classification, and diffuse ISR was defined as lesions > 10 mm.

Three ISR treatment modalities were used: 1) a two-stent technique using DES; 2) DCB angioplasty with a DES; and 3) DCB angioplasty. The first two modalities were considered "new-DES" strategies, and the third was termed the "DCB-only" strategy.

Statistical analysis

The demographic characteristics of the patients receiving the new-DES and DCB-only strategies were compared. Continuous variables are expressed as mean and standard deviation (SD) values, and differences between groups were assessed using independent-samples t tests. Categorical variables are presented as number and percentage, and differences were assessed using χ^2 tests. Kaplan-Meier survival analyses were performed for MACEs and analysis of individual endpoints. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from the included studies by using the total number of patients and MACEs to compare the clinical outcomes of the new-DES and DCB-only strategies. A p value of < 0.05 was considered statistically significant. All analyses were performed using SPSS version 23 (IBM), R version 4.0.1 with the survminer package version 0.4.8, and RevMan version 5.3 (Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Patients

We screened 10,885 intervention reports from our electronic medical records database from January 2009 to December 2019. Among these reports, we screened those involving a LM stent; after manual review, 86 patients were considered to have significant ISR. Among them, 40 patients (age, 66.4 ± 9.4 years, 75.0% male) were treated with the new-DES strategy, 22 with the DCB-only strategy (age, 68.4 ± 9.8 years, 59.1% male), 10 with CABG (age, 69.7 ± 6.7 years, 80% male), and 14 with other strategies (medical control or simple balloon angioplasty; Figure 1 and Table 1).

No statistically significant differences were observed between the new-DES (n = 40) and DCB-only (n = 22) groups in any clinical or demographic aspect, including age, gender, underlying comorbidities, left ventricular ejection fraction, or medications. The median follow-up durations were 581.5 and 642.5 days in the new-DES and DCB-only groups, respectively.

Intervention

At the index PCI, compared with the DCB-only group, the new-DES group had greater proportions of true bifurcation ISR (80.0% vs. 54.5%, p = 0.051) and diffuse ISR (55.0% vs. 27.2%, p = 0.032), and a smaller proportion of patients with two stents previously deployed (21.2% vs. 57.1%, p = 0.010), with no significant statistical differences in main vessel (3.45 ± 0.30 vs. 3.35 ± 0.30 mm, p = 0.217) or side-branch vessel size (3.04 ± 0.46 vs. 3.23 ± 0.48 mm, p = 0.144) size or indications for intervention (p = 0.569; Table 1 and Supplemental Table 1).

Clinical outcomes

The cumulative incidence rate of the composite endpoint of MACEs did not differ significantly between the

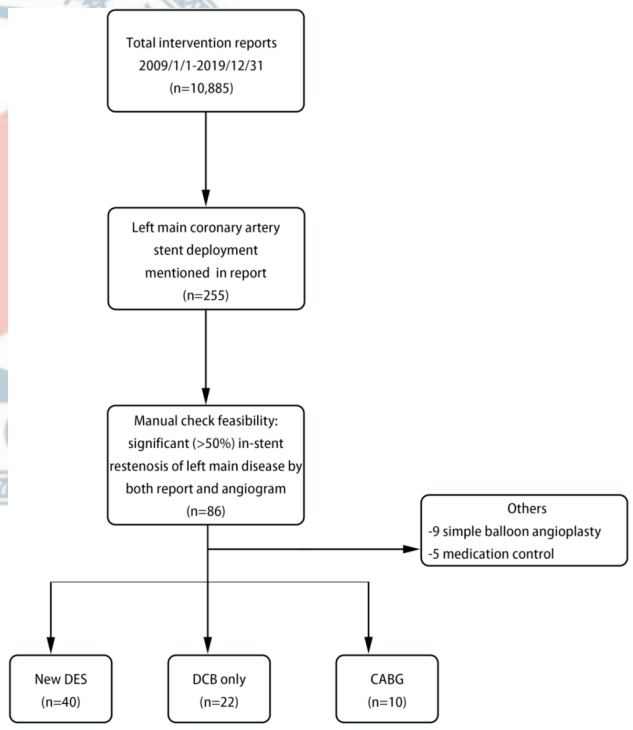

Figure 1. *We screened all cardiovascular intervention reports from January 2009 to December 2019, excluding reports not involving coronary intervention. Patients with multiple reports were selected only when left main intervention was mentioned. Finally, we included patients who were documented to have a left main stent deployed with in-stent restenosis confirmed by a coronary angiography report. We divided patients into groups based on the treatment received. CABG, coronary artery bypass graft surgery; DCB, drug-coated balloon; DES, drug-eluting stent.*

Table 1. Demography

	New DES (n = 40)	DCB only (n = 22)	p value
	Mean ± SD; Number (%)		
Age (year)	66.4 ± 9.4	68.4 ± 9.8	0.432
Gender (male)	30 (75.0)	13 (59.1)	0.221
Hypertension	33 (82.5)	17 (77.3)	0.625
Diabetes mellitus	28 (70.0)	16 (72.7)	0.824
Hyperlipidemia	38 (95.0)	20 (90.9)	0.538
Chronic kidney disease	30 (75.0)	15 (68.2)	0.572
Atrial fibrillation	8 (20.0)	2 (9.1)	0.229
LVEF (%)	52.28 ± 14.36	57.96 ± 15.70	0.246
LVEDD (mm)	5.47 ± 0.75	5.09 ± 0.90	0.155
Median follow up time (day)	581.5	642.5	
Medication			
Aspirin	39 (97.5)	22 (100.0)	0.645
P2Y inhibitor	38 (95.0)	22 (100.0)	0.412
Statin	30 (75.0)	17 (77.3)	0.550
Beta-blocker	12 (30.0)	9 (40.9)	0.277
ACEi/ARB	17 (42.5)	11 (50.0)	0.381
Spirolactone	4 (10.0)	6 (27.3)	0.082
Intervention			
ISR duration (day)	857 ± 1214	541 ± 578	0.175
Syntax score	43.73 ± 10.14	41.34 ± 10.59	0.388
EuroSCORE II (%)	4.05 ± 4.14	3.16 ± 2.13	0.347
True bifurcation	32 (80.0)	12 (54.5)	0.051
Previous two stents	7 (21.2)	12 (57.1)	0.010
Indication of index intervention			0.569
Elective intervention	3 (7.5)	1 (4.5)	
UA	20 (50.0)	11 (50.0)	
NSTEMI	17 (42.5)	9 (40.9)	
STEMI	0 (0.0)	1 (4.5)	
Main branch size (mm)	3.45 ± 0.30	3.35 ± 0.30	0.217
Side branch size (mm)	3.04 ± 0.46	3.23 ± 0.48	0.144
Diffuse ISR	22 (55.0)	6 (27.2)	0.032
Image guide procedure			0.709
IVUS	16 (40.0)	8 (36.4)	
OCT	1 (2.5)	0 (0.0)	

ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; DCB, drug-coated balloon; DES, drug-eluting stent; ISR, in-stent restenosis; IVUS, intravascular ultrasound; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NSTEMI, non-ST elevation myocardial infarction; OCT, optical computed tomography; SD, standard deviation; STEMI, ST elevation myocardial infarction; UA, uric acid.

new-DES and DCB-only groups (both 50.0%, p = 0.974), but patients who underwent CABG experienced significantly fewer MACEs (p = 0.032 and p = 0.015, respectively). For the individual clinical endpoints, no statistically significant differences between the new-DES and DCB-only groups were detected for cardiac death (27.5% vs. 13.6%, p = 0.214), nonfatal MI (30.0% vs. 31.8%, p = 0.214), or TLR (35.0% vs. 45.5%, p = 0.542; Table 2, Supplemental Table 2, Figure 2, and Supplemental Figure 1 and 2). In subgroup analysis, no significant differences were observed in age, gender, underlying comorbidities, previous deployment of two stents, or ISR (Figure 3).

Four studies were reviewed from the PubMed database search (Table 3). Ojeda et al. compared simple and complex intervention strategies for LMISR. The three other studies adopted similar composite MACE defini-

Table 2. Clinical outcomes

	New stent (n = 40)	DCB only (n = 22)	p value*
	Number (%)		
Primary end point			
Major cardiovascular adverse event	20 (50.0)	11 (50.0)	0.974
Secondary end point			
Cardiovascular death	11 (27.5)	3 (13.6)	0.214
Non-fatal myocardial infarction	12 (30.0)	7 (31.8)	0.835
Ischemic stroke	2 (5.0)	0 (0.0)	0.333
Target lesion revascularization	14 (35.0)	10 (45.5)	0.542
Heart failure driven hospitalization	16 (40.0)	10 (45.5)	0.778

DCB, drug-coated balloon.

* Kaplan-Meier method and log-rank.

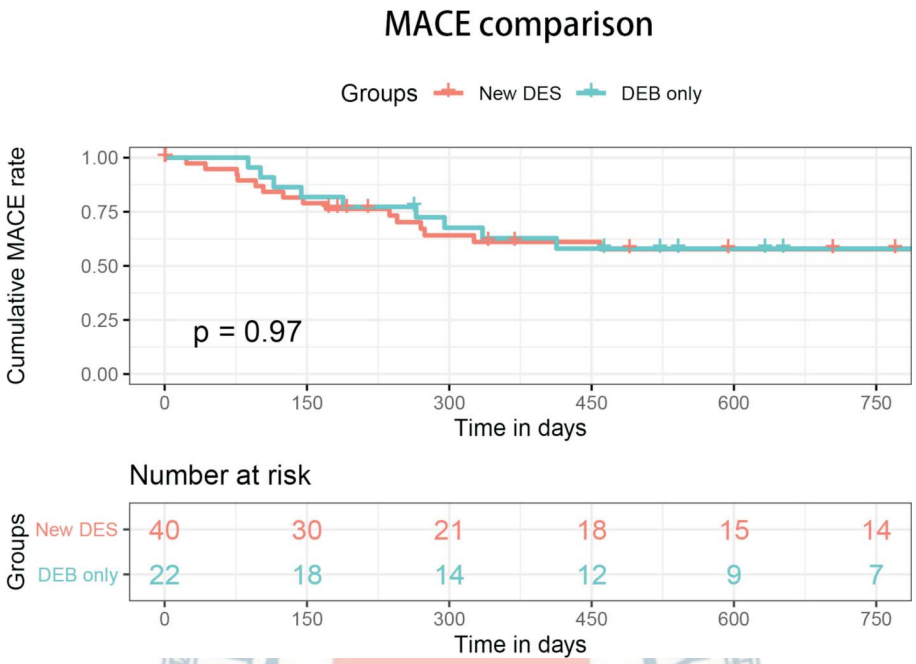

Figure 2. *Incidence rate of major adverse cardiac events by group. No significant difference was observed between the drug-eluting stent and drug coated balloon angioplasty groups. DEB, drug eluting balloon; DES, drug-eluting stent.*

tions and similar comparisons between DES and DCB strategies for coronary bifurcation ISR, two of which were specific to the LM, and were enrolled. All four studies reported no significant differences in their results; similarly, joint analysis revealed no significant difference in MACEs (OR: 1.02, 95% CI: 0.63-1.65; Figure 4 and Table 3).

DISCUSSION

In the present study, we evaluated the long-term MACEs associated with new-DES and DCB-only strategies after stenting with ISR in the treatment of LMCAD. The incidence of MACEs was similar between the two groups during medium-term follow-up (581.5 and 642.5 days for the new-DES and DCB-only groups, respectively).

Evidence regarding the long-term clinical outcomes of DES and DCB strategies in patients with LMISR is limited. The following Milan and New-Tokyo (MITO) Registry data are from before the era of DCB treatment. Of 474 patients with LM involvement, 92 (19.4%) developed restenosis, and 84 (91.3%) were treated with repeat PCI (43 with plain old balloon angioplasty and 41 with

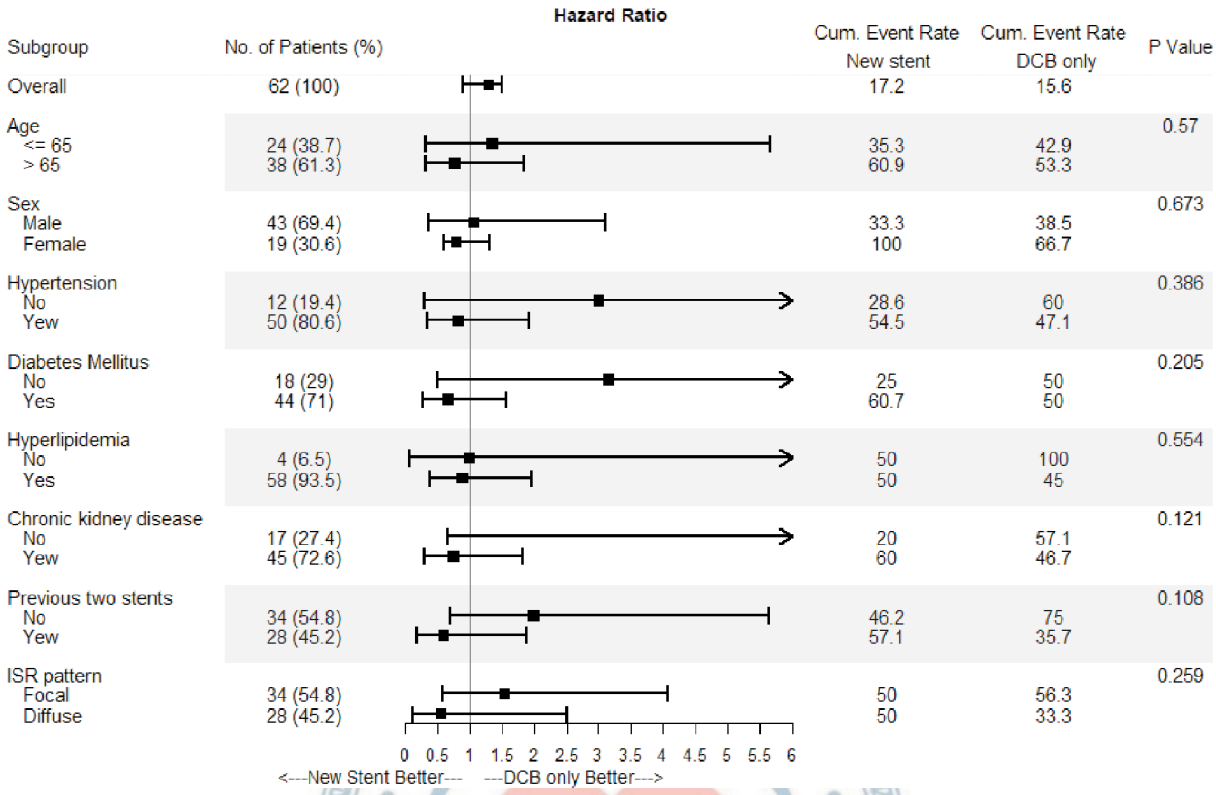

Table 3. Enrolled studies

Study	Country	Publication year	Lesion site	Comparison	Primary endpoint	MACE definition	Patient numbers	Median follow-up duration	Outcomes (DCB vs. DES)
Naganuma et al.[14]	Japan	2016	ISR involve bifurcation	DCB vs. DES	MACE	CV death, MI, TLR	DEB: 73, DES: 85	701 days	MACE: 32.1% vs. 27.6% CV death: 5.0% vs. 2.6%
Lee et al.[13]	Taiwan	2018	ISR involve LM bifurcation	DCB vs. DES	MACE	CV death, MI, TLR, stroke	DEB: 75, DES: 29	NA	MACE: 20.3% vs. 24.0% CV death: 0% vs. 10.7% MI: 6.0% vs. 12.5%
Kook et al.[12]	South Korea	2020	ISR involve LM bifurcation	DCB vs. DES	MACE	CV death, MI, TLR, CABG, stent thrombosis	DCB: 24, DES: 51	868 days	MACE: 25.5% vs. 25.0% CV death: 2% vs. 0% MI: 2% vs. 0%
Our study	Taiwan		ISR involve LM bifurcation	DCB vs. DES	MACE	CV death, MI, TLR	DCB: 22, DES: 40	642.5 days	MACE: 50.0% vs. 50.0% CV death: 13.6% vs. 27.5% MI: 31.8% vs. 30.0%

CABG, coronary artery bypass graft surgery; CV, cardiovascular; DCB, drug-coated balloon; DEB, drug eluting balloon; DES, drug-eluting stent; ISR, in-stent restenosis; LM, left main; MACE, major adverse cardiovascular event; MI, myocardial infarction; NA, not available; TLR, target lesion revascularization.

further DES implantation). The POBA strategy resulted in significantly more recurrent stenosis than the DES strategy (hazard ratio: 4.14; 95% CI: 1.21-14.25; p = 0.02).[10] The major difference between the MITO study and later studies is the inclusion of the DCB strategy, which was introduced in 2010. Several randomized trials have compared the efficacy of repeat DES and DCB angioplasty in patients with non-LM DES ISR lesions. For example, the Restenosis Intra-Stent of Drug-Eluting Stents: Drug-Eluting Balloons vs. Everolimus-Eluting Stents (RIBS IV) trial

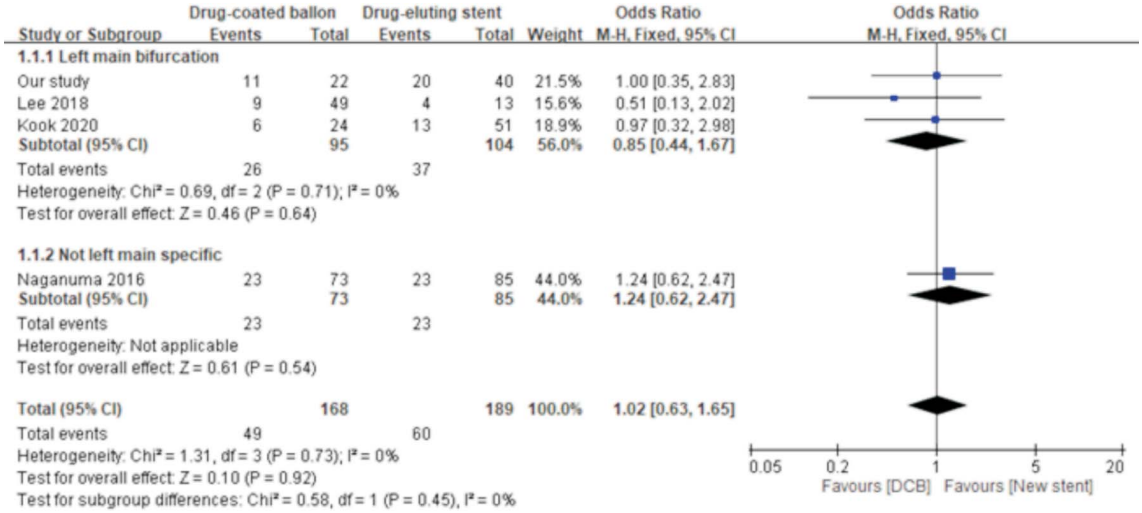

Figure 4. *Major adverse cardiac event analysis of studies enrolled. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by using the total number of patients and major adverse cardiac events to compare the clinical outcomes between the drug-eluting stent and drug coated balloon percutaneous coronary intervention strategies.*

revealed that, compared with DCB angioplasty, the implantation of second-generation everolimus-eluting stents resulted in superior angiographic and clinical outcomes.[11]

However, concerns remain that the multiple metal layers left behind by repeat DES implantation in the coronary arteries could increase the risk of recurrent restenosis or stent thrombosis owing to the risk of delayed re-endothelization and inflammation. Naganuma et al. first demonstrated the comparable efficacy of both the DCB and DES approaches in the treatment of coronary bifurcation ISR (not specific to the LM); Kook et al. and Lee et al. reported similar findings in the treatment of LM ISR in terms of clinical outcomes.[12-14] However, these studies were limited by their small and unbalanced sample sizes due to the low prevalence of ISR in the DES era. We therefore reviewed and analyzed all available relevant data, including ours, and found comparable clinical outcomes of the two strategies. Nevertheless, although statistically insignificant, our study showed a relatively higher cardiovascular death rate in new-DES group than in the DEB-only group (27.5% vs. 13.6%, p = 0.214), which is similar to the report of Lee et al. One possible explanation may be due to the relatively higher true bifurcation rate in the new-DES group (80% vs. 54.5%, p = 0.051, respectively), and more stent deployment may lead to greater metallic burden.

According to our results, CABG is still the most favorable option for treating patients, especially for those who have two stents already deployed and exhibit a diffuse ISR pattern (Figure 1 and Table 1). For patients unable to undergo CABG, the new-DES and DCB-only strategies demonstrated similar clinical efficacy, and the decision may be left to the operator's discretion. However, the CORPAL registry trial results suggested a simpler strategy.[15]

Our study has several limitations. First, because it was retrospective and observational, selection bias was inevitable and may have affected our interpretation. Second, the sample size was small, especially in the DCB-only group, and it may be insufficient to draw definite conclusions. Third, the clinical conditions, lesion complexities, and procedural characteristics of the patients enrolled were highly heterogeneous; thus, our findings may not be generalizable to all LM ISR cases. Fourth, although comparable in both groups, the relatively lower usage of image guidance in our study may have lost important information of lesion characteristics or previous stent deployment, which may have led to certain bias. In addition, health insurance policies may have influenced clinical decisions; for example, the Taiwan National Health Insurance program reimburses for the use of DCB angioplasty, but not DES, in the treatment of ISR; this may have financially motivated the patients to choose the more economical strategy.

CONCLUSIONS

In patients who underwent interventions for LM ISR

and were clinically judged to be unsuitable for CABG, our results demonstrated that DCB angioplasty and repeat DES implantation yielded comparable clinical results in terms of MACEs in the medium term.

ACKNOWLEDGEMENTS

This manuscript was edited by Wallace Academic Editing.

FUNDING SOURCES

This study was supported by grant D110-G2512 from the Higher Education Sprout Project, Ministry of Education, to the Headquarters of University Advancement at National Cheng Kung University.

DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. General demography of each groups

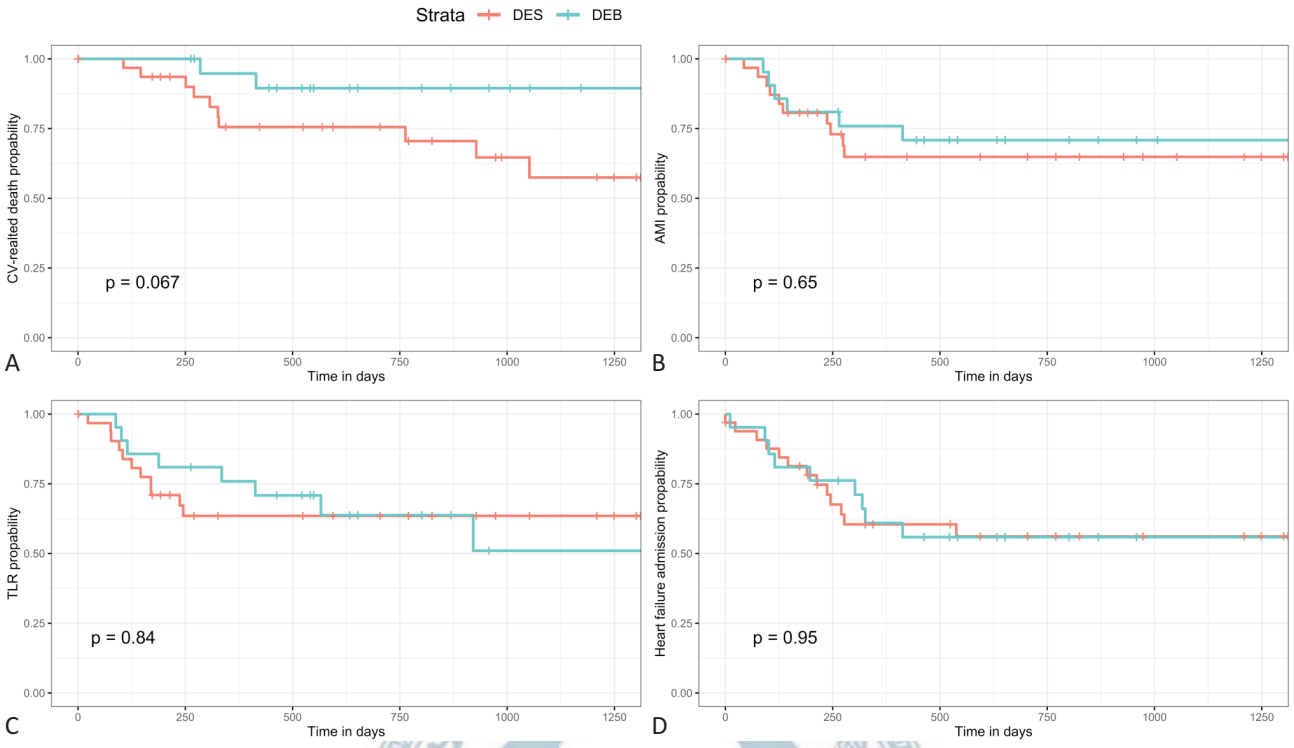
	New DES (n = 40)	DCB only (n = 22)	p value	CABG (n = 10)
	Mean ± SD; Number (%)			
Age	66.4 ± 9.4	68.4 ± 9.8	0.432	69.7 ± 6.7
Gender (male)	30 (75.0)	13 (59.1)	0.221	8 (80.0)
Hypertension	33 (82.5)	17 (77.3)	0.625	8 (80.0)
Diabetes mellitus	28 (70.0)	16 (72.7)	0.824	5 (50.0)
Hyperlipidemia	38 (95.0)	20 (90.9)	0.538	10 (100.0)
Chronic kidney disease	30 (75.0)	15 (68.2)	0.572	6 (60.0)
Atrial fibrillation	8 (20.0)	2 (9.1)	0.229	4 (40.0)
LVEF (%)	52.28 ± 14.36	57.96 ± 15.70	0.246	48.33 ± 26.38
LVEDD (mm)	5.47 ± 0.75	5.09 ± 0.90	0.155	4.15 ± 2.29
Median follow up time (day)	581.5	642.5		872.5
Medication				
Aspirin	39 (97.5)	22 (100.0)	0.645	10 (100.0)
P2Y inhibitor	38 (95.0)	22 (100.0)	0.412	10 (100.0)
Statin	30 (75.0)	17 (77.3)	0.550	9 (90.0)
Beta-blocker	12 (30.0)	9 (40.9)	0.277	5 (50.0)
ACEi/ARB	17 (42.5)	11 (50.0)	0.381	9 (90.0)
Spirolactone	4 (10.0)	6 (27.3)	0.082	5 (50.0)
Intervention				
ISR duration (day)	857 ± 1214	541 ± 578	0.175	461 ± 711
True bifurcation	32 (80.0)	12 (54.5)	0.051	10 (100.0)
Previous two stents	7 (21.2)	12 (57.1)	0.010	5 (62.5)
Indication of index intervention			0.569	
Elective intervention	3 (7.5)	1 (4.5)		2 (20.0)
UA	20 (50.0)	11 (50.0)		2 (20.0)
NSTEMI	17 (42.5)	9 (40.9)		5 (50.0)
STEMI	0 (0.0)	1 (4.5)		1 (10.0)
Main branch size (mm)	3.45 ± 0.30	3.35 ± 0.30	0.217	3.25 ± 0.35
Side branch size (mm)	3.04 ± 0.46	3.23 ± 0.48	0.144	2.78 ± 0.34
Diffuse ISR	22 (55.0)	6 (27.2)	0.032	8 (80.0)
Image guide procedure			0.709	
IVUS	16 (40.0)	8 (36.4)		
OCT	1 (2.5)	0 (0.0)		

ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CABG, coronary artery bypass graft; DCB, drug-coated balloon; DES, drug-eluting stent; ISR, in-stent restenosis; IVUS, intravascular ultrasound; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NSTEMI, non-ST elevation myocardial infarction; OCT, optical computed tomography; SD, standard deviation; STEMI, ST elevation myocardial infarction; UA, uric acid.

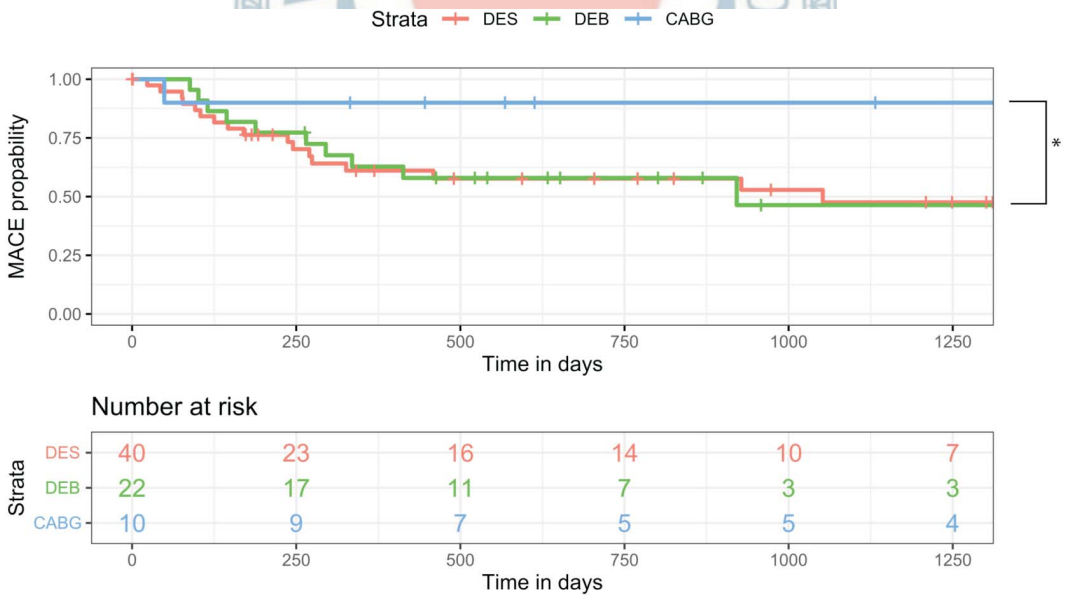
Supplementary Table 2. Outcomes

	New stent (n = 40)	DCB only (n = 22)	p value*	CABG (n = 10)
	Number (%)			
Primary end point				
Major cardiovascular adverse event	20 (50.0)	11 (50.0)	0.974	1 (10.0)
Secondary end point				
Cardiovascular death	11 (27.5)	3 (13.6)	0.214	1 (10.0)
Non-fatal myocardial infarction	12 (30.0)	7 (31.8)	0.835	0 (0.0)
Ischemic stroke	2 (5.0)	0 (0.0)	0.333	0 (0.0)
Target lesion revascularization	14 (35.0)	10 (45.5)	0.542	2 (20.0)
Heart failure driven hospitalization	16 (40.0)	10 (45.5)	0.778	0 (0.0)

CABG, coronary artery bypass graft; DCB, drug-coated balloon.
* Kaplan-Meier method and log-rank.



Supplementary Figure 1. *Comparison of individual outcomes: (A) Cardiovascular death, (B) Nonfatal myocardial infarction, (C) Target lesion revascularization incidence, and (D) Heart failure-related admission rate. AMI, acute myocardial infarction; CV, cardiovascular; DEB, drug eluting balloon; DES, drug-eluting stent; TLR, target lesion revascularization.*



Supplementary Figure 2. *Incidence rate of major adverse cardiac events by groups including CABG group. CABG, coronary artery bypass graft surgery; DEB, drug eluting balloon; DES, drug-eluting stent.*