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Angioplasty of unprotected left main coronary stenosis: Real world experience of a single-operator group from eastern India



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ABSTRACT

Background: Coronary artery bypass graft surgery is the standard treatment of unprotected left main coronary stenosis (ULMCA). However, in the real world scenario, many of these patients are unfit for CABG or prefer angioplasty as an alternative when offered the choice. Methods: A total of 86 clinically stable patients with ULMCA stenosis who were unfit or unwilling for CABG underwent PCI with DES at two tertiary care centers in Kolkata. Patients were followed up prospectively for a median of 34.6 months for major adverse cardiovascular events. Angiographic follow-up was done after 1 year of index procedure or earlier, if indicated. Results: Fifty-five patients (64%) had distal left main stenosis. Two-stent technique was used in 19 patients (22%) and single-stent technique in 36 patients (42%) with distal left main lesion. Thirteen patients (15.1%) had left ventricular ejection fraction (LVEF) of ≤45%. There was no in-hospital death, MI, or stent thrombosis. During follow-up, major adverse cardiac event (MACE) occurred in 9 patients (10.5%). Our study revealed significantly greater MACE in patients with distal left main lesion with LVEF \leq 45% (50% vs 6.38%, *p* = 0.0002), high SYNTAX score (36.36% vs 6.82%, p = 0.008), and diabetes (17.95% vs 0.00%, p = 0.07). Overall, also patients with Diabetes, LVEF \leq 45%, and SYNTAX score >32 had significantly higher MACE. Use of IC Stent, IVUS, or procedural strategy in distal lesion did not affect MACE.

Conclusion: In selective patients with low-intermediate SYNTAX score and without diabetes and LV dysfunction, ULMCA PCI with DES is feasible.

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1. Introduction

Significant, unprotected left main coronary stenosis (ULMCA) is a life threatening condition. It is found in 3-10% of the patients undergoing coronary angiogram.^{1,2} Treated medically, this condition has unacceptably high 1-year mortality of 21%³ and 3-year mortality of 30–40%.^{4–7} Coronary artery bypass graft surgery has shown improved long-term survival in several trials,^{4–7} and currently, the standard of care for ULMCA stenosis.⁸ PCI has long been tried as an alternative option in treatment of coronary artery disease. PCI with bare metal stents (BMS) were found to have low-procedural complications but they had unacceptably higher rate of repeat revascularization rate.⁹⁻¹² Since the advent of drug eluting stents (DES) in 2002, with the promise of vastly reduced rate of restenosis, there has been a resurgence of interest of ULMCA stenting. Several registries from different parts of the world have shown comparable short-term outcomes in terms of death or MI that rivals those of CABG.^{13–19} Guidelines support PCI in patients with ULMCA stenosis who are not suitable for CABG.⁸ Here we present our experience in ULMCA PCI from two tertiary care hospitals in Kolkata using DES.

2. Methods

Study objective. Primary study objective was to assess major adverse cardiac events (MACE), including all cause mortality, MI, and TVR. Secondary objective was stent thrombosis (ST).

Patient population. From October 2008 to February 2014, patients with de novo ULMCA stenosis, treated with new DES implantation at two centers (AMRI Hospital, Salt Lake and Fortis Hospitals, Anandapur, Kolkata) by a single group of interventional cardiologists, were included in our registry. Patients presenting with STEMI were excluded. Patients with NSTE-ACS or unstable angina were medically stabilised before PCI. SYNTAX score was calculated for all patients. As ULMCA disease is still a Class I indication for surgery in the current guidelines, patients were enrolled after proper counseling by interventional cardiologists, cardiac surgeons, and internists (Heart Team since 2012) in situations like (a) advanced age, (b) critical co-morbidities, (c) patient unwilling for CABG, (d) Estimated short life expectancy (known malignancy) and (e) post-CABG with occlusion of left internal mammary artery/ RSVG graft to LAD & LCx making the situation as unprotected LMCA disease.

Medications and PCI. Each patient was preloaded with clopidogrel (600 mg) and used 75 mg in combination with aspirin 150 mg daily for 12 months. Aspirin 75 mg was continued indefinitely thereafter. All the procedures were performed via transfermoral route. Intraprocedural unfractionated heparin (with a goal activated clotting time of \geq 300 s) was administered during the procedure.

Coronary angioplasty and stent implantation, including bifurcation strategy in the case of distal disease, were performed according to the operator's preference, with the aim of complete coverage of the diseased segment. The use of prophylactic intra-aortic balloon pump (IABP), periprocedural glycoprotein IIb/IIIa inhibitors, atherectomy devices, IVUS guidance (Boston Scientific), and Enhanced Stent Visualisation (ESV) system (Siemens IC Stent) was at operator discretion. Stents used in our patients include Cypher (Cordis) Sirolimus eluting stent, Taxus Liberte (Boston Scientific) Paclitaxel eluting stent, Promus Element/Promus Element Plus/Synergy (Boston Scientific) or Xience V/Xience Prime (Abbot Vascular) Everolimus eluting stent, and Endeavour Sprint/Endeavour Resolute/Integrity Resolute (Medtronic) Zotarolimus eluting stent.

All patients gave informed written consent for the procedure and subsequent data collection during follow-up. The study was approved by ethical committees of the respective institutes.

Follow-up. All patients were followed up during hospital stay, after discharge at 1 month, 6 months, 1 year and then yearly by clinic visit or telephonic contact. Coronary angiogram was planned in all patients after 1 year of index procedure or earlier if indicated. Follow up was recorded till February 2015.

Definitions. Death was classified as either cardiac or noncardiac according to the Academic Research Consortium (ARC) definitions.²⁰

Periprocedural non-Q wave MI was defined as elevation of the serum creatinine kinase isoenzyme MB (CK-MB) to 3-times the upper limit of normal, in the absence of new pathological Qwaves. Q-wave MI was defined as the development of new pathological Q-waves in 2 or more contiguous leads, with or without CK-MB elevation above normal. Spontaneous MI was defined as the occurrence after hospital discharge of any value of troponin and/or CK-MB greater than the upper limit of normal if associated with clinical and/or electrocardiographic changes.

TVR was defined as any repeat PCI or surgical bypass of any segment of the target vessel, defined as the entire major coronary vessel proximal and distal to the target lesion, including upstream and downstream branches and the target lesion itself.

TLR was defined as any repeat PCI of the target lesion, or bypass surgery of the target vessel performed for restenosis. The *target lesion (restenosis)* was defined as the treated segment from 5 mm proximal to 5 mm distal to the stent.

Definite, probable, and possible ST were determined according to the ARC definitions. $^{\rm 20}$

Statistical analysis. Data are presented in percentages and mean \pm S.D. Categorical variables are presented as percentages and compared with chi-square testing. Statistical significance was established at $\alpha = 0.05$ level. Kaplan–Meier survival curves were obtained along with 95% confidence limits for survival curves in overall population and analysed with log rank test method. Cox's proportional hazard model was used to determine hazard ratios (using Efron approximation). Analysis was performed using Statistical software R (R Foundation for Statistical Computing, version 2.6.2).

3. Results

A total of 86 patients with de novo ULMCA stenosis treated with DES were included in the study. Baseline patient characteristics and angiographic characteristics are shown in Tables 1 and 2.

Table 1 – Baseline clinical characteristics in patients with ULMCA stenosis undergoing PCI with DES.

Population characteristics	No. of patients (n = 86) (%)/Mean \pm SD
Male	65 (75.58%)
Female	21 (24.42%)
Age (Years) (Mean)	59.43 ± 11.29
Presenting features	
Stable angina	14 (16.28%)
Unstable angina	49 (56.98%)
NSTEMI	20 (23.26%)
Post STEMI angina (<2 weeks after thrombolysis)	1 (1.16%)
Post CABG LIMA/RSVG occlusion	2 (2.32%)
LV ejection fraction (Mean)	$54.02\% \pm 7.33\%$
Co-morbidities	
Hypertension (HTN)	75 (87.21%)
Diabetes mellitus (DM)	58 (67.44%)
Smoking	38 (44.19%)
CRF	3 (3.49%)
Hypertension & diabetes mellitus	51 (59.30%)
Hypertension, diabetes mellitus & smoking	15 (17.44%)
Hypertension, diabetes mellitus, smoking & CRF	1(1.16%)
LV ejection fraction ≤45%	13 (15.12%)

Table 2 – Angiographic characteristics in patients with ULMCA stenosis undergoing PCI with DES.

Angiographic characteristics	No. of patients (n = 86) (%)
Isolated LMCA disease LMCA + 1-vessel disease (LAD/LCx/RCA)	59 (68.6%) 27 (31.4%)
CMCA + right coronary total occlusion Ostial or shaft lesion	2 (2.33%) 31 (36.05%) 55 (62.95%)
Calcified distal lesions	18 (20.93%)
Distal disease and bifurcation type (n = 55) Medina 1, 1, 1	12 (21.82%)
Medina 0,1,1 Medina 1, 0, 1	7 (12.73%) 6 (10.91%)
Medina 1, 1, 0 Syntax score (23.44 ± 8.64)	30 (54.54%)
0-22 23-32	54 (62.79%) 20 (23.26%)
≥33	12 (13.95%)

The mean age was 59.43 ± 11.29 years, 65 (75.58%) were male, and 58 (67.44%) were diabetic. Among the total of 86 patients, 14 patients had stable angina, 49 had unstable angina, 20 patients had NSTEMI, 1 patient had post-STEMI angina after thrombolysis (<2 weeks), and 2 patients had post-CABG occlusion of LIMA-RIMA to LAD & LCx. Thirteen (15.12%) patients had left ventricular ejection fraction (LVEF) <45%.

Fifty-nine patients (68%) had isolated left main coronary disease. Fifty-five patients (63.95%) had distal LMCA lesion Medina 1,1,1 bifurcation lesion was present in 19 patients (34.55%). Mean SYNTAX score of the study population was 23.44 \pm 8.64 with majority of patients (62.79%) having low SYNTAX score.

Table 3 – Procedural characteristics in patients withULMCA stenosis undergoing PCI with DES.Procedure characteristicsNo of patients

Procedure characteristics	No of patients (%)			
Use of IABP	2 (2.33%)			
Use of GP2b3a	15 (17.44%)			
Type of DES				
Paclitaxel eluting stent	19 (22.1%)			
Sirolimus eluting stent	30 (34.88%)			
Everolimus eluting stent	25 (29.07%)			
Zotarolimus eluting stent	12 (13.95%)			
Distal lesion				
1 Stent (Provisional Stenting strategy)	36/55 (64.45%) ^a			
2 Stents strategy	19/55 (34.55%)			
Distal lesion with 2 Stents				
Simultaneous Kissing stenting	7/19 (36.84%)			
Double Kissing Crush	12/19 (63.16%)			
Use of IC stent	66 (76.74%)			
Use of IVUS	18 (20.93%)			
Use of Rotablation	18 (20.93%)			
$^{\rm a}$ Two patients required second stent (T and proprusion).				

Procedural characteristics are shown in Table 3. Among the 55 patients with distal lesions, two-stent technique was employed in 19 patients (34.55%). Among those, simultaneous kissing stent technique was applied in 7 (36.84%) and double kissing crush (DK Crush) technique was applied in 12 (63.16%). Rest of the patients were treated by provisional stenting strategy (65.45%). Among them, 2 patients required a second stent, which was implanted by T and protrusion technique.

Procedural success was achieved in all patients. There were no in-hospital deaths or periprocedural MI. Minimum followup period was 1 year, and maximum follow-up period was 6.5 years. During follow-up 9 patients (8.24%) had MACE, including 3 deaths (3.49%). Two patients had MI due to ST. During angiographic follow-up, 4 patients (4.65%) had in-stent restenosis.

Table 4 shows MACE in different subgroups. Age or sex did not affect MACE in our cohort. As a whole, patients with distal lesion were not found to have higher incidence of MACE compared to those with non-distal lesion. However, patients with high SYNTAX score (>32) had a significantly higher MACE compared to those with low to intermediate (≤32) SYNTAX score (p = 0.005). Patients with distal LMCA lesion with high SYNTAX score had significantly higher MACE compared to those with distal LMCA lesion and low-intermediate SYNTAX score (6.82% vs 36.36%, p = 0.008). Also, incidence of MACE in patients with LVEF \leq 45% (30.77%) is significantly higher than patients with LVEF >45% (6.85%), with p value 0.007 (Fig. 1). Also, in patients with distal ULMCA lesion, those with LVEF ≤45% had significantly greater incidence of MACE than those with LVEF > 45% (50% vs 6.38%, HR = 10.04, p = 0.0002). Moreover, patients with distal lesion and LVEF ≤45% had higher MACE compared to patients with non-distal lesion and LVEF \leq 45% (50% vs 0%, *p* = 0.07), though it did not reach statistical significance.

Patients with distal lesion and diabetes had higher but statistically non-significant MACE compared to those with distal lesion and no diabetes (17.95% vs 0%, p = 0.08). But as a

Table 4 – Incidence of MACE in different subgroups of the study population.					
Characteristics	PTCA	MACE	% of MACE	HR	log rank p value
Male	65	5	7.69%	HR = 2.69	0.125
Female	21	4	19.05%	95% CI (0.722, 10.0)	
Age ≤60 years	45	3	6.67%	HR = 2.26	0.236
Age >60 years	41	6	14.63%	95% CI (0.566, 9.04)	
Non-calcified lesion	68	6	8.82%	HR = 1.91	0.354
(Non-calcified distal lesion				95% CI (0.477, 7.62)	
/Non-distal lesion)					
Calcified distal lesion	18	3	16.67%		
No distal lesion	31	2	6.45%	HR = 2.02	0.371
Distal lesion	55	7	12.73%	95% CI (0.42, 9.72)	
Diabetes	58	0	0.00%	-	0.0306*
No diabetes	28	9	32.14%		
LV ejection fraction >45%	73	5	6.85%	HR = 5.07	0.00713*
LV ejection fraction ≤45%	13	4	30.77%	95% CI (1.36, 18.9)	
Syntax score ≤32	74	5	6.76%	HR = 5.36	0.00511
Syntax score >32	12	4	33.33%	95% CI (1.44, 20)	
No distal lesion & LV ejection fraction ≤45%	5	0	0.00%	-	0.0758
Distal lesion & LV ejection fraction ≤45%	8	4	50.00%		
No distal lesion & LV ejection fraction >45%	26	2	7.69%	HR = 0.8200	0.8276
Distal lesion & LV ejection fraction >45%	47	3	6.38%	95% CI (0.137, 4.908)	
No distal lesion & diabetes mellitus	19	2	10.53%	HR = 1.75	0.479
Distal lesion & diabetes mellitus	39	7	17.95%	95% CI (0.364, 8.43)	
PTCA with IC Stent (ESV)	66	6	9.09%	HR = 1.8080	0.396
PTCA without IC Stent	20	3	15.00%	95% CI (0.452, 7.231)	
PTCA with IVUS	18	1	5.55%	HR = 2.24	0.434
PTCA without IVUS (with/without IC Stent)	68	8	11.76%	95% CI (0.281, 17.9)	
* Statistically significant at $p < 0.05$.					

whole, patients with diabetes had a significantly higher MACE (p = 0.03).

Incidence of MACE with distal lesion treated by different techniques did not vary significantly. Incidence of MACE did not differ significantly in patients with distal ULMCA lesion treated with single- or double-stent strategy (p = 0.19) (Table 5).

IC Stent or IVUS use was not associated with significant difference in incidence of MACE in patients with non-distal/ distal lesion in this study cohort (Tables 5 and 6).



Kaplan-Meier Survival Curve for LV Ejection Fractions

Fig. 1 – Kaplan–Meier's Survival curves for two groups of LMPCI population – LV ejection fraction >45% (upper curve) and LV ejection fraction ≤45% (lower curve) log rank p value 0.007. All MACE found in our study occurred within 1 year of index procedure. Kaplan–Meier analysis of survival free of MACE was found to be 89.5% in these patients at 1-year follow-up (Fig. 2).

4. Discussion

The study was conducted with the purpose of analyzing the ULMCA PCI patients in a real world scenario. The longest available follow-up in our study is 6.3 years and a median follow-up of 34.6 months. During hospital stay, no patient had MACE. During follow up, period MACE occurred in 10.5% patients. The major findings of this study are: (1) PCI of patients with ULMCA disease with DES is a viable option in view of a promising survival rate; (2) age, sex, or type of stenting technique did not affect MACE; (3) in patients with diabetes, compromised LV function (EF <45%) and high SYNTAX score MACE rate are high; (4) patients with distal ULMCA lesion with LV dysfunction (EF ≤45%) had significantly higher MACE; (5) patients with distal ULMCA lesion and high SYNTAX score had significantly higher MACE and (6) Use of IVUS and ESV (IC Stent) technology is not associated with lower incidence of MACE.

Several trials have presented outcomes of ULMCA PCI using DES over the recent years.^{21–24} Results reported in these studies vary widely due to variation in patient selection and procedural technique. Most of these studies have shown that lesions involving left main ostium and shaft have better outcomes than distal left main lesions in terms of MACE. Significantly higher MACE was demonstrated in emergent or urgent ULMCA PCI, whereas favorable short- and long-term

Table 5 – Incidence of MACE in patients with distal LMCA lesion.					
Characteristics	PTCA	MACE	% of MACE	HR	log rank p value
LV ejection fraction >45%	47	3	6.38%	HR = 10.0409	0.000209*
LV ejection fraction ≤45%	8	4	50.00%	95% CI (2.234, 45.14)	
Syntax score ≤32	44	3	6.82%	HR = 5.93	0.0083*
Syntax score >32	11	4	36.36%	95% CI (1.32, 26.6)	
1 Stent PTCA	36	3	8.33%	HR = 2.6048	0.1933
2 Stents PTCA	19	4	21.05%	95% CI (0.5825, 11.65)	
2 Stents SKS PTCA	7	0	0.00%	-	0.101
2 Stents DKS PTCA	12	4	33.33%%		
No diabetes mellitus	16	0	0.00%	-	0.07734
Diabetes mellitus	39	7	17.95%		
PTCA with IC Stent (ESV)	43	4	9.30%	HR = 3.2232	0.1054
PTCA without IC Stent	12	3	25.00%	95% CI (0.7202, 14.43)	
PTCA with IVUS	13	1	7.69%	HR = 1.989	0.5163
PTCA without IVUS (with/without IC Stent)	42	6	14.29%	95% CI (0.2394, 16.52)	
* Statistically significant at $p < 0.05$.					

Table 6 – Incidence of MACE in patients with No distal LMCA lesion.					
Characteristics	PTCA	MACE	% of MACE	log rank p value	
LV ejection fraction $>$ 45%	26	2	7.69%	0.5311	
LV ejection fraction \leq 45%	5	0	0.00%		
PTCA with IC Stent	8	0	0.00%	0.399	
PTCA without IC Stent	23	2	8.70%		
PTCA with IVUS	5	0	0.00%	0.5311	
PTCA without IVUS (with/without IC Stent)	26	2	7.69%		
Syntax score ≤32	30	2	6.67%	0.795	
Syntax score >32	1	0	0.00%		

outcomes were shown in elective ULMCA stenting.^{25–27} In our study, more than half of the patients had distal LM involvement, with Medina classification 1.1.0 and 1.1.1 being the most prevalent disease patterns. This finding is consistent with data from previous trials and registries, including the SYNTAX trial.²⁸

The SYNTAX trial was a randomized controlled trial that evaluated the efficacy and safety of PCI using PES for



Fig. 2 – MACE free survival of overall population with ULMCA PCI with data showing population at risk.

1800 patients with three-vessel and/or left main disease. In the left main subgroup analysis for 348 patients undergoing CABG and 357 receiving PCI, PCI demonstrated equivalent 1-year clinical outcomes of MACCE, including death, MI, stroke, and repeat revascularization compared with CABG. The SYNTAX study group created the SYNTAX score to classify angiographic complexity and predict outcomes of patients who are treated with revascularization. The score takes into account, anatomic complexities including calcification, bifurcation lesions, total occlusion, thrombus, and long lesions. In spite of some limitations, such as absence of clinical profiles and wide interobserver variation, the score is considered to be a useful predictor for the extent of coronary disease and provides important information for deciding the revascularization strategy. In the SYNTAX study, the low (0-22; 26% vs 28.4%; p = 0.6) and intermediate SYNTAX (23-32; 29.5% vs 29.7%; p = 0.9) score groups had comparable 4-year incidences of MACCE between PCI and CABG groups.¹⁸ However, in the highscore group (≥33), PCI showed a higher incidence of MACCE than CABG (42.6% vs 26.3%; p < 0.003).

Mean SYNTAX score observed in our cohort was lower than that reported in the left main subset of PCI-treated patients of the SYNTAX trial (23.44 ± 8.64 vs 28.1 ± 12.4). However, patients with high SINTAX score had significantly higher MACE compared to those with low-intermediate SYNTAX score. In our study, there was no significant difference in MACE between distal and non-distal lesions. But interestingly, patients with distal lesion and high SYNTAX score had significantly higher MACE compared to those with distal lesions with low-intermediate SYNTAX score (p = 0.008). On the other hand, patients with non-distal ULMCA lesion even with high SYNTAX score did not have higher MACE compared to patients with low-intermediate SYNTAX score and nondistal lesions. A study by Kim et al. showed that the angiographic SYNTAX score plays a partial role in predicting long-term adverse events after PCI for ULMCA stenosis and suggested that including clinical risks may improve the predictive ability of the score.²⁹

All the MACE observed in our study occurred within 1-year follow-up. MACE observed in our study is lower than other similar studies.^{30,31} The reason may be that highly selective and mostly clinically stable patients were included in our study. Distal LMCA bifurcation treated with multiple stents was found to be associated with worse outcome.^{32–35} In our study, 64.45% patients with distal LMCA stenosis were treated by single stent strategy.

Mostly simultaneous kissing stenting (SKS) and Double kissing crush (DKC) were the techniques selected for 2-stent strategy. None of the techniques were found to be superior to the other in terms of MACE. Simultaneous kissing stenting in our study was done mostly in patients with Medina 0,1,1 lesions with <5 mm proximal overlap. Probably that may be the reason that there was no restenosis in this group. Recent studies show that if stenting is performed by experienced operators, either single- or two-stent techniques for bifurcation yielded a comparably feasible long-term outcome compared to CABG, even for bifurcation ULMCA stenosis.³⁶

In recent years, data have been published showing the role of ESV technique in complex PCI.^{37–40} This technique is helpful during stent placement and guides optimal stent expansion. It involves the creation of an enhanced exposure image that clearly outlines the geometry of the deployed stent from a fixed viewing direction. The enhancement is achieved by employing a motion-compensation process and temporal integration of the image sequence to increase contrast visibility. IVUS is considered the gold standard for assessment of stent malapposition. Improved procedural outcomes, such as increased luminal diameter and reduced restenosis rates, have been documented when using IVUS with PCI.41,42 ESV is considered to be complimentary to IVUS. However, in our study, use of IC Stent was not associated with better clinical outcome in terms of MACE (p = 0.4). Use of IVUS was associated with a lower MACE compared to no IVUS (5.55% vs 11.76%), though it did not reach statistical significance.

Studies have shown that low EF is an independent predictor of mortality following LMCA PCI.^{30,43} Recently, developed SYNTAX score II, which combines both the anatomical and clinical factors to assess risk after PCI, has included LV EF as a major clinical risk factor with great prognostic value.⁴⁴ DELTA registry,⁴⁵ the multinational all-comer registry of ULMCA PCI with DES has shown that SYNTAX score and LVEF are predictors of primary endpoints.

In our study, left ventricular EF \leq 45% was found to be associated with significantly higher MACE in the overall study population. In patients with distal LMCA, lesion EF \leq 45% was also associated with significantly higher MACE.

Diabetes has been shown to be associated with increased MACE in ULMCA disease treated with DES.⁴⁶ In our study also, we found higher MACE in patients with diabetes compared to those with no diabetes (p = 0.03).

5. Study limitations

This study has several limitations. First, small sample size prevents us to draw any firm conclusion regarding clinical outcomes. This analysis is intended for descriptive purpose only. Second, selection of clinically stable patients for elective PCI prevents the findings to be extrapolated to patients with STEMI or cardiogenic shock. There was no comparison with CABG. Operator preference was used in each procedure regarding use of ESV/IVUS, choice of technique, and stent used to treat the lesion, which may lead to confounding. Mostly, first-generation stents were used in this study. We also did not look at the risk scores of the study population. Despite these limitations, this analysis provides a descriptive assessment of outcomes of clinically stable patients with significant ULMCA lesion undergoing PCI with DES.

6. Conclusion

Elective PCI with DES is a viable option in selective patients with ULMCA stenosis. Patients with high SYNTAX score, left ventricular dysfunction with EF \leq 45%, and diabetes are at higher risk for developing MACE following ULMCA PCI. Role of IVUS or Enhanced Stent Visualisation in clinical outcome should be evaluated in a larger population.

Conflicts of interest

The authors have none to declare.

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