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Received: 22 January 2019 | Revised: 1 May 2019 | Accepted: 22 June 2019

DOI: 10.1002/ccd.28387

ORIGINAL STUDIES

WILEY

Long-term outcome in patients treated with first- versus second-generation drug-eluting stents for the treatment of unprotected left main coronary artery stenosis

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Abstract

Objective and background: The study aim is to provide long-term clinical outcome after percutaneous coronary intervention (PCI) for unprotected left main coronary arteries (ULMCA) stenosis with the first-generation (1st-gen) drug-eluting stents (DES) in comparison to 2nd-gen DES, since this is largely unknown.

Methods: Between May 2002, and December 2014, a consecutive series of 656 all-comer patients underwent a PCI for ULMCA stenosis at the Erasmus Medical Center. A total of 235 patients were treated with 1st-gen DES, while a total of 421 patients were treated with 2nd-gen DES.

Results: Overall, the population consisted of 73% males and 58% presented with an acute coronary syndrome. Median follow-up time was 1,361 days (range from 0 to 5,031). At 5 years, the cumulative incidence of major adverse clinical events (the primary composite endpoint of all-cause death, any myocardial infarction or target lesion revascularization; MACE) did not differ between 1st- and 2nd-gen DES (36.8 vs. 38.6%, respectively, Log Rank $p = .79$, adjusted hazard ratio [HR] = 1.28 [95% confidence interval (CI) 0.94–1.74]). No difference was found in the individual endpoints of all-cause mortality (29.5 vs. 29% respectively, $p = .88$, adjusted HR = 1.19 [95% CI, 0.84–1.68]), target vessel myocardial infarction (5.0 vs. 8.4%, $p = 0.17$, adjusted HR = 1.75 [95% CI, 0.78–3.96]) and target lesion revascularization (8.1 vs. 9.8%, $p = .94$, adjusted HR = 1.16 [95% CI, 0.59–2.29]) between the 1st- and 2nd-gen DES cohorts, respectively.

Conclusions: In this large cohort of consecutive patients treated for ULMCA stenosis, no significant differences were found in the safety and efficacy of 1st versus 2nd-gen DES at 5 years follow-up.

KEYWORDS

DES, first-generation, long-term outcome, second-generation, ULMCA

Abbreviations: CABG, coronary artery bypass grafting; DES, drug eluting stents; PCI, percutaneous coronary intervention; ULMCA, unprotected left main coronary artery.

1 | INTRODUCTION

Treatment of unprotected left main coronary artery (ULMCA) stenosis by percutaneous coronary intervention (PCI) is now recognized as an alternative to coronary artery bypass grafting (CABG) in selected patients.[1–4] A recent large-scale patient level meta-analysis demonstrated no difference in long-term mortality in patients with left main coronary artery disease treated with CABG or PCI (irrespective of SYNTAX score or diabetes).[4] However, the vast majority of patients enrolled in these trials were treated with either bare metal stents or first generation (1st-gen) drug eluting stents (DES).[4] In order to decrease the incidence of adverse events like late and very late stent thrombosis, 2nd generation DES were developed with better deliverable alloys, less thrombogenic surface and thinner struts.[5–7] Although the success of these device iterations was proven by better outcomes in a general PCI population, little data are available on the potential benefit of the 2nd-gen DES as compared to 1st-gen DES in real world patients with ULMCA disease.[8] Previous studies either primarily focused on 1st-gen DES, lacked long-term follow-up or enrolled only selected patients.[9–16] Therefore, the aim of this study was to assess the 5-year clinical outcome of 1st-gen versus 2nd-gen DES for the treatment of ULMCA stenosis.

2 | METHODS

2.1 | Patient selection and procedural characteristics

Between May 2002, and December 2014, all patients who underwent PCI for ULMCA stenosis at our institution (Erasmus Medical Center, Rotterdam, the Netherlands) with either a 1st- or 2nd-gen DES were included. ULMCA stenosis was defined as stenosis in either the ostial, mid, distal segment and/or the bifurcation. While patients with failed grafts on either the left anterior descending artery (LAD) or left circumflex artery (LCX) were included, patients with functioning LAD or LCX grafts were excluded. Multiple segments could be stenosed at the same time. In addition, the Medina classification was used to further identify the specific characteristics of ULMCA bifurcation lesions.[17] Main branch stenting was defined as a stenting technique which did not involve a stent implantation of either the proximal LAD or proximal LCX. Angiographic success was defined as TIMI III flow in the left coronary system and no residual relevant stenosis in the stented segment. 1st-gen DES comprised sirolimus-eluting Cypher™ stents (Cordis Corporation, Johnson & Johnson, Warren, New Jersey) or paclitaxel eluting TAXUS™ stents (Boston Scientific Nattick, Massachusets). 2nd-gen DES included everolimus-eluting Xience™ stents, Xience V™, Xience Prime™, Xience Xpededition™ (Abbott Vascular, Santa Clara, California), Promus™ and Promus Premier™ (Boston Scientific, Nattick, Massachusets), Biolimus eluting BioMatrix™ (Biosensors Interventional Technologies Pte Ltd., Singapore) or Zotarolimus eluting Endeavor Resolute™ (Medtronic, Santa Rosa, California).

2.2 | Endpoints and definitions

The primary endpoint of the study was the adjusted hazard ratio (HR) for major adverse cardiac events (MACE: the primary composite endpoint of all-cause death, target vessel myocardial infarction or target lesion revascularization). Clinical follow-up data were collected by hospital visit, chart review, or telephone contact.

Secondary safety endpoints were death from any cause, target vessel myocardial infarction (MI) defined as any MI to the left coronary tree; target vessel revascularization (TVR) defined as any repeat intervention of any segment of the left coronary artery system; including bypass grafting, finally target lesion revascularization (TLR) defined as revascularisation of the ULMCA and finally stent thrombosis defined as definite stent thrombosis according to the ARC criteria.[18]

2.3 | Statistical analysis

Statistical analyses were performed using SPSS (version 24.0, SPSS Inc., Chicago Ill). Baseline and categorical variables are reported as either counts or percentages and compared using the Chi Square test. Baseline, continuous variables are reported as mean ± *SD* and were compared using an independent *t*-test or Wilcoxon-Mann–Whitney test. For the survival analysis a cut-off of 80% noncensored patients was taken in order to demonstrate a valid long-term follow-up analysis. Missing data were handled using the multiple imputations method. Only impaired left ventricular ejection fraction (LVEF) (<35%) had missing values (34.9%). Values were imputed using the patients' clinical data. Results from five imputed data sets were pooled to obtain risk estimates. The survival analysis was performed with the Kaplan–Meier method and tested for significant differences with the Log-Rank test. Hazard ratios (HR) with pertinent 95% confidence intervals were calculated using Cox proportional hazards model. Finally, a multivariate cox-regression analysis was performed in order to assess the adjusted HR with the corresponding 95% confidence intervals (CI). The multivariate model consisted of all variables that differed significantly between the two generations DES type with the exclusion DAPT prescription since this was based on clinical guidelines and mid ULMCA lesions, which was exchanged for ostial ULMCA lesions for practical reasons. In addition, diabetes, prior MI, prior CABG, ACS as a clinical presentation and main branch stenting only were included in the cox regression model.

3 | RESULTS

The present analysis comprises 656 consecutive all-comer patients who underwent a PCI for ULMCA stenosis at our institution. While 235 patients were treated with 1st-gen DES, a total of 421 patients were treated with 2nd-gen DES. Within the 1st-gen DES cohort, 91% received a Paclitaxel-eluting stent. In the 2nd-gen DES cohort, 96% received an Everolimus-eluting stent. Baseline characteristics are depicted in Table 1. In brief, the population consisted of 73% males and 18% presented with an ST-segment elevation myocardial infarct, 7% presented in cardiogenic shock and 14.8% had a LVEF <35%. Mean age was lower in the 1st-gen DES cohort as compared to the 2nd-gen DES cohort (66.5 ± 11.7 vs. 68.4 ± 11.5, $p = .04$, respectively)

TABLE 1 Patient baseline characteristics

Variable	First generation (*n* = 235)	Second generation (*n* = 421)	*p*-value
Age (years)	66.5 ± 11.7	68.4 ± 11.5	.038
Male gender	174 (74%)	304 (72%)	.613
Hypertension	131 (56%)	262 (62%)	.104
Hypercholesterolemia	142 (60%)	273 (65%)	.260
Diabetes	48 (21%)	101 (24%)	.296
Smoking history	83 (35%)	125 (30%)	.137
Peripheral arterial disease	35 (15%)	83 (20%)	.123
Prior myocardial infarction	93 (40%)	121 (29%)	.005
Prior PCI	61 (26%)	122 (29%)	.408
Prior PCI left main	2 (1%)	5 (1%)	.687
Prior CABG	29 (12%)	32 (8%)	.045
Prior stroke	20 (9%)	48 (11%)	.244
BMI (kg/m^2)	26.6 ± 3.9	27.2 ± 4.9	.098
Hb level (mmol/L)	8.3 ± 1.2	8.3 ± 1.2	.706
Creatinine level (μmol/L)	99.0 ± 71.9	97.8 ± 52.0	.811
Indication for PCI			
Stable angina	101 (43%)	176 (42%)	.770
Non-ST-segment elevation ACS	94 (40%)	164 (39%)	.793
ST segment elevation ACS	40 (17%)	81 (19%)	.482
Patient in shock	11 (5%)	36 (9%)	.065
Left ventricular ejection fraction <35%[a]	27 (21%)	36 (12%)	.026

Note: Data are *n* (%) or mean ± *SD*.
Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass grafting; DES, drug-eluting stents;
[a]43.4% missing in the first-generation DES cohort, 29.9% missing in the second-generation DES (*p* = .001).

and a prior MI and coronary artery bypass grafting (CABG) were more frequent in the 1st-gen DES cohort. Concomitant RCA disease was more frequent in the 2nd-gen DES cohort (Table 2). Finally, significant differences were found in procedural characteristics between both cohorts, mainly driven by a more frequent use of new generation P2Y12 inhibitors, radial artery access and intravascular imaging, along with a lower number of stents, less frequent dual anti-platelet therapy prescription and higher percentage of complete revascularization in the 2nd-gen DES cohort (Table 3).

3.1 | Clinical follow-up

Median follow-up time was 1,361 days (range from 0 to 5,031). The overall cumulative incidence of MACE at 5 years was 37.9%. At 5 years, the cumulative incidence of MACE did not differ between 1st- and 2nd-gen DES (36.8 vs. 38.6%, respectively, Log Rank *p* = .79, adjusted HR = 1.23 [95% CI, 0.94–1.74]) (Figure 1). No difference was observed in all-cause mortality between the 1st-gen DES and 2nd-gen DES cohorts (29.5 vs. 29%, respectively, *p* = .88, adjusted HR = 1.19 [95% CI, 0.84–1.68]). Also, cumulative incidences of TV MI (5.0 vs. 8.4%, respectively, *p* = .17, adjusted HR = 1.75 [95% CI, 0.78–3.96]), TVR (17.5 vs. 20.9% respectively, *p* = .87, adjusted HR = 1.21 [95% CI, 0.77–1.91]), TLR (8.1 vs. 9.8%, respectively, *p* = .94, adjusted HR = 1.16 [95% CI, 0.59–2.29]) and definite stent thrombosis (2.0 vs. 1.7% respectively, *p* = .82, adjusted HR = 0.29 [95% CI, 0.028–2.99]) did not differ significantly.

In the cox multivariate regression analysis, Age (adjusted HR 1.02; 95% CI 1.01–1.03), diabetes (adjusted HR 1.54; 95% CI 1.14–2.08); acute coronary syndrome (ACS) at presentation (adjusted HR 1.45; 95% CI 1.07–1.96); a two-vessel bifurcation stenting technique (adjusted HR 1.83; 95% CI 1.24–2.71) were associated with an increased risk for MACE at 5 years, while complete revascularization (adjusted HR 0.65; 95% CI 0.47–0.90) was associated with a decreased risk for 5-year MACE (Table S1).

The cause of death was cardiovascular in 39% of cases, while 29% was noncardiovascular. In 32%, no details on the cause of death could be retrieved.

4 | DISCUSSION

In the present study comparing the clinical outcome of patients treated with 1st- and 2nd-gen DES for ULMCA disease, no difference between the two generations of DES was found up to 5 years. The present study provides the longest follow-up to date of patients treated with both generations DES for ULMCA disease. However,

TABLE 2 Angiographic characteristics

Variable	First generation DES (*n* = 235)	Second generation DES (*n* = 421)	*p*-value
Lesion location			
Ostial	70 (30%)	117 (28%)	.542
Mid	58 (25%)	143 (34%)	.016
Distal	151 (64%)	287 (68%)	.343
Bifurcation	163 (69%)	293 (70%)	.987
Medina class			
1,1,1	77 (47%)	117 (40%)	
1,1,0	38 (23%)	116 (40%)	
1,0,1	18 (11%)	26 (9%)	
0,1,1	6 (4%)	4 (1%)	
1,0,0	7 (4%)	11 (1%)	
0,1,0	11 (7%)	16 (6%)	
0,0,1	6 (4%)	3 (1%)	
Concomitant LAD disease	182 (78%)	344 (82%)	.225
Concomitant RCX disease	153 (65%)	265 (63%)	.581
Concomitant RCA disease	107 (46%)	230 (55%)	.029
Chronic occlusion RCA	20 (9%)	59 (14%)	.038
RCA dominant	227 (97%)	382 (91%)	.005
In-stent restenosis	8 (3%)	8 (2%)	.231

Note: Data are *n* (%).
Abbreviations: DES, drug-eluting stents; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

TABLE 3 Procedural characteristics

Variable	First generation DES (*n* = 235)	Second generation DES (*n* = 421)	*p*-value
Radial access	3 (1%)	97 (23%)	<.001
Intravascular imaging	84 (36%)	192 (46%)	.014
IVUS	84 (36%)	184 (44%)	.047
OCT	0 (0%)	10 (2%)	.017
Predilatation	152 (65%)	251 (60%)	.202
Rotablation	2 (1%)	9 (2%)	.218
Intra-aortic balloon pump	31 (13%)	56 (13%)	.968
Glycoprotein IIb/IIIa inhibitors	38 (16%)	41 (10%)	.015
Stent diameter ULMCA (mm)	3.5 (3.0–4.0)	3.5 (3.5–4.0)	.136
Stent length ULMCA (mm)	20 (12–24)	16 (12–20)	<.001
Total stent length (mm)	52 (31–88)	39 (20–67)	<.001
Number of stents	3 (2–5)	2 (1–4)	<.001
Only main branch stenting	167 (71%)	323 (77%)	.110
Post dilatation	171 (73%)	277 (66%)	.066
Kissing balloon	95 (40%)	129 (31%)	.011
Max balloon diameter (mm)	4.0 (3.5–4.5)	4.0 (3.5–4.0)	.343
Complete revascularization	136 (58%)	294 (70%)	.002
Angiographic success	228 (97%)	418 (99%)	.052
Use of Prasugrel or Ticagrelor	3 (1%)	78 (19%)	<.001
Anti-platelet therapy prescription duration[a]	12 (12–12)	12 (12–12)	<.001

Data are *n* (%), mean ± *SD* or median (IQR).
Abbreviations: IVUS, intravascular ultrasound, OCT, optical coherence tomography, ULMCA, unprotected left main coronary artery, DAPT, dual anti-platelet therapy.
[a]Mean values for anti-platelet therapy duration are 8.6 ± 3.2 and 12.0 ± 0.9 for the first and second generation DES, respectively.

MACE rates at 5 years were as high as 37.9%, illustrating the high-risk nature of the present real-world population.

Although CABG has long been considered the treatment of first choice for patients presenting with left main disease, PCI is currently accepted as an alternative to CABG for patients with left main disease.[3,4,19–21] Unfortunately, only 34% of the PCI patients in the dedicated randomized PCI versus CABG trials were treated with 2nd generation DES.[4] This is an important limitation since newer generation DES proved successful in reducing issues of delayed healing, late and very late stent thrombotic events, and late restenosis.[22–27] The latter resulted in new dedicated randomized trials such as the NOBLE, EXCEL, and SYNTAX, investigating the difference in outcome of PCI versus CABG in patients with left main coronary artery disease specifically.[1,2,10] Besides their partly conflicting results, the one thing these three trials had in common was that they still included selected patients. None of the trials included patients with complex multivessel disease, presentation with acute myocardial infarction or shock and or frailty. These figures call for registries assessing the outcome of patients treated in real world clinical practice. In the present study, 53% of the population either presented with a STEMI, cardiogenic shock or had 3-vessel disease.

Previous research by Moynagh et al. demonstrated that in a propensity matched cohort, Everolimus-eluting stents (2nd-gen DES) were safer and more effective as compared to Paclitaxel-eluting stents (1st-gen DES) in 344 patients, with a reduction of TLF up to 53% at 2 years (cumulative incidence of 7.6 vs. 16.3%, respectively) a difference mainly driven by a discordance in stent thrombosis and target vessel MI, a superiority which was also seen in the ERACI IV registry (216 patients).[28,29] Although we were not able to show a difference between 1st and 2nd gen DES used for treating ULMCA disease up to 5 years in a significantly larger series of patients (*n* = 656), our results extend and concur with the findings of a recent combined analysis of the ISAR-LEFT MAIN and ISAR-LEFT MAIN two trial showing comparable findings at 3 years in 1,257 patients.[15] Additionally, also in the 24 months follow-up FINE registry (183 patients) and 18 months follow-up PRECOMBAT-2 study (661 patients) no differences were found between both generations of DES.[30,31] Additionally, we found MACE rates that exceeded those reported in previous studies with more selective inclusion criteria. In the present study, 5-year MACE rates accrued to 39.5 and 39.7% in the 1st and 2nd-gen DES cohort respectively. These rates were mainly driven by high all-cause mortality figures of 30 and 29%, respectively. In comparison, in the combined ISAR trials,

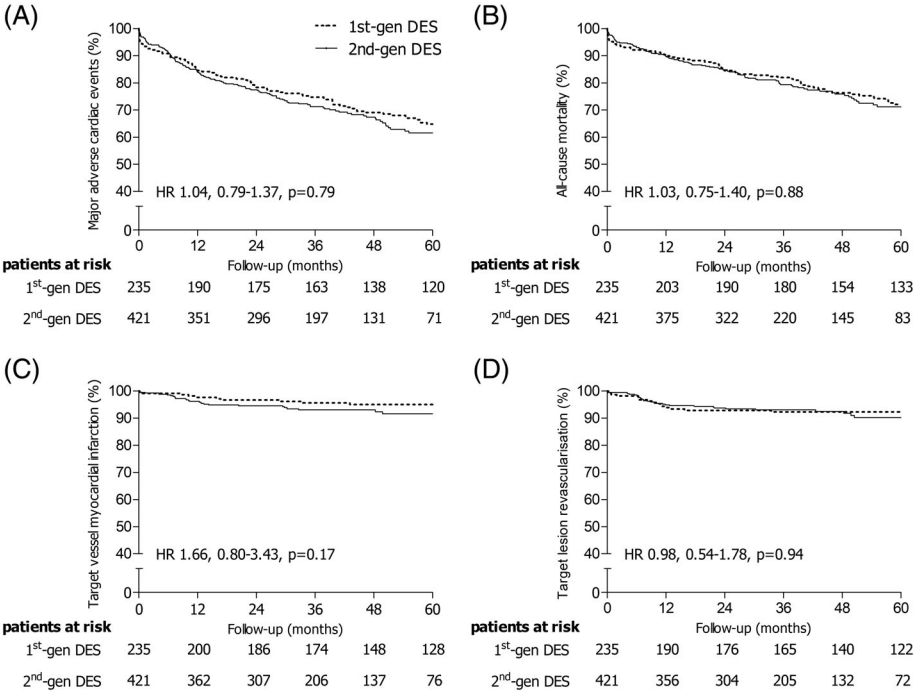

FIGURE 1 Outcome Kaplan-Meijer curves for both first- and second-generation drug eluting stents, including unadjusted hazard ratios and log rank *p* values at 5 years follow-up. (a) All-cause mortality event free survival at 5 years follow-up. (b) All-cause mortality event free survival at 5 years follow-up. (c) Target vessel myocardial infarction event free survival at 5 years follow-up. (d) Target lesion revascularization event free survival at 5 years follow-up

the cumulative incidence of major adverse cardiac and cerebrovascular events (MACCE) was 28% after 3 years, while all-cause mortality was observed in only 13%. However, also the ISAR trials had strict exclusion criteria, such as presence of STEMI, previous CABG, malignancies, cardiogenic shock or a life expectancy <12 months. In addition, the high event rates in the present study cohort, irrespective of the type of DES used, indicates the extreme high risk nature of the present ULCA patient population. It is therefore likely that the small number of events driven by differences in stent type was mitigated by the events linked to the overall patient risk and frailty, both cardiac and noncardiac of many of these patients. The latter calls for better pharmacotherapy, tools and techniques to optimize the outcome of these high-risk patients.

In a dedicated cox multivariable regression analysis, we were able to demonstrate that Age, diabetes, ACS at presentation, a two-stent technique and incomplete revascularization were associated with an increased risk for MACE at 5 years. The latter is in line with prior research on 2 year follow-up, indicating worse outcome in patients presenting with ACS.[32] Furthermore, also diabetes has previously been shown to negatively influence MACCE rates at 1–3 years follow-up after treatment of ULMCA stenosis.[15,33,34] Regarding the use of a 1- versus 2-stent strategy to treat LMCA bifurcation lesions, most previous trials concluded noninferiority between strategies.[34–38] Nevertheless, the recent DK crush V trial suggested a lower rate of TLF at 1 year in the two-stent strategy group as compared to a one stent provisional stenting technique.[39] However, the study protocol advocated a truly complex two-vessel stenting technique, which, in common practice might not always be a realistic solution.

Finally, complete percutaneous revascularization has been shown to significantly reduce cardiovascular endpoint in patients with multivessel disease in a large meta-analysis of trials mainly focusing on patients with stable or unstable coronary artery disease.[40] Conversely, in the recently published CULPRIT Shock trial multivessel PCI did not reduce the primary composite endpoint of death or severe renal failure within 30 days after randomization as compared to culprit artery only revascularization.[41] Instead, the 30-day risk of the primary endpoint was lower among those who initially underwent PCI of the culprit lesion only than among those who underwent immediate multivessel PCI. Of note, only 8% of the patients in this trial presented with left main disease and longer-term follow-up of these patients is not yet available. To date, no dedicated randomized trial has assessed the superiority of complete revascularization as compared to culprit only PCI in patients with ULMCA stenosis. In order to indefinitely adjudicate, the potential influence of multiple stenting techniques, large randomized controlled trials are warranted, for example the EBC MAIN (NCT02497014).

5 | LIMITATIONS

Several limitations need to be mentioned. First, all patients from the current study were included in a large tertiary referring hospital, inducing possible inclusion bias and external validity is therefore not verified. Second, the allocation to treatment with either a 1st- or 2nd-gen DES was determined by the time at which a patient was included. The latter resulted in two consecutive real-world patient cohorts included over a time period of 12 years in which routine clinical practice changed. As a result, several significant differences were found between both cohorts in baseline and procedural characteristics. It is likely, that despite extensive regression models we were not able to fully account for the differences between both cohorts. In addition, given the retrospective nature of the study cohort going back to patients treated in 2002 we were not able to obtain the cause of

death in a significant proportion of patients. Cerebrovascular events were not assessed in the current study and therefore, a completely valid comparison to for example the combined ISAR trial and SYNTAX trial might not be possible. Finally, clinical events were adjudicated by local interventional cardiologists (JD, RvB) with access to all patient data, without external validation.

6 | CONCLUSION

In this large cohort of consecutive patients treated for ULMCA stenosis, no significant differences were found in the safety and efficacy of 1st-versus 2nd-gen DES at 5 years follow-up. Long-term adverse event rates following ULMCA stenting remain high.

6.1 | What is known about the topic?

Treatment of unprotected left main coronary artery stenosis (ULMCA) with drug eluting stent (DES) is now recognized as an alternative to coronary artery bypass grafting in selected patients. In order to decrease the incidence of adverse events like late and very late stent thrombosis with the 1st generation DES, 2nd generation DES were developed with better deliverable alloys, less thrombogenic surface and thinner struts. The success of these device iterations was proven by better outcomes in a general PCI population.

6.2 | What does this study add?

In the present study, comparing the clinical outcome of patients treated with 1st- and 2nd-gen DES for ULMCA disease, no difference between the two generations of DES was found up to 5 years. The present study provides the longest follow-up to date of patients treated with both generations DES for ULMCA disease. However, MACE rates at 5 years were as high as 37.9%, illustrating the high-risk nature of the present real-world population.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: van Zandvoort LJC, van Bommel RJ, Masdjedi K, et al. Long-term outcome in patients treated with first- versus second-generation drug-eluting stents for the treatment of unprotected left main coronary artery stenosis. *Catheter Cardiovasc Interv*. 2019;1–7. https://doi.org/10.1002/ccd.28387