Original Contribution

New-Generation Drug-Eluting Stent Experience in the Percutaneous Treatment of Unprotected Left Main Coronary Artery Disease: The NEST Registry

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ABSTRACT: Objectives. To explore the 2-year clinical outcomes in patients with unprotected left main coronary artery (ULMCA) disease treated with overall new drug-eluting stent (DES) options. Background. Recent available data have shown the feasibility and the safety of new DESs, mainly evaluating the everolimus-eluting stents in the setting of ULMCA disease. Methods. Patients with ULMCA disease undergoing percutaneous coronary intervention (PCI) with everolimus-, zotarolimus-, and biolimus A9-eluting stents were prospectively evaluated. The study objective was the composite of major adverse cardiac events (MACEs), consisting of all-cause mortality, myocardial infarction (MI), and target vessel revascularization (TVR) at 2-year clinical follow-up. Results. A total of 154 patients were analyzed. The mean EuroSCORE and SYNTAX scores were 4.7 ± 2.6 and 27.5 ± 8.3, respectively. Distal location was present in 126 patients (81.8%) and 96 lesions (76.3%) were true Medina bifurcations. The 2-stent technique was used in 73 cases (57.9%). Everolimus-, zotarolimus-, and biolimus A9-eluting stents were implanted in 68 patients (44.2%), 46 patients (29.9%), and 40 patients (25.9%), respectively. At a median clinical follow-up of 551.5 days (interquartile range, 360.8-1045.5 days), MACEs occurred in 29 patients (18.8%). Ten patients (6.5%) died, and 2 deaths (1.3%) were adjudicated as cardiac. No patient had myocardial infarction or definite stent thrombosis (ST). One probable and 1 possible ST (1.3%) were adjudicated as cardiac. No patient had myocardial infarction or stroke. Conversely, target vessel revascularization (TVR) remained significantly higher in patients treated with percutaneous coronary intervention (PCI).3

Recently, new DES options have been demonstrated to be more effective than first-generation DESs in complex patient and lesion subsets.5 The efficacy and safety of new DES options have led to expanded use for off-label indications, such as the percutaneous treatment of ULMCA lesions. Everolimus-eluting stent implantation has been more extensively evaluated in this setting.5,6 Nevertheless, there is a paucity of data supporting the use of overall new DESs in ULMCA lesions.

The aim of this study was to assess 2-year clinical outcomes in patients undergoing ULMCA PCI with currently available new DES options.

Methods

Patient population. All eligible patients from January 2007 to December 2010, with de novo ULMCA stenosis, treated with new DES implantation at two centers (San Raffaele Hospital and EMO-GVM, Centro Cuore) were included in our registry.

The eligibility inclusion criteria were: de novo ULMCA stenosis ≥50% by visual estimate and/or confirmed myocardial ischemia related to ULMCA disease. In cases of intermediate ULMCA stenosis by angiographic visual estimation, a minimum lumen area (MLA) ≤5.9 mm2 on intravascular ultrasound (IVUS) evaluation was used as a cut-off value to indicate significant stenosis.9

Patients who had cardiogenic shock or ST-elevation myocardial infarction were excluded. The decision to perform PCI instead of surgery was considered when patients were deemed high risk for CABG by the cardiothoracic surgeon and in situations when the patient and referring physician preferred PCI.

Patients were stratified using standard European System for Cardiac Operative Risk Evaluation (EuroSCORE), Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX), and Global Risk Classification (GRC) scores.10-12 Baseline diagnostic coronary angiograms were reviewed by two experienced interventional cardiologists.
cardiologists who scored all angiograms according to the SYNTAX score algorithm.

Medications and PCI. Each patient was preloaded with clopidogrel (600 mg) or treated with clopidogrel 75 mg daily starting 5 days prior to the procedure and used in combination with aspirin 100 mg for 12 months. Aspirin 100 mg was continued indefinitely thereafter. Either intraprocedural heparin (with a goal activated clotting time of ≥250 s) or bivalirudin 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, and IVUS guidance were at operator discretion.

Treatment of concomitant lesions during the same procedure was chosen on the basis of the extent of inducible ischemia in non-invasive provocative testing in stable patients.

New DESs used in our cohort were: Xience V/Xience Prime (Abbott Vascular) or Promus/Promus Element (Boston Scientific) everolimus-eluting stent (EES); Endeavor Resolute (Medtronic) zotarolimus-eluting stent (ZES); and BioMatrix (Biosensors, Inc) or Nobori (Terumo Medical Corporation) biolimus-A9 eluting stent (BES).

Angiographic follow-up was only scheduled if staged revascularization was required or if non-invasive evaluation or clinical presentation suggested ischemia.

All patients gave full written consent for the procedure and subsequent data collection as per our hospital policy.

Follow-up, study objectives, and definitions. Information about in-hospital outcomes was obtained from an electronic clinical database. After discharge, all clinical follow-up data on medical therapy and clinical status were prospectively gathered for all patients at 1, 6, 12, and 24 months by telephone or clinic visit. Additional information, if necessary, was collected from the referring cardiologist, general practitioners, and patients themselves. All data related to the new revascularization procedures, both percutaneous and surgical, and rehospitalization data were prospectively included in our electronic database during follow-up.

The primary study objective was the composite of major adverse cardiac events (MACEs) consisting of all-cause mortality, any MI, and TVR at 2-year clinical follow-up. Secondary study objectives were cardiac death, TLR, and stent thrombosis (ST).

Death was classified as either cardiac or non-cardiac according to the Academic Research Consortium (ARC) definitions.13 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 Q-waves. 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 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.13 Clinical events of interest were verified by collecting source documentation and were adjudicated by two independent blinded endpoint experienced interventional cardiologists.

Quantitative coronary angiography analysis. Coronary angiograms were analyzed with a validated edge-detection system (CMS, version 5.2; Medis) by two experienced interventional cardiologists.

In patients undergoing angiographic follow-up, minimal lumen diameter (MLD), reference vessel diameter (RVD), and percent diameter stenosis (DS) were measured at baseline, postprocedure, and at follow-up. Acute gain was defined as the difference between the MLD immediately after the procedure and the baseline. Late lumen loss was defined as the difference between the MLD immediately after the procedure and at follow-up.

Angiographic restenosis was defined as diameter stenosis 50% by quantitative coronary angiography within a previously stented segment (stent and 5 mm proximal and distal) at the follow-up angiogram.

Statistical analysis. Continuous variables are presented as mean ± standard deviation (SD) if normally distributed or as median and interquartile range (IQR) if not normally distributed. Categorical variables are expressed as counts and percentages. The Kaplan-Meier method was used to estimate the incidence of primary study objective in the overall population. Statistical analysis was performed with SPSS, version 18 (SPSS Inc, Chicago).

Results

A total of 154 patients with de novo ULMCA disease were treated with new DESs and were included in this analysis. The baseline clinical and angiographic characteristics are shown in Tables 1 and 2.

The mean age was 67.8 ± 10.8 years, 129 (83.8%) were male, and 42 (27.3%) had diabetes. The mean EuroSCORE and SYNTAX scores were 4.7 ± 2.6 and 27.5 ± 8.3, respectively. Intermediate and high GRC scores were present in 64 patients (41.6%) and 32 patients (20.8%), respectively (Figure 1). Multivessel involvement and right coronary artery (RCA) chronic total occlusion were present in 111 patients (72.1%) and 48 patients (31.1%), respectively. Regarding the complexity of disease, the target lesion involved the distal ULMCA in 126 patients (81.8%) and 96 of the lesions (76.3%) were true Medina bifurcations (Figure 2). The 2-stent technique was used in 73 cases (57.9%), and the “culotte” was the most commonly utilized technique, in 31 patients (42.5%) (Table 3). Of note, IVUS guidance was used
in 91 cases (59.1%). EESs were implanted in the majority of patients (68; 44.2%), followed by ZESs in 46 patients (29.9%) and BESs in 40 patients (25.9%). During the index procedure, the concomitant treatment of RCA lesions was performed in 41 patients (26.6%), and staged revascularization was adopted in 34 patients (22.1%). In the 48 patients with RCA occlusion, the vessel was successfully reopened in 27 (56.3%).

The rate of adherence to dual-antiplatelet therapy (DAPT) in our population was 100%. In 17 patients (11.0%), the DAPT was prescribed indefinitely. The median duration of DAPT was 379.5 days (IQR, 368.0-680.0 days).

In-hospital outcomes. Outcomes during the hospitalization are reported in Table 4. Technical success was achieved in all patients. There were no in-hospital deaths. While no cases of Q-wave MI occurred, 4 patients (2.6%) had periprocedural non-Q wave MI. Interestingly, no target vessel or lesion revascularization were required. The overall incidence of in-hospital MACE was 2.6%.

Two-year outcomes. Clinical events at follow-up are shown in Table 4. Clinical follow-up was performed in 152 patients (98.7%) over a median of 551.5 days (IQR, 360.8-1045.5 days). MACE occurred in 29 patients (18.8%). Kaplan-Meier survival-free from MACE is shown in Figure 3. Ten patients (6.5%) died; in only 2 patients (1.3%), the death was adjudicated as cardiac. No patient had MI during follow-up. Notably, no patients had evidence of definite ST. In 1 patient (0.6%) probable ST was adjudicated due to sudden unexplained death at day 20 (treated with ZES) and in 1 patient (0.6%), possible ST at 991 days (treated with EES) was noted. Both patients had events while on dual-antiplatelet therapy (DAPT).

Of note, TLR was required in only 7 patients (4.5%) and TVR in 19 patients (12.3%). Among patients with TLR, only 1 was correlated to inducible ischemia.

Angiographic follow-up. Baseline and follow-up angiographic results are shown in Table 5. Overall, angiographic follow-up was performed on 82 patients (53.2%) at a median of 217.5 days (IQR, 171.3-345.5 days). Seven in-stent binary restenoses were observed; all of them were focal. There was 1
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Case of ostial left main restenosis in a segment not covered in the prior procedure. In all remaining cases, restenosis occurred at the ostium of the circumflex artery. Repeat revascularization was successfully performed in all patients utilizing stenting in 5 cases and balloon angioplasty in 2 cases.

Discussion

This study characterizes a group of patients who underwent ULMCA PCI using new-generation DESs. The major findings of this report are: (1) the incidence of MACEs at 2-year clinical follow-up in patients with ULMCA disease treated with new-generation DESs is relatively low; (2) the safety profile of these stents is encouraging, as demonstrated by the low rates of overall and cardiac mortality and absence of MI or definite ST; and (3) TLR occurrence was low despite the presence of a high number of complex distal ULMCA bifurcations requiring a 2-stent approach.

A good safety and efficacy profile has been shown with the use of first-generation DESs for the treatment of UMLCA disease, with a significant decrease in the need for repeat revascularization when compared to bare-metal stents.14,15 A systematic review and meta-analysis of 1278 patients with ULMCA stenosis treated with first-generation DESs reported a MACE rate of 16.5% at a median follow-up of 10 months (range, 6-19 months).16

At present, the information currently available in this field comes from studies that have mostly evaluated the role of
Moreover, the preliminary results of the Prospective Randomized Trial of Everolimus- and Zotarolimus-eluting Stents for Treatment of Unprotected Left Main Coronary Artery Disease (ISAR-LEFT MAIN) trial, which compares EES (Xience V/Xience Prime) vs ZES (Endeavor Resolute) have recently been reported, and show favorable outcomes.

Our analysis, which to date has examined the MACE rate in higher-risk profile patients at mid-term follow-up, is encouraging, reporting a cumulative MACE rate of 18.8%. In line with our observations, the rate of major adverse cardiac or cerebrovascular event (MACCE) was found to be particularly favorable when compared to other studies evaluating the clinical impact of EES use. In the LEMAX-Pilot study, 173 patients with ULMCA disease were treated with the Xience V EES. At 1-year clinical follow-up, death, MI, and TVR were 2.9%, 4.7%, and 7.0%, respectively, with a cumulative MACCE rate of 15.0%.5 The Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT-2) study reported their outcomes with EES use for the treatment of ULMCA stenosis in 334 consecutive patients in comparison with sirolimus-eluting stent (SES) use and CABG. The 18-month MACCE rates in the EES cohort were compared with those of a randomized study comparing patients who received SES (n = 327) or CABG (n = 272). EES use showed a comparable incidence of MACCE versus SES (8.9% vs 10.8%; adjusted hazard ratio [aHR] of EES, 0.84; 95% confidence interval [CI], 0.51-1.40; P=.51) and CABG (6.7%; aHR of EES, 1.40; 95% CI, 0.78-2.54; P=.26).6 In the Florence ULMCA PCI registry, the 1-year MACCE rate was 10.2%.8 The clinical outcomes in the ULMCA lesions treated with ZES have been evaluated retrospectively in 40 patients, with a MACE rate of 15.0% at an average clinical follow-up of 12.4 months.17

These results are certainly promising. Nevertheless, CABG surgery has demonstrated to be associated with positive clinical outcomes and lower morbidity/mortality for ULMCA disease. Two British studies reported excellent 2-year survival rates of 94% and 95%.19,20 However, as for all PCI and cardiac surgical procedures, the mortality rate is strongly influenced by comorbidities. Ellis et al reported that 3-year mortality for CABG in ULMCA stenosis varied from 4% in low-risk patients to 40% in those with significant and multiple comorbidities.21 To date, four trials have compared the efficacy of PCI with CABG for the treatment of left main disease. The Left Main Coronary Artery Stenting (LE MANS) trial used surrogate endpoints, such as the change in left ventricular ejection fraction.
fraction (LVEF), whereas the other three trials had a non-inferiority design with respect to hard endpoint (death, MI, TVR, and cerebrovascular events). These studies reported similar rates of the composite endpoint of death, MI, and stroke. Conversely, TVR remained significantly higher in patients treated with PCI. Furthermore, the 5-year outcomes of the SYNTAX trial, which compared PCI with paclitaxel-eluting stent (PES) vs CABG for ULMCA, recently reported a MACCE rate of 36.9% in the PCI group and 31.0% in the CABG cohort (P<.12).

Regarding the safety profile of the new DESs, it is important to emphasize that overall mortality in high-risk patients in our study, wherein 59 patients (36.4%) had a EuroSCORE ≥ 6, was 6.5%, which is in line with previously published PCI studies. Moreover, no patients in our study had MI or definite ST at 2-year clinical follow-up. Interestingly, we observed only 2 cases of probable/possible ST, with a cumulative incidence of 1.3%. These findings are consistent with the current literature.

A multicenter international registry of 731 patients undergoing elective ULMCA stenting with first-generation DES has previously reported a cumulative incidence of definite or probable ST of 0.95% at 30 months of clinical follow-up. Encouraging safety profiles in other patient and lesion subsets have also been reported with new DESs. The LEXMAX study reported a rate of definite/probable ST of 0.6% at 1 year of clinical follow-up; in the Florence registry, the rate of possible ST at a median of 17.7 months was 1.8% in 166 patients, while the PRECOMBAT-2 did not observe definite ST, as in our experience.

Concerning the efficacy endpoints in our cohort, a very low rate of TLR (4.5%) was observed despite the fact that most patients (76.3%) had complex distal bifurcations requiring a 2-stent approach in 57.9%. Conversely, in the LEXMAX registry, 31.4% were complex distal ULMCA bifurcations and the 2-stent technique was used only in a minority of the patients (22.5%). With such an approach, the TLR rate at 1 year was 2.9%.

Similarly, the TLR rate in our population with more complex distal disease was extremely favorable as compared to the 7.5% observed in a series of 40 patients treated with ZES at 12.4 ± 1.8 months of clinical follow-up.

The site of restenosis in this population of distal ULMCA PCI was predominantly the ostial circumflex, occurring in 5/6 of the in-stent restenosis (ISR) cases. However, it is important to underline that in this study, the LCX-ISR TLR was clinically driven in only 1 patient. In the remaining 5 cases, ISR was detected only by angiography performed at the time of revascularization of the RCA. Furthermore, the high utilization of a 2-stent technique to treat complex distal ULMCA lesions may explain the higher occurrence of LCX-ISR.

There are several reasons for the low TLR rates in our study. One factor may be related to improved patient selection as operators gain more experience. A better understanding of the ULMCA anatomy, together with a more liberal use of adjunctive tools such as IVUS, most likely has played a role in the achievement of better results as compared to our prior experience. As evaluated by IVUS, incomplete lesion coverage, stent underexpansion, and incomplete stent apposition have been found to be predictors of early and late/very-late ST after DES implantation.

Moreover, the use of new DESs may contribute to a lower TLR occurrence. Indeed, the combination of new platforms, more biocompatible or biodegradable polymers, and alternative antiproliferative-eluting drugs has already provided good results, ensuring more effective suppression of neointimal hyperplasia and rapid endothelialization, as compared to first-generation DESs.

Our results in terms of TVR occurrence are comparable to the currently available studies that compared EES with first-generation DESs. In the PRECOMBAT-2 trial, the incidence of ischemia-driven TVR in the EES group (6.5%) was comparable to SES (8.2%; aHR of EES, 1.14; 95% CI, 0.64-2.06; P=.65). Angiographic restenosis rates were similar in the SES and EES groups (13.8% vs 9.2%, respectively; P=.16). On the other hand, in an observational analysis, the EES exhibited a clear advantage versus the PES in ULMCA PCI. A total of 390 patients underwent PCI (166 with EES and 224 with PES). The EES was associated with a reduced incidence of 1-year MACE (10.2% vs 21.9%; P=.002), target vessel failure (7.8% vs 20.5%; P=.001), and restenosis (5.2% vs 15.6%; P=.002) as compared to PES implantation.

As reported before, the ISAR-LEFT MAIN 2 trial is the first and largest randomized, multicenter comparison trial between ZES and EES in ULMCA lesions. The study was designed to assess the non-inferiority of ZES versus EES regarding the primary endpoint, ie, incidence of MACE, which was defined as the composite of death, MI, or TLR at 1-year follow-up. Secondary endpoints included the incidence of definite/probable ST at 1-year follow-up and angiographic restenosis at 6-9 months of follow-up. A total of 650 patients with ULMCA lesions pretreated with 600 mg clopidogrel were randomized to treatment with ZES (n = 324) and EES (n = 326). Interestingly, MACE rate was not different in the 2 groups (17.5% in ZES vs 14.3% in EES; HR, 1.26; 95% CI, 0.85-1.85; P=.25). Moreover, TLR was comparable (11.7% in ZES vs 10.7% in EES; HR, 1.26; 95% CI, 0.78-2.06; P=.35). The incidence of definite ST was 0.6% in both groups, while probable ST occurred in 0.3% of the ZES group and 0% of the EES group. Angiographic restenosis occurred in 21.5% of the ZES group and 16.8% of the EES group. Consistent with our experience, these preliminary results of the ISAR-LEFT MAIN 2 trial indicate that the use of second-generation DESs in ULMCA lesions in relatively unselected patients is feasible, safe, and effective.

These findings are certainly encouraging; however, larger ongoing multicenter randomized trials utilizing second-generation DESs, such as the Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial, will hopefully answer the question whether second-generation EESs are non-inferior or in the composite incidence of death, MI, or cerebrovascular events versus CABG in the treatment of ULMCA disease in patients with intermediate SYNTAX score. In this study, 2634 patients with ULMCA and a SYNTAX score ≤32 are currently randomized to either CABG or a second-generation
DES (Xience Prime; Abbott Vascular). The primary endpoint will be the composite incidence of death, MI, or cerebrovascular events at a median follow-up at 3 years, powered for sequential non-inferiority and superiority testing.

The Nordic-Baltic-British Left Main Revascularization Study; Coronary Artery Bypass Grafting Versus Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis (NOBLE) is currently enrolling patients with ULMCA disease. Its aim is to compare clinical outcome parameters in patients treated with CABG versus PCI with DES (Biometrica; Biosensors, Inc). A total of 1200 patients will be included. The primary combined endpoint of death, stroke, non-index-treatment related MI and new revascularization (PCI or CABG) will be evaluated after 2 years.

These studies will provide further insight into results of ULMCA PCI with new-generation DESs.

**Study limitations.** The small sample size of the population cannot allow us to draw any firm conclusions regarding clinical outcomes. Therefore, this analysis is intended for descriptive and hypothesis-generating purposes only. The lack of a comparison with first-generation DESs is one of the main limitations of this study. However, our goal is to provide a snapshot of what currently happens in daily practice, using newer, safer, and more efficient devices. Despite the above limitations, our analysis provides a descriptive assessment of the outcomes of patients with significant left main disease using all new DESs currently available in clinical practice. Further studies with larger sample sizes are required to investigate the differential impact of new-generation DESs in this patient subset.

**Conclusion**

In this observational analysis, the use of new DESs for the treatment of ULMCA disease, including complex distal disease treated with a high proportion of 2-stent technique, appears to have promising safety and efficacy, with encouraging results at 2-year clinical follow-up.

**References**


