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Unprotected left main coronary artery stenting with everolimus (Xience V) drug-eluting stents: A single center retrospective experience

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ABSTRACT

Objectives: We sought to evaluate the efficacy and safety of unrestricted implantation of everolimus eluting stent Xience V (EES-XV) in a cohort of real-world patients with unprotected left main coronary disease (ULMCD). Background: The second-generation EES-XV stent is currently one of the most commonly used drug-eluting stents in clinical practice. It has been shown to be superior to paclitaxel-eluting stents, but its relative merits on unprotected left main coronary disease have been less extensively assessed. Methods: Between 2007 and 2010, in this single-center registry, we evaluated the clinical outcomes of 98 patients with ULMCD who underwent percutaneous coronary intervention (PCI) with EES-XV. Results: There were no in-hospital deaths. At 25.63 ± 14.41 months of follow-up, 17 patients (17.3%) experienced major adverse coronary event (MACE), death from cardiovascular disease (n = 6; 6.1%) and target lesion revascularization (TLR; n = 7; 7.1%). The predictors of death from cardiovascular disease were: previous PCI and left ventricular dysfunction. The only predictor of TLR was the placement of 2 stents in the left main coronary artery. Conclusions: In this single-center real-world registry, we found that elective ULMCD stenting with EES-XV provided good short-, medium- and long-term outcomes, with an estimated cumulative need for TLR of 7.1%, a cardiac mortality rate of 6.1%, and a MACE rate of 17.3% at 2 years.

Keywords: Percutaneous Coronary Interventions; "Off Label" Lesions; Prognosis

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1. INTRODUCTION

Traditionally, coronary artery bypass graft (CABG) has been considered the gold standard treatment for obstructive disease of the LMCA [1]. However, recent studies have demonstrated an acceptable safety profile for percutaneous coronary interventions (PCI) with stenting for unprotected left main coronary artery (ULMCA) lesions. The PCI procedure is becoming more commonly used despite the available data [2-7] being limited to first generation drug-eluting stents (DES) such as sirolimus-eluting stents (SES) and paclitaxel eluting stents (PES). The XIENCE V everolimus eluting stent (EES-XV) was designed to release everolimus from a thin (7.8 mm), non-adhesive, durable, biocompatible, fluorinated, copolymer coated onto a low profile, flexible, cobalt-chromium, stent with 0.003200 mm strut thickness. A number of randomized controlled trials have demonstrated its superiority over the first-generation PES [8-11].

Recently, a meta-analysis of randomized clinical trials comparing outcomes of EES-XV vs. SES did not show any statistically significant differences between the stents [12]. Although there are data from off-label studies on the safety and efficacy of EES-XV stent use, to date there have not been any publications that have specifically evaluated the medium-to-long-term use of EES-XV in ULMCA lesions [13].

The aim of the present, single-centered, "real-world" registry was to examine prospectively the medium-to-long-term outcome of patients who underwent elective PCI for ULMCA disease using only 1 type of DES; the EES-XV.

2. METHODS

2.1. Patients

We retrospectively assessed patients with ULMCA le-

sions treated with EES-XV between March 2007 and July 2010 in our Cardiology Unit of the *Complejo Hospitalario de Jaén* (Spain). Presence of other types of ULMCA stents, shock at presentation or previous coronary artery bypass graft (CABG) with at least one permeable bridge in the left coronary artery (protected left main) were considered as the exclusion criterion. All procedures were approved by the Institution Review Board (IRB) of the Hospital and all patients provided written consent to participation in the study. Data for inclusion into the registry were coded so as to maintain anonymity. During the period of the study, 180 patients were diagnosed with stenosis involving the LMCA; 33 patients were referred for revascularization surgery, 10 patients were excluded because of cardiogenic shock at the time of the angiography, 4 patients had CABG (protected LM) and 35 patients had a different stent to that of the EES-XV implanted in the LMCA. In these patients there had not been an EES-XV implant in the LMCA in the majority of the cases due to stent measurement ≥4.5 mm diameter. The remaining 98 patients are the subject of the present study.

Indications for angiography ranged from acute coronary syndrome (ACS), defined as those patients being evaluated for ST-segment elevated myocardial infarction (STEMI), non-ST-segment elevated MI (NSTEMI), or unstable angina (UA), and those with stable angina with or without high risk ischemia.

2.2. Procedure

Cases were collected from several operators using the femoral artery approach. Interventional techniques and medications were at the discretion of the individual attending cardiologists but under current clinical guidelines including the use of intra-aortic balloon pumps (IABPs), intra-vascular ultrasound (IVUS) and glycolprotein IIb/IIIa inhibitors.

ULMCA lesions were defined as: ostial, midshaft or distal/bifurcation. The presence of multi-vessel disease vs. the isolated ULM disease was also recorded.

Angiographic success was defined as stenosis <30% and thrombolysis in myocardial infarction (TIMI) 3 flow in the stented lesion, and <50% in the unstented SB. Procedural success was defined as the absence of procedural complications, or major adverse cardiac events (MACE) within the setting of angiographic success.

Cardiac enzymes serial measurements and electrocardiograms (ECGs) were performed post-procedure.

Following the index intervention, patients were maintained on dual anti-platelet therapy with acetylsalicylic acid (ASA; 100 mg daily) indefinitely and clopidogrel (75 mg/d) for a minimum of 12 months.

2.3. Study Definitions

The primary endpoint was MACE, as defined by death, non-fatal acute myocardial infarction (AMI), and target lesion revascularization (TLR) over the period of follow-up.

Death was classified as cardiac or non-cardiac. Deaths due to undetermined causes were classified as cardiac. A diagnosis of AMI was based on total creatine kinase (CK) elevated by >3 times the upper limit of normal (ULN) with a concomitant elevation of troponin I. TLR was defined as any repeat percutaneous intervention or surgical bypass of the target lesion performed for >50% restenosis of the treated segment from 5 mm proximal to the stent and 5 mm distal to the stent in the LMCA.

Restenosis was defined as >50% angiographic narrowing of any previously successfully treated lesion.

Stent thrombosis (ST) was defined, according to the Academic Research Consortium, as definite, probable, or possible [14].

Target vessel revascularization (TVR) was defined as any new revascularizations of the patient in follow-up due to a restenosis or progressive disease in the rest of the coronary arteries (excluding the LMCA).

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) was used to stratify the risk of death at 30 days. Patients were stratified as "high risk" in the presence of a logistic EuroSCORE of 6.

For the present study, the Syntax Score (SS) for each angiogram was assessed by one experienced intervenetional cardiologist. Each lesion with >50% diameter stenosis in vessels >1.5 mm in diameter was scored using the SS algorithm, fully described elsewhere [15].

2.4. Patient Follow-Up Procedures

All patients were followed-up by outpatient clinical visit or telephone call at 1 month, 6 months, 1 year, and currently up to Aug. 2011. When the patient was lost to follow-up, the family, physician, or cardiologist was contacted. In case of failure to contact any of the persons responsible, information regarding death was obtained from the population registry. Follow-up angiography was performed only in case of clinical indications, as judged by the attending physician; essentially following signs or symptoms suggestive of angina or ischemia.

2.5. Statistical Analyses

Continuous variables are presented as mean ± standard deviation (SD) and the categorical variables as percentage frequencies. The continuous variables were compared using the Student t-test. Categorical variables were compared with the chi-square or the Fisher exact test. Univariate and multivariate logistic regression analyses

were used to identify independent predictors of MACE. For each of the events-of-interest considered, observation time began on the date of stent implantation and ended either on the date of MACE occurrence or on the last day of patient contact, whichever occurred first. Cox proportional hazard models were fitted for comparisons of selected outcomes of patient or procedural characteristics. All analyses were performed using the SPSS software package (version 15.0). A value of $p < 0.05$ was considered statistically significant.

3. RESULTS

3.1. Baseline Clinical Data

Baseline clinical characteristics are presented in **Table 1**. Included in the study were 98 patients undergoing elective PCI for ULMCA disease using the EES-XV at our Center during the study period. Patients in this cohort had cardiovascular disease risk factors such as diabetes mellitus (40.8% of cases), hypertension (65.3%), hypercholesterolemia (54.1%), and smoking habit (46.9%); 71.4% underwent PCI for NSTEACS and 40.8% presented high-risk (additive EuroSCORE > 6).

Table 1. Baseline demographic and clinical characteristics of the 98 patients entered in the registry.

Characteristic		N
Age; mean ± SD		66.53 ± 10.06
Males; n (%)		75 (76.5)
Risk factors; n (%)		
	Diabetes	40 (40.8)
	Hypertension	64 (65.3)
	Hypercholesterolemia	53 (54.1)
	Smoking habit	46 (46.9)
Previous AMI; n (%)		23 (23.5)
Previous PCI; n (%)		20 (20.4)
Clinical indication for intervention; n (%)		
	Stable angina	22 (22.4)
	UA/NSTEMI	70 (71.4)
	Post-STEMI	6 (6.1)
LVEF; % mean ± SD		62.56 ± 13.09
Syntax score (SS)		
	mean ± SD	25.61 ± 10.19
	SS > 32, n (%)	23 (23.5)
High-risk (additive EuroSCORE > 6); n (%)		40 (40.8)

AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; LVEF = left ventricular ejection fraction; STEMI = ST elevated myocardial infarction; UA/NSTEMI = unstable angina/non-ST elevated myocardial infarction.

3.2. Angiographic and Procedural Data

The angiographic and procedural data are presented in **Table 2**. There were 77 patients (78.6%) who had distal LMCA bifurcation disease. In most patients (72.5%) a provisional T-stenting technique had been used. There were 9 patients (9.2%) treated with 2 stents technique: 8 patients crush/minicrush technique and 1 patient "V" stenting technique. The mean Syntax Score (SS) was 25.61 ± 10.19. There were 52 patients (53%) who had multi-vessel disease. The mean length of stent used was 72.35 ± 44.61 mm. Quantitative angiographic data of treated lesions are presented in **Table 3**.

Table 2. Baseline lesion and procedural characteristics in the 98 patients.

Characteristic		N
Vessels treated per patient; n (%)		
	LM only	16 (16.3)
	LM + 1 vessel	30 (30.6)
	LM + 2 vessels	36 (36.7)
	LM + 3 vessels	16 (16.3)
Overall stent length; mm, mean ± SD		72.35 ± 44.61
Distal LM artery bifurcation; n (%)*		77 (78.6)
	Type 1-0-0	6 (6.1)
	Type 1-1-0	24 (24.5)
	Type 1-1-1	21 (21.4)
	Type 0-1-0	14 (14.3)
	Type 0-0-1	2 (2.0)
	Type 0-1-1	6 (6,1)
	Type 1-0-1	4 (4.1)
Bifurcation treatment technique; n (%)		
	Provisional T (1 stent)	66 (67.4)
	Provisional T (2 stents)	5 (5.1)
	Crush/minicrush	8 (8.2)
	"V" stenting	1 (1)
Final kissing balloon, n (%)		50 (51)
Intravascular ultrasound used, n (%)		65 (66.3)
Intra-aortic balloon pump; n (%)		2 (2)
Glycoprotein IIb/IIIa inhibitor; n (%)		41 (41.8)

*The coronary bifurcation lesion classification proposed by Medina; LM = left main.

Table 3. Quantitative angiographic analysis of treated lesions (n = 98).

Variable	Before procedure	After procedure
LM reference diameter, mm ± SD	3.42 ± 0.52	3.74 ± 0.53
LM minimum lumen diameter, mm ± SD	1.12 ± 0.42	3.19 ± 0.52
LM percent stenosis, % ± SD	68 ± 12.17	14.09 ± 6.09
SB reference diameter, mm ± SD	2.84 ± 0.86	3.01 ± 0.74
SB minimum lumen diameter, mm ± SD	1.30 ± 1.06	2.34 ± 0.77
SB percent stenosis, % ± SD	42.79 ± 36.79	24.74 ± 22.63
Angiographic success, % of patients		100

LM = left main; SB = side branch.

3.3. In-Hospital Outcomes

Angiographic success was achieved in 100% of patients. There were no deaths nor need for emergency revascularization during hospitalization. There were 15 patients (15.3%) who had elevated levels of markers of myocardial damage after PCI, of whom only 3 had a significant elevation of tnI (>20 ng/dL). These patients had multivessel disease which required multi-stenting.

3.4. Long-Term Outcomes

At 25.63 ± 14.41 months of follow-up (range: 1 - 53 months), 17 patients (17.3%) experienced MACE. Data are summarized in **Table 4**. Twelve patients died during follow-up; 6 from non-cardiac causes (4 from cancer, 1 pulmonary thromboembolism and 1 cerebrovascular accident); 6 patients died from cardiovascular causes (see **Table 5**). There were 7 patients (7.1%) who underwent revascularization of the LMCA due to clinical recurrence and angiographic restenosis of the stent: 2 restenoses of the ostia of the TCI (proximal border of the stent), one focal restenosis of the circumflex artery origin, one focal restenosis of the body of the stent, and 3 diffuse restenoses of the stents. Five patients were treated with a repeat PCI and 2 cases were referred for CABG.

3.5. Predictors of MACE

The following variables were entered into a stepwise multivariable Cox proportional hazard model for long-term survival and event-free survival: age, gender, left ventricular ejection fraction (LVEF), ventricular dysfunction (EF < 40%), prior MI, prior PCI, hypertension, hypercholesterolemia, diabetes, smoking, use of glycolprotein IIb/IIIa antagonists, Euro-SCORE (Euro-SCORE ≥ 6), SYNTAX score (SYNTAX score ≥ 33), distal bifurcation lesion, 2 implants in the LMCA, dimensions of the stents implanted, IVUS, kissing balloon technique. The predictors of cardiovascular death in follow-up were: previous revascularization and left ventricular dysfunction. The only predictor of AMI in follow-up was having had a previous PCI (in any vessel) and the predictor of TLR was the implantation of 2 stents in LMCA (**Table 6**).

Table 4. Long-term outcomes.

Outcome	Number of patients (%)
MACE	17 (17.3)
Total mortality	12 (12.2)
Cardiac death	6 (6.1)
Myocardial infarction	4 (4.1)
Target lesion revascularization	7 (7.1)
Target vessel revascularization	10 (10.2)

4. DISCUSSION

The major findings of this single-center, observational study are: 1) PCI with EES-XV in ULMCA is feasible and has high clinical and procedural success rates; 2) A low rate of MACE during follow-up (25.63 ± 14.41 months); 3) The independent predictors of cardiovascular death were previous PCI and left ventricular dysfunction.

Literature data on long-term outcomes post-PCI in the LMCA population are scarce. Park *et al*. [16] reported 3-year safety composite rates (death, Q-wave MI, or stroke) of 9.7%, with TVR rate of 12.6%. Vaquerizo *et al*. [17] demonstrated, in 291 patients from a multi-centered registry, the device-oriented composite end point at 2 years of 12.6% post-UCLMA stenting with paclitaxel-eluting stents. In the DELFT (Drug-Eluting Stent for Left Main) registry, Meliga *et al*. [18] reported 3-year MACE rate (a composite of cardiac mortality, MI, and TVR) of 26.5%, cardiac mortality of 9.2%, and TLR of 14.2%. Wood *et al*. [19], in a long-term follow-up of 100 patients with high surgical risk post-PCI, observed all-cause mortality at 28 months of 21%, with event-free survival around 65% at 27 months

Toyofuku *et al*. [20] published their 3-year follow-up of 582 patients treated with Cypher stent implant (SES) en ULMCA patients in the j-Cypher registry. In a patient population with similar characteristics to our study, the event rates observed were very similar to ours (14.6% all-cause deaths, 7.3% cardiac deaths, 3.7% myocardial infarction, 14.8% TLR).

In a single-centered registry of patients with lesions treated with PCI with SES, XiaFan Wu *et al*. [21] reported an incidence of cardiac death of 4% and TLR of 11.9% at 3 years of follow-up. Impaired LVEF (<40%)

Table 5. Characteristics of the patients in whom the outcome was cardiac death in the course of follow-up.

Patient	Age	Gender	EF	Type of lesion	Technique	IVUS	Months post-PCI	Comments
1	72	F	70	Distal	"V" stenting	No	37	Sudden death
2	75	M	55	Distal	"Crush" stenting	Yes	11	Restenosis of both ostia, death during re-PCI
3	74	M	55	Distal	PTS (1 stent)	Yes	4	Restenosis with thrombus → CABG → death post-operative
4	71	M	60	Midshaft	Direct stenting	Yes	19	Restenosis of a stent inserted in the anterior descending artery → cardiogenic shock
5	77	M	19	Distal	PTS (1 stent)	No	3	Cardiac death
6	61	F	34	Distal	PTS (1 stent)	Yes	8	Sudden death

Gender (M = male, F = female); EF = ejection fraction; IVUS = intra-vascular ultra-sound; PTS = provisional "T" stenting; CABG = coronary artery bypass graft.

Table 6. Multivariate analyses.

Dependent variable	Independent variable	p	Odds ratio
Cardiovascular MACE			
	Diabetes	0.026	5.31 (1.22 - 23.01)
	Two stents	0.019	6.74 (1.36 - 33.30)
Cardiovascular death			
	Previous PCI	0.016	16.41 (1.699 - 158.55)
	LVD	0.022	20.21 (1.55 - 263.22)
AMI			
	Previous PCI	0.028	13.588 (1.33 - 138.72)
TLR			
	Two stents	0.041	5.45 (1.075 - 27.67)

PCI = percutaneous coronary intervention; LVD = left ventricular dysfunction; TLR: target lesion revascularization.

and high surgical risk (Euroscore > 6) were the independent predictors of MACE.

Data from ISAR-LEFT-MAIN (Intracoronary Stenting and Angiographics Results: Drug-Eluting Sents for Unprotected Coronary Left Main Lesions) trial [4] and sub-analysis of the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneus Coronary Angioplasty Versus Surgical Revascularization) registry [22] showed that SES and PES were equally effective and safe in patients undergoing ULMCA stenting.

To date, there have not been any studies published that evaluated the use of EES-XV in patients with ULMCA. Our study results demonstrated that treatment with EES-XV offers excellent medium-term results, comparable with respect to efficacy and safety to the published findings in 1st generation pharmaco-active stents. Despite excluding cardiogenic shock, this cohort of patients can be considered at high risk of ischemic events in follow-up. The patients are, in greater part, those with distal LMCA lesions (78.6%), high percentage with diabetes (40.8%), with multiple lesions apart from LMCA (72.35 ± 44.61 mm total stent length) and 40.8% with high-risk (additive EuroSCORE > 6). Taking into account these characteristics we believe that the use of the EES-XV in ULMCA patients results in a low rate of MACE, at least in the medium term.

Latib *et al*. [23] demonstrated that the use of EES-XV in off-label lesions offered excellent results. Real-world registry of patients of high angiographic complexity entered in clinical trials show a cumulative MACE of 10.6% and TLR of 7.9%.

In our study the only predictors of cardiovascular death were left ventricular dysfunction (LVD) and previous percutaneous revascularization. LVD is a known predictor of cardiovascular mortality. Previous percutaneous revascularization can highlight a group of patients with long-term coronary disease, or even identify a group of patients in whom PCI with stent implant would not be a good option. In this sub-group of patients, perhaps surgical revascularization of the coronaries could be the preferred therapeutic option.

Another aspect of note in our study is that the only predictor of TLR in follow-up is the insertion of 2 stents in the LMCA lesions involving bifurcation. This finding can have two interpretations: 1) A strategy of 2 stents in bifurcation lesions of ULMCA carries a higher rate of TLR in follow-up; 2) Two stents are used only for bifurcation lesions of high angiographic complexity (very calcified lesions, very severe lesion of both ostia) which carry high risk of restenosis and TLR in follow-up. The only way to clarify this question would be to conduct a randomized clinical trial with 2 strategies (1 or 2 stents) in true bifurcation lesions (X, 1, 1) of ULMCA.

EES has been proposed as having a theoretical advantage over first-generation DES in relation to safety *i.e*. the thin strut design might result in more rapid stent endothelialization [24,25]. Our study was unable to demonstrate this contention, but there was a low incidence of thrombosis in whatever presentation (definite, probable, possible).

4.1. Limitations

The present study was non-randomized, with a relatively small sample size, and a relatively short follow-up. Comparison with surgical revascularization was not performed for this patient sub-group. Follow-up angiography was not performed in all patients. Hence, the true restenosis rate cannot be known.

4.2. Conclusion

In this single-center real-world registry, we found that elective ULMCA stenting with EES-XV, provided good short-, medium- and long-term results; 7.1% cumulative need for TLR, 6.1% cardiac mortality rate, and 17.3% MACE rate at 2 years. Data from randomized trials should help to select the stent-of-choice for use in ULMCA and the strategy for use in true bifurcations.

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