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Immediate Results and Long-Term Clinical Outcome of Patients With Unprotected Distal Left Main Restenosis

The CORPAL Registry (Córdoba and Las Palmas)

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Objectives The goal of this study was to assess the immediate and long-term outcomes in patients undergoing percutaneous coronary intervention (PCI) for in-stent restenosis (ISR) in an unprotected distal left main coronary artery (UDLM).

Background PCI for UDLM-ISR can be complex. Limited information is available on procedural and clinical outcomes.

Methods Between May 2002 and February 2011, UDLM-ISR after drug-eluting stent implantation was observed in 79 of 1,102 patients (7%). Seventy-five were treated by repeat PCI using a simple approach (balloon/in-stent implantation) or a complex strategy (additional stent/double-stenting technique). A diagnosis of mild or severe restenosis was considered depending on the number of bifurcation segments affected (1 vs. >1). Major adverse cardiac events (MACE) were defined as cardiac death, target lesion revascularization, and myocardial infarction.

Results ISR treatment was performed using a simple approach in 44 (58%) patients, and using a complex strategy in 31 (42%). After 46 ± 26 months, the MACE rate was 22%. Patients treated with a simple approach had a lower incidence of MACE at follow-up compared with patients treated with a complex strategy, regardless of the restenosis extent (mild restenosis: 93% vs. 67%, $p < 0.05$; severe: 70% vs. 23%, $p < 0.05$). On Cox regression analysis, diabetes was the only predictor of MACE (hazard ratio [HR]: 4.94; 95% confidence interval [CI]: 1.03 to 23.70; $p < 0.05$), whereas a simple strategy for ISR treatment was associated with lower risk (HR: 0.25; 95% CI: 0.08 to 0.79; $p = 0.02$).

Conclusions PCI for UDLM-ISR is safe and feasible, with a high rate of procedural success and an acceptable long-term MACE rate. A simple strategy, when applicable, appears to be a good treatment option, associated with a lower event rate at follow-up. (J Am Coll Cardiol Intv 2014;7:212–21)

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The use of drug-eluting stents (DES) has become widespread for the percutaneous coronary intervention (PCI) of an unprotected distal left main coronary artery (UDLM), and it may be an alternative to coronary artery bypass graft surgery (1 10). However, the risk of restenosis in this subset of lesions could pose a limitation. Unprotected left main PCI and the location of the bifurcation lesion have been reported as predictors of restenosis after DES implantation, with an increased incidence when both conditions are present (11 16).

Repeat PCI in UDLM can be more complex. Furthermore, limited information is available regarding the optimal revascularization strategy and clinical outcomes in this particular type of patient.

The present study aimed to analyze the management, immediate angiographic results, and long-term clinical outcomes, as well as to evaluate the outcomes of the different treatment strategies, in patients undergoing PCI for in-stent restenosis (ISR) in cases with a stented UDLM.

Methods

Patients. Between May 2002 and February 2011, 1,102 consecutive patients with all types of Medina bifurcation lesions (17) involving the UDLM were treated with DES in 2 high-volume centers. Figure 1 shows the flow chart of the study. Patients were angiographically re-evaluated when symptoms or signs of ischemia occurred. At follow-up, 79 patients presented with significant ISR (>50% diameter stenosis) affecting the left main coronary artery (LM), left circumflex coronary artery (LCX), or left anterior descending coronary artery (LAD). A retrospective analysis was performed in the subgroup of 75 patients with UDLM-ISR treated with repeat PCI. At least 2 years of clinical follow-up beyond the documentation of UDLM-ISR treatment was required for inclusion.

Patients with protected distal LM disease (defined as the presence of at least 1 patent graft to the left coronary artery), patients treated with a precise adjustment of the stent in the LCX or LAD ostium, and patients with a contraindication to 1 year of dual antiplatelet therapy were excluded from this study.

Written informed consent was obtained from all patients.

First procedure. The baseline bifurcation anatomy was assessed according to the Medina classification (17). The main vessel was always considered the LM into the LAD, and the side branch was the LCX artery. The technique for stent implantation was provisional stenting that has been described previously (18). Pre-dilation of the side branch was at the discretion of the operator. After LM stent implantation, a kissing balloon or single side-branch post-dilation was performed if stenosis ≥50% of the LCX ostium remained or a coronary TIMI (Thrombolysis In Myocardial Infarction) flow grade <3 occurred. Stenting of the side branch was only considered in cases with suboptimal angiographic results after side-branch ballooning. The use of a kissing balloon was mandatory when a complex technique was performed. Angiographic re-evaluation was strongly recommended when symptoms or silent ischemia was observed.

Index procedure. According to the extension of the restenosis, 2 types of restenosis complexity were defined: mild restenosis affecting only 1 bifurcation segment, and severe restenosis if more than 1 bifurcation segment was affected, regardless of the degree of lesion severity. The angiographic patterns of restenosis were classified as focal (Mehran ISR pattern I), diffuse (Mehran patterns II and III), or occlusion (Mehran pattern IV) (19). Multifocal restenosis was considered as diffuse.

The type of treatment of the UDLM-ISR and the technique used were at the discretion of the operator. Four modalities for ISR treatment were used: 1) plain old balloon angioplasty (POBA); 2) in-stent implantation; 3) 1 additional stent implantation in a segment that was not previously stented (complex approach performed in 2 stages); and 4) a 2-stenting technique. The first 2 were considered simple approaches, and the other 2 were considered complex strategies.

In cases requiring a new stent, a different type of DES from the 1 implanted in the first procedure was usually chosen (20). The operators were encouraged to perform an intravascular ultrasound (IVUS) study to assess the mechanism of ISR and the result after PCI.

Abbreviations and Acronyms

CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
IQR = interquartile range
ISR = in-stent restenosis
IVUS = intravascular ultrasound
LAD = left anterior descending coronary artery
LCX = left circumflex coronary artery
LM = left main coronary artery
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
POBA = plain old balloon angioplasty
TLR = target lesion revascularization
UDLM = unprotected distal left main coronary artery

At the time of PCI, all patients were on double antiplatelet therapy, which was continued in all patients for at least 12 months. During the procedure, patients received unfractionated heparin. The use of glycoprotein IIb/IIIa inhibitors, as well as the use of intra-aortic balloon pump, was left to the operator's discretion.

Serial determinations of the troponin I and creatine kinase levels were performed before and every 6 h after the procedure for the first 24 h.

Study objectives. The primary study objective was to analyze the occurrence of major adverse cardiac events (MACE) in patients with UDLM-ISR treated by PCI and for at least

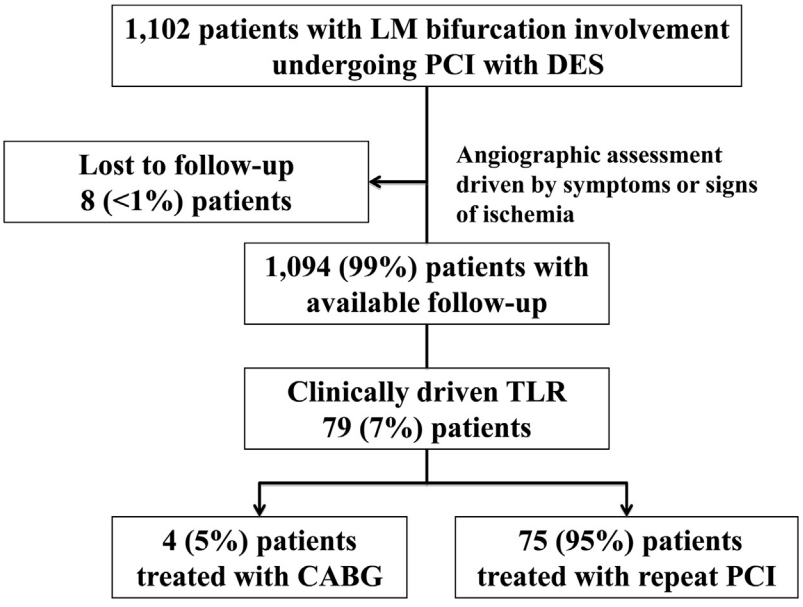

Figure 1. Study Flow Chart Overall Study Profile

CABG = coronary artery bypass graft; DES = drug eluting stents; LM = left main coronary artery; PCI = percutaneous coronary intervention; TLR = target lesion revascularization.

2 years of clinical follow-up. MACE were defined as cardiac death, myocardial infarction (MI), and target lesion revascularization (TLR). MI and stent thrombosis were defined according to the Academic Research Consortium criteria (21).

After the treatment of UDLM-ISR, the patients were monitored closely by scheduled visits and phone calls (at 1 month, every 6 months for the first 2 years, and annually thereafter). A new cardiac catheterization was recommended in the presence of clinical recurrence.

Statistical analysis. Continuous variables are expressed as mean ± SD or median (interquartile range [IQR]) and were compared using the Student *t* test or the Mann-Whitney *U* test. Categorical variables are presented as counts and percentages and were compared using the chi-square test or the Fisher exact test, as appropriate. TLR- and MACE-free survival were analyzed by the Kaplan-Meier method, and differences between groups were analyzed with the log-rank test. Independent predictors of long-term follow-up MACE were analyzed using Cox proportional hazards regression models. Variables with a p value ≤0.1 in univariate analyses were introduced into a multivariate Cox regression model. A value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed with SPSS version 20.0.0 software (IBM, Armonk, New York).

Results

Baseline clinical, angiographic, and procedural data at the first procedure. From a total of 1,102 patients with UDLM disease treated percutaneously, 606 had an angiogram at follow-up. Clinically-driven TLR occurred in 79 (7%) patients, and 75 of these were treated with repeat PCI. The remaining 4 patients underwent surgery (Fig. 1).

All patients were treated with DES. Sirolimus-eluting stents were the most often implanted (41%). A single-stent strategy across the LCX was the technique used in the majority of patients (87%), whereas a complex technique was required in 10 patients (13%). Approximately 68% of the patients had additional vessel involvement beyond UDLM disease that required PCI.

Glycoprotein IIb/IIIa was used in 11% of patients.

Clinical, angiographic, and procedural data of the patients with ISR. The clinical, angiographic, and procedural characteristics of the 75 patients with UDLM-ISR treated with PCI are summarized in Table 1. The mean age was 65 ± 11 years. Most patients were male (n = 63, 84%), and 49% had diabetes.

The mean time from first treatment to the diagnosis of ISR was 14 ± 16 months (median 9 months, IQR: 6 to 16 months). In more than 25% of cases, restenosis occurred in the first 7 months, whereas in nearly 70% of cases, it occurred in the first year after UDLM treatment.

Table 1. Baseline Clinical, Angiographic, and Procedural Characteristics of Patients With ISR

	First Procedure (n 79)*	Index Procedure (n 75)†
Clinical		
Age, yrs	64 ± 11	65 ± 11
Male	66 (83)	63 (84)
Currently smoking	15 (19)	10 (13)
Hypercholesterolemia	35 (44)	33 (44)
Hypertension	37 (47)	34 (45)
Diabetes	40 (51)	37 (49)
Clinical presentation		
Stable angina	11 (14)	17 (23)
Unstable angina	49 (62)	49 (65)
Acute myocardial infarction	15 (19)	4 (5)
Silent myocardial ischemia	4 (5)	5 (7)
Angiographic		
LV ejection fraction, %	54 ± 14	51 ± 12
Medina classification		
1,1,1	42 (53)	10 (13)
1,1,0	19 (24)	4 (5)
1,0,1	11 (14)	11 (15)
0,1,1	3 (4)	4 (5)
1,0,0	0	13 (18)
0,1,0	3 (4)	10 (13)
0,0,1	1 (1)	23 (31)
Main vessel reference, mm	3.7 ± 0.3	
Side branch reference, mm	2.8 ± 0.3	
Minimal lumen diameter, mm‡	0.71 ± 0.3	0.71 ± 0.4
Procedural		
Main vessel stent diameter	3.5 ± 0.2	3.4 ± 0.4
Maximal pressure, atm	16 ± 2	18 ± 3
Bifurcation treatment		
Simple	69 (87)	44 (58)
Complex	10 (13)	31 (42)
Type of stent		
Sirolimus	32 (41)	18 (24)
Paclitaxel	26 (33)	25 (33)
Everolimus	20 (25)	20 (27)
Zotarolimus	1 (1)	12 (16)
Lesions treated at remote sites	54 (68)	28 (37)
IVUS	57 (72)	59 (79)
IABP	4 (5)	7 (9)

Values are mean ± SD or n (%). *Patients who presented with restenosis at follow-up. †Patients with restenosis treated percutaneously. ‡At the worst point of the 3 segments.
IABP intra-aortic balloon pump; ISR in-stent restenosis; IVUS intravascular ultrasound; LV left ventricular.

Restenosis was located in the main vessel (LM-LAD) in 25 patients (33%). The isolated ostial LCX was affected in 24 (32%), and restenosis involved both vessels in the remaining 26 patients (35%). The angiographic pattern of restenosis was focal in 35 patients (47%), diffuse in 38 (51%), and total occlusion of the side branch in 2 patients (2%).

An IVUS study was conducted in 59 (79%) patients. In 8 (14%) of them, stent underexpansion was the main mechanism of restenosis, whereas drug failure was identified in 51 (83%) patients.

A simple approach for ISR treatment was used in most of the patients (n = 44, 58%): POBA was performed in 13 (17%), and in-stent implantation in 31 (41%) patients. POBA was the definitive treatment in 5 (38%) patients with focal restenosis of the circumflex coronary artery and in 8 (62%) with stent underexpansion by IVUS. Conversely, a complex strategy was used in the remaining 31 (42%) patients: 1 additional stent implantation in 22 (30%), and a 2-stent implantation in 9 (12%). Figure 2 shows the location of restenosis according to the Medina classification and the treatment modality used in each case.

In-hospital and long-term clinical follow-up MACE. During the hospital stay, 2 patients suffered a non Q-wave MI, and 3 (4%) died: 2 of heart failure despite successful angiographic results, and another patient of cardiogenic shock after LM MI (1 probable stent thrombosis).

The long-term follow-up data were available in 100% of patients after an average of almost 4 years after ISR treatment. The overall MACE rate at the long-term follow-up (mean 46 ± 26 months, median 39 months, IQR: 24 to 64 months) was 22%. Six patients (8%) died from cardiac causes (3 from sudden death, 2 from heart failure, and 1 from inferior MI), and 3 (4%) had a nonfatal MI. Nine of 10 patients who required a new revascularization were treated again by PCI. We identified 3 cases of possible stent thrombosis. No cases of definite or probable stent thrombosis were found.

Figure 3 shows survival free from TLR and MACE according to the complexity of the UDLM-ISR. MACE-free survival was significantly higher in patients undergoing ISR affecting only 1 bifurcation segment compared with patients with more than 1 segment involved (84% vs. 47%; $p < 0.05$).

The influence of the modality of ISR treatment on the results at the long-term follow-up was also analyzed. No clinical or angiographic differences were found between patients treated with simple or complex strategies (Table 2). Patients treated with only POBA or with in-stent implantation, that is, with a simple approach, had a lower incidence of events at follow-up compared with patients undergoing a complex approach, including TLR (event-free survival 97% vs. 63%; $p < 0.05$) and MACE (85% vs. 53%; $p < 0.05$) (Fig. 4). To determine whether this finding was related to the complexity of the ISR, the patients were divided into 2 groups according to the type of ISR (as previously defined), and similar results were obtained. Figure 5 depicts the event-free survival in patients with ISR affecting only 1 bifurcation segment in relation to the type of the treatment used. The event incidence was clearly lower in patients treated with a simple strategy (TLR-free survival 96% vs. 67%, $p < 0.05$; MACE-free survival 93% vs. 67%, $p < 0.05$). The same results were found when analyzing the influence of the treatment in patients with ISR affecting more than 1

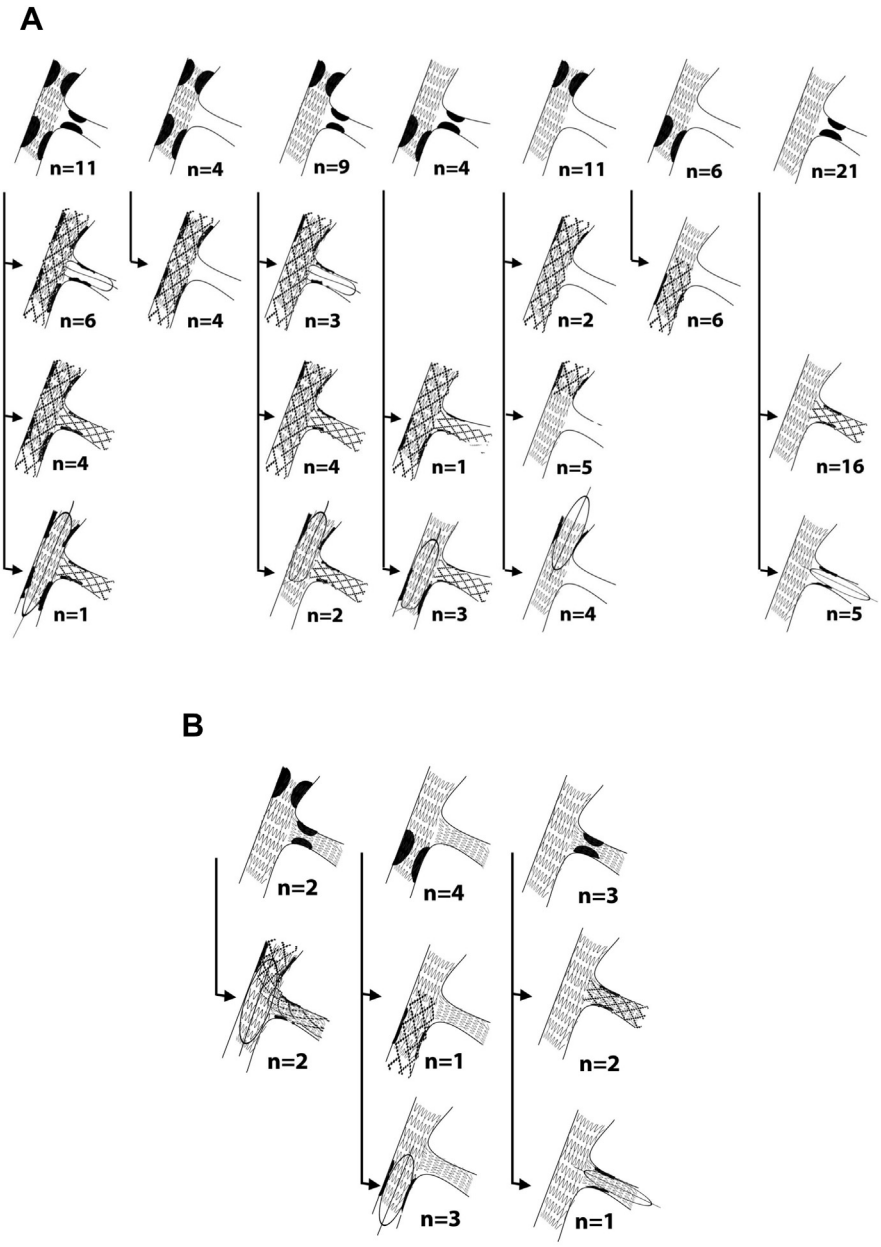

Figure 2. Location of Restenosis According to the Medina Classification and the Treatment Modality Used in Each Situation

(A) Patients treated at the first procedure by a simple approach. **(B)** Patients treated at the first procedure by a complex strategy.

bifurcation segment (TLR-free survival 100% vs. 50%, $p < 0.05$; MACE-free survival 70% vs. 23%, $p < 0.05$) (Fig. 6).

Predictors of MACE at follow-up. The multivariate predictors of overall MACE are shown in Table 3. Diabetes was the only independent predictor of MACE (hazard ratio [HR]: 4.94; 95% confidence interval [CI]: 1.03 to 23.70; $p < 0.05$), whereas ISR treatment using a simple strategy was independently associated with a lower risk of MACE at the long-term follow-up (HR: 0.25; 95% CI: 0.08 to 0.79; $p = 0.02$).

Discussion

Since the introduction of DES, a growing number of observational studies and randomized clinical trials have supported their safety and efficacy in the percutaneous

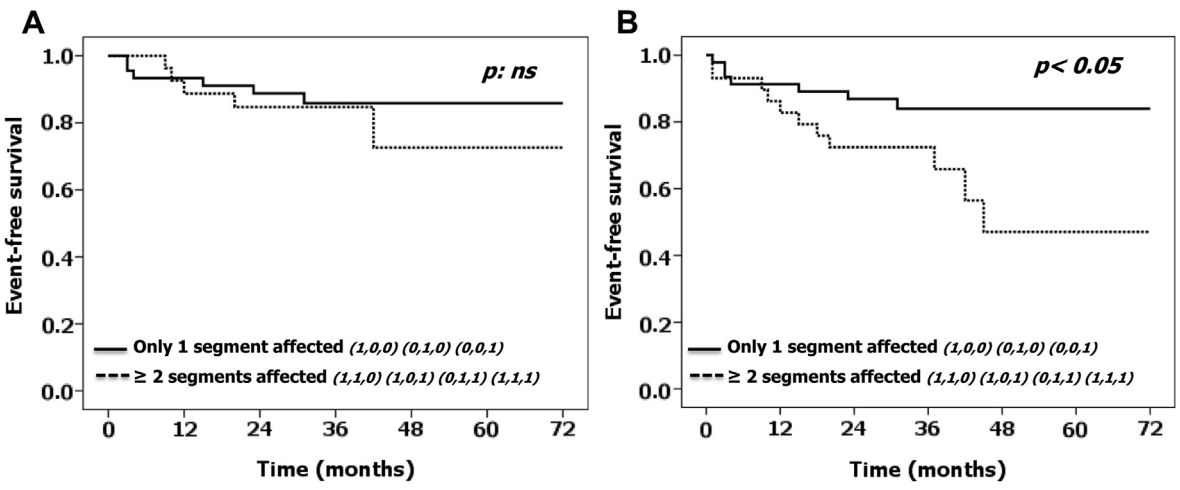

Figure 3. Event-Free Survival Following the Extension of Restenosis

The survival rates for 1 segment versus more than 1 segment affected are shown. **(A)** Target lesion revascularization. **(B)** Major adverse cardiac events.

Table 2. Baseline Clinical, Angiographic, and Procedural Characteristics of Patients According to the Treatment Strategy at the Index Procedure

	Simple Approach (n 44)	Complex Approach (n 31)	p Value
Clinical			
Age, yrs	66 ± 10	64 ± 12	NS
Male	34 (77)	29 (93)	0.06
Currently smoking	6 (14)	4 (13)	NS
Hypercholesterolemia	17 (39)	16 (52)	NS
Hypertension	18 (41)	16 (52)	NS
Diabetes	23 (52)	14 (45)	NS
Clinical presentation			
Stable angina	10 (23)	7 (22)	
Unstable angina	28 (64)	21 (68)	
Acute myocardial infarction	2 (4)	2 (6)	NS
Silent myocardial ischemia	4 (9)	1 (3)	
Angiographic			
LV ejection fraction, %	51 ± 13	52 ± 13	NS
Extension of restenosis			
1 bifurcation segment affected	29 (64)	16 (36)	NS
More than 1 segment affected	15 (50)	15 (50)	
Main vessel diameter, mm	3.6 ± 0.2	3.7 ± 0.4	NS
Side branch diameter, mm	2.7 ± 0.2	2.8 ± 0.3	NS
*Minimal lumen diameter, mm	0.65 ± 0.38	0.69 ± 0.31	NS
Procedural			
Main vessel stent diameter	3.4 ± 0.2	3.5 ± 0.3	NS
Maximal pressure, atm	17 ± 3	16 ± 2	NS
Type of stent previously used			
Sirolimus	18 (41)	13 (42)	
Paclitaxel	16 (36)	10 (32)	NS
Everolimus	10 (23)	8 (26)	
IVUS	35 (79)	24 (77)	NS

Values are mean ± SD or n (%). *At the worst point of the 3 segments.
NS non statistically significant; other abbreviations as in Table 1.

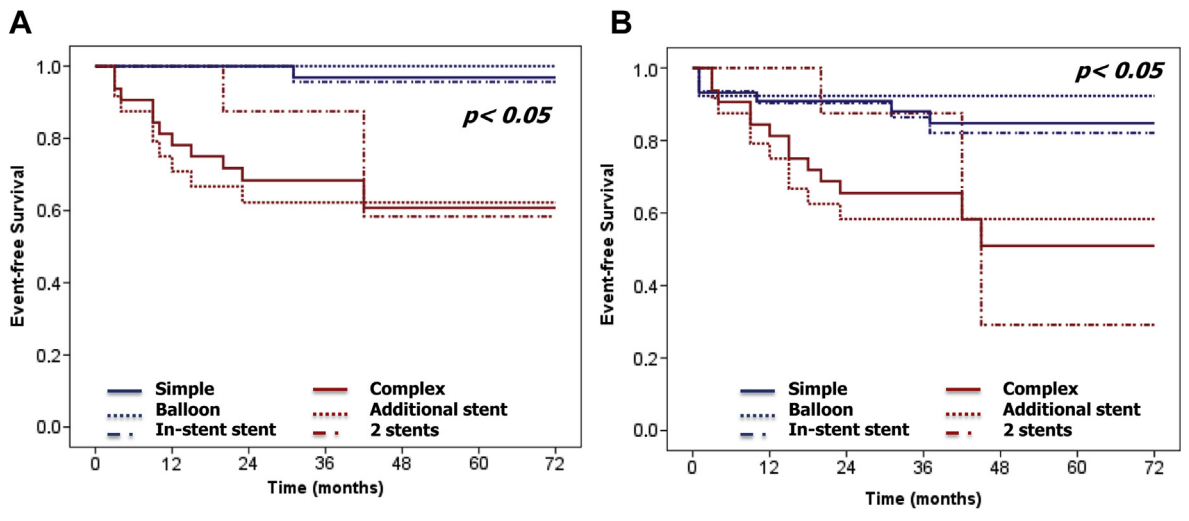

Figure 4. Event-Free Survival According to the Restenosis Treatment Modality in the Global Series

(A) Target lesion revascularization. **(B)** Major adverse cardiac events.

treatment of UDLM. Nevertheless, ISR in this subset of lesions represents an increasing problem in daily practice, and currently, there is insufficient information to determine the best treatment option (3,14,22–25).

In the present study, which includes 75 patients with UDLM-ISR from 1,102 patients with LM bifurcation treated percutaneously with DES, we found that repeat PCI was safe and feasible at 4-year clinical follow-up and may be a good option for treatment. In our registry, in which almost 90% of the patients were treated by provisional stenting at the first procedure, ISR treatment with the same strategy (simple approach) was associated with a lower occurrence of MACE at the long-term follow-up as compared with a complex treatment strategy.

The clinically-driven TLR rate in our series was overall low (7%). This fact could be explained by the high rate of patients treated by a simple approach at the first procedure and the absence of routine angiographic follow-up (13,26,27). It is known that 2-stent techniques are associated with less favorable outcomes when a bifurcation lesion

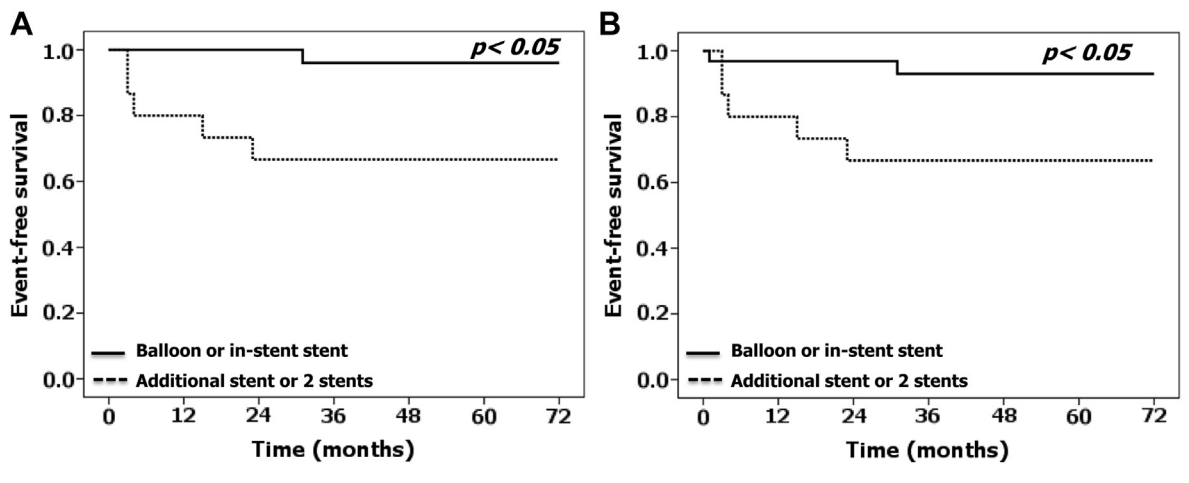

Figure 5. Event-Free Survival According to the Restenosis Treatment Modality in Patients With Restenosis Affecting Only 1 Bifurcation Segment

Medina classification of the bifurcation lesions (1, 0, 0), (0, 1, 0), and (0, 0, 1) are shown. **(A)** Target lesion revascularization. **(B)** Major adverse cardiac events.

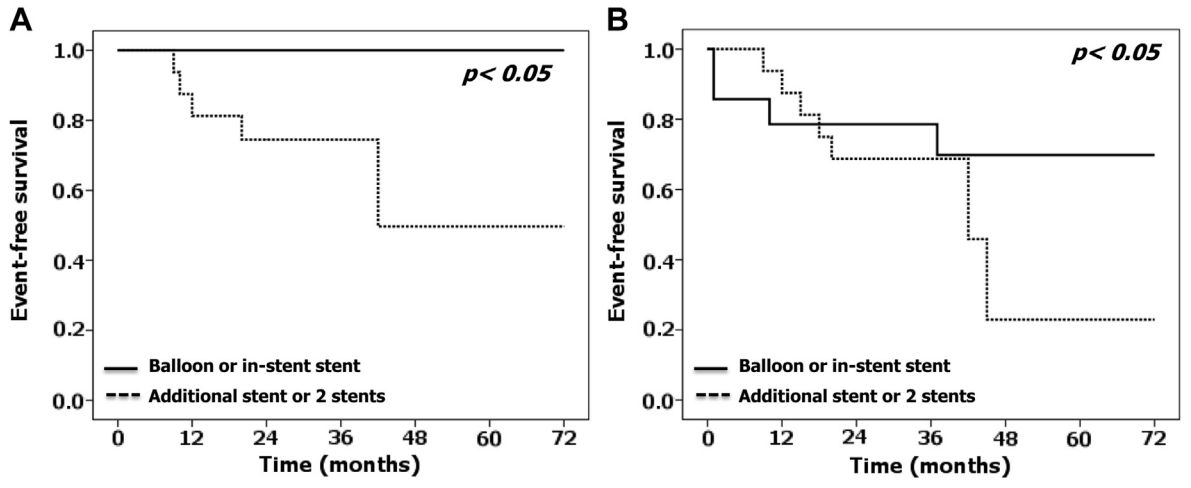

Figure 6. Event-Free Survival According to the Restenosis Treatment Modality in Patients With Restenosis Affecting More Than 1 Bifurcation Segment

Medina classification of the bifurcation lesions (1, 1, 0), (1, 0, 1), (0, 1, 1), and (1, 1, 1) are shown. **(A)** Target lesion revascularization. **(B)** Major adverse cardiac events.

is treated. Although some patients with UDLM and complex anatomy could require 2 stents, our large series of patients treated demonstrates that a simple approach would be suitable for the majority of these patients.

The incidence, management, predictors, and prognosis of patients with UDLM-ISR after DES implantation have been studied in previous studies. Sheiban et al. (28) and Lee et al. (29) studied approximately 70 patients with restenosis, analyzing 3 types of treatment: medical therapy, repeat PCI, and coronary artery bypass graft surgery. Although both studies provide valuable information, neither of them focused on UDLM with its special feature, characteristic regarding risk of restenosis and percutaneous treatment. In contrast to the present registry, their objective was to assess the 3 possible treatments stated in the preceding text. Consequently, details about different percutaneous strategies were not reported. The small size of the groups did not allow the detection of significant differences among them.

To the best of our knowledge, the only study published to date focusing on UDLM and on PCI for restenosis treatment is the MITO (Milan and New-Tokyo) registry (30). Of 474 patients with UDLM involvement, 92 developed restenosis, and 84 (19%) were treated with repeat PCI (43 with POBA and 41 with further DES implantation). They found that the majority of patients with focal LCX restenosis were asymptomatic, and the POBA strategy resulted in significantly more recurrence than the use of DES (HR: 4.14; 95% CI: 1.21 to 14.25; p = 0.02). These findings are contradictory to those reported by us, given that we observed that POBA provided excellent results at follow-up in cases of focal LCX restenosis and when stent underexpansion (by IVUS) was the main mechanism of restenosis. Differences in clinical and procedural characteristics between the study population in the 2 studies could explain the different results. In the MITO registry (30), the number of patients treated at the first procedure with a complex strategy was higher (58%) than in our series (13%), and this fact could have influenced the results observed with the following different strategies of percutaneous treatment. On the other hand, the use of POBA was high in this study (51% of the patients), and the criteria for choosing each treatment are not specified. Probably, POBA does not work properly in all

Table 3. Univariate and Multivariate Predictors of MACE at Follow-Up

	Univariable HR (95% CI)	p Value	Cox Regression Adjusted HR (95% CI)	p Value
Age ≥70 yrs	2.20 (0.89–5.49)	0.1		
EF <45%	3.63 (1.35–9.78)	0.01		
Diabetes mellitus	3.05 (1.00–9.28)	0.05	4.94 (1.03–23.70)	0.046
Restenosis extension: 1 bifurcation segment	0.31 (0.12–0.78)	0.014		
Treatment strategy: simple approach	0.30 (0.12–0.78)	0.013	0.25 (0.08–0.79)	0.02

CI confidence interval; EF ejection fraction; HR hazard ratio; MACE major adverse cardiac events.

of the mechanisms of restenosis and should be used only in particular cases.

Regarding the best alternative to treat this specific group of patients, we found that a simple approach (POBA and/or in-stent implantation) was correlated with a lower TLR and MACE as compared with a complex strategy. This finding has to be put in context of the treatment used at the first procedure and is concordant with previous studies in native bifurcation reporting the clinical advantages of provisional stenting compared with double-stenting techniques (31). Accordingly, Coroleu et al. (32), in a recently published study on percutaneous treatment for the in-stent restenosis of bifurcated lesions, have also demonstrated a lower incidence of MACE in patients treated with a provisional single DES implantation. Therefore, it appears that restenotic lesions in bifurcated locations should be approached as native bifurcation lesions when applicable, for which provisional stenting is considered the choice technique.

Study limitations. This was an observational, non-randomized study. The restenosis treatment modality was left to the operator's discretion, and therefore, no definitive conclusions on the best technique for the ISR treatment of the DLM can be drawn from our study. Nevertheless, the absence of significant differences between patients treated with simple and complex strategies, as well as the multivariate analyses, support the simple approach as the most suitable treatment option. The number of patients included was relatively small, but because of the low rate of restenosis, it was difficult to obtain a large sample size. Furthermore, the small event rate can reduce the ability to control potentially confounding variables. Finally, drug-eluting balloons were not available in our institutions at the time that the patients were treated. Although these balloons can play an important role in this subset of lesions, their use would have to be evaluated.

Conclusions

Our study shows that the incidence of clinically-driven TLR in an unselected population of patients with UDLM after DES implantation is low. Treatment with repeat PCI in this subset of lesions appears to be safe and effective, with a high rate of angiographic and procedural success and an acceptable long-term MACE rate. Our findings also suggest that a simple strategy in the ISR approach is correlated with lower TLR and consequently MACE as compared with a more complex approach. Further randomized studies will be necessary to confirm these results.

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