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Clinical Impact of Intravascular Ultrasound Guidance in Drug-Eluting Stent Implantation for Unprotected Left Main Coronary Disease

Pooled Analysis at the Patient-Level of 4 Registries

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Objectives This study sought to investigate the clinical impact of the use of intravascular ultrasound (IVUS) during revascularization of patients with left main coronary artery (LM) disease with drug-eluting stents (DES).

Background Whether the use of IVUS during the procedure adds a clinical benefit remains unclear. There is only 1 previous observational study, with relevant limitations, supporting the value of this strategy.

Methods We performed a patient-level pooled analysis of 4 registries of patients with LM disease treated with DES in Spain. A propensity score-matching method was used to obtain matched pairs of patients with and without IVUS guidance.

Results A total of 1,670 patients were included, and 505 patients (30.2%) underwent DES implantation under IVUS guidance (IVUS group). By means of the matching method, 505 patients without the use of IVUS during revascularization were selected (no-IVUS group). Survival free of cardiac death, myocardial infarction, and target lesion revascularization at 3 years was 88.7% in the IVUS group and 83.6% in the no-IVUS group ($p = 0.04$) for the overall population, and 90% and 80.7%, respectively ($p = 0.03$), for the subgroups with distal LM lesions. The incidence of definite and probable thrombosis was significantly lower in the IVUS group (0.6% vs. 2.2%; $p = 0.04$). Finally, IVUS-guided revascularization was identified as an independent predictor for major adverse events in the overall population (hazard ratio: 0.70, 95% confidence interval: 0.52 to 0.99; $p = 0.04$) and in the subgroup with distal lesions (hazard ratio: 0.54, 95% confidence interval: 0.34 to 0.90; $p = 0.02$).

Conclusions The results of this pooled analysis show an association of IVUS guidance during percutaneous coronary intervention with better outcomes in patients with LM disease undergoing revascularization with DES. (J Am Coll Cardiol Intv 2014;7:244–54) © 2014 by the American College of Cardiology Foundation

Percutaneous revascularization of unprotected left main coronary artery (LM) disease has been a controversial subject during recent years. Even though LM treatment has been traditionally reserved for surgery, there have been numerous registries with drug-eluting stents (DES) that have shown favorable outcomes (1–5). Randomized studies have shown that percutaneous coronary intervention (PCI) of these lesions with paclitaxel and sirolimus-eluting stents, respectively, may offer results comparable to surgery up to 3 years, as long as the complexity and extent of the coronary disease are not high (6–8). In a meta-analysis of randomized trials, PCI with DES was associated with nonsignificantly different 1-year rates of major adverse cardiac and cerebrovascular events, a lower risk of stroke, and a higher risk of target vessel revascularization compared with surgery (9).

This has resulted in LM PCI being included in clinical guidelines as an alternative to surgery in cases when the latter represents a high risk (10,11). The practice of PCI on unprotected LM is increasing significantly in Spain (12).

In this uniquely challenging anatomic scenario, the use of intravascular ultrasound (IVUS) has been advocated as a means to optimize procedural results with the hope that this may translate into improved long-term clinical outcomes. However, there is a dearth of appropriately-designed studies examining whether a benefit is derived from the use of IVUS during PCI in patients with LM disease, and available recommendations are mostly supported by retrospective registries and expert opinion (13–15), without consistent results and subjected to important limitations (16). The guideline recommendation for using IVUS guidance during LM PCI is Class IIb (11).

In this study, we sought to investigate the clinical impact of the use of IVUS in patients with LM disease undergoing PCI with DES. For this purpose, we pooled data at the patient level from 4 registries originally designed to evaluate outcomes of patients with LM lesions treated with stents (17,18).

Methods

The present study consists of the pooled analysis of the following Spanish LM registries:

1. **ESTROFA-LM.** ESTROFA-LM (Grupo Español de Estudio de Stents Farmacoactivos: Left Main) was a multicenter, retrospective registry that included 770 patients treated with DES in 21 centers from 2004 to 2009. Patients with angiographically-significant lesions in unprotected LM treated with DES were included. Only patients with cardiogenic shock at the time of procedure were excluded. Patients had stable or unstable ischemic heart disease, and LM lesions that were considered significant and with an indication for revascularization. Patients undergoing treatment of lesions in other vessels were also included. All clinical, angiographic, and procedural data were reported in a common database specifically designed for this study. At the same time, all information about the clinical follow-up was also submitted and adequately updated through registry and hospital database reviews, as well as through contact with patients. The 3-year follow-up outcomes have been published elsewhere (17).
2. **RENACIMIENTO.** RENACIMIENTO (Registro Nacional Sobre el Tratamiento del Tronco Común) was a multicenter, prospective registry performed at 30 hospitals in Spain. From November 2007 to November 2008, 1,493 consecutive patients with a significant angiographic involvement of unprotected LM, with indication of revascularization, treated with PCI or surgery were included in a database. In 596 patients, DES were implanted. For the purpose of the present analysis, patients with cardiogenic shock were excluded. This registry was designed for 1-year follow-up.
3. **Bellvitge.** In the Bellvitge registry, 236 consecutive patients were included with angiographically-significant lesions in unprotected LM treated with stents in the period from 2002 to 2010. Among these, 189 were treated with DES. Exclusion criteria were patients undergoing PCI in ST-segment elevation myocardial

Abbreviations and Acronyms

DES = drug-eluting stent(s)
IVUS = intravascular ultrasound
LM = left main coronary artery
MI = myocardial infarction
PCI = percutaneous coronary intervention
TLR = target lesion revascularization

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infarction (MI) or in cardiogenic shock. The results of this registry have been partially published (18). Planned follow-up was for 3 years.

4. **Valdecilla.** In the Valdecilla registry, 200 consecutive patients with significant lesions in unprotected LM treated with DES from 2002 to 2010 were included. There was no clinical or angiographic type of exclusion, except for the presence of cardiogenic shock at the time of procedure. Planned follow-up was for 3 years.

The ESTROFA-LM and RENACIMIENTO registries were promoted and supported by the Spanish Working Group of Interventional Cardiology of the Spanish Society of Cardiology.

It is important to note that none of these 4 registries was specifically designed to formally evaluate the efficacy of IVUS use in LM PCI; however, in all of them, information regarding use of IVUS was systematically requested. Given that some centers participated in 2 or 3 of these registries, and there was a possibility for partial overlap during the enrollment periods, we carefully searched for potential duplicated inclusions (n = 85), which were subsequently deleted from the final database. The 4 databases were pooled and analyzed at the coordination center, Hospital Universitario Marques de Valdecilla, Santander, Spain, by 2 investigators (J.T.H., T.G.C.) blinded to group allocation. There were no meaningful differences in the event definitions among these studies, but events were adjudicated according to the definitions finally provided in this paper that resulted from a consensus. The pooling investigators reviewed every event adjudication and the clinical data provided for patients with adjudicated and not adjudicated events. Additional information was requested and discussed with the corresponding main investigators when any doubts existed, and re-adjudication was done in order to guarantee a homogeneous event adjudication process.

Objectives and definitions. As has been indicated previously, these registries were not specifically designed to address the role of IVUS in LM PCI. Therefore, there were no specific IVUS criteria for device sizing, or identification and treatment of malapposition and/or underexpansion. The decisions taken after the IVUS examination were left up to the operator. The primary objective of the study was to compare the major adverse cardiac event-free survival (cardiac death, MI, and target lesion revascularization [TLR]) at 3 years between patients undergoing PCI with DES in LM with IVUS guidance or with angiographic guidance alone. Secondary objectives included: all-cause mortality, cardiac mortality, survival free of infarction, survival free of TLR, and incidence of definite and probable stent thrombosis.

The following major adverse cardiac events were defined: mortality as all-cause death; cardiac death as mortality from cardiac etiologies such as infarction, heart failure, or stent thrombosis, and including any sudden death by undefined cause; and MI. MI was defined as: 1) detection of rise and fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least 1 of the following: chest pain, electrocardiographic changes (new ST-T changes or new left bundle branch block), development of pathological Q waves, or new regional wall motion or perfusion abnormalities; 2) sudden death involving cardiac arrest, often with previous symptoms suggestive of ischemia, and accompanied by presumably new ST-segment elevation, or new left bundle branch block and/or evidence of fresh thrombus in angiography and/or at autopsy, but death occurring before blood samples could be obtained at a time before the appearance of cardiac markers in blood; or 3) pathological findings of an acute MI. PCI-related MI was defined as an increase of biomarkers >3 times the 99th percentile of the upper reference limit.

TLR was defined as revascularization for LM restenosis (>50%), also including proximal or distal segments (5 mm) adjacent to the stent or stents used for treatment of the lesion, and including the first distal 5 mm to the ostial left anterior descending or circumflex arteries. Therefore, this would consider a TLR to be an intervention upon a restenotic lesion in the distal edge of a stent in LM that extended to the proximal left anterior descending coronary artery or upon the distal edge of a stent implanted in the ostial–proximal left circumflex. Any surgical revascularization as the result of restenosis as previously defined was also considered a TLR. Definite or probable stent thrombosis was considered according to the definitions by the Academic Research Consortium (19). It is definite when confirmed by angiography or when pathological confirmation of acute thrombosis is done in patients with acute coronary syndromes. Probable stent thrombosis is defined as any unexplained death within 30 days or as target vessel infarction without angiographic confirmation of thrombosis or other identified culprit lesion.

Statistical analysis. Continuous variables are presented as mean ± SD. Categorical variables are expressed as percentages. Continuous variables were compared with the Student *t* test if they followed a normal distribution, and with Wilcoxon tests when they did not (assessment of type of distribution by the Kolmogorov-Smirnov test). The categorical variables were compared with the chi-square test or Fisher exact test, as required. Kaplan-Meier curves for event-free survival were obtained for each group or subgroup considered in the analysis and compared using the log-rank test. Cox proportional hazard multiple regression analysis was used to determine independent predictors of major cardiac adverse events during the follow-up period. The model included all variables that showed association with major adverse cardiac events (death, infarction, and TLR) in univariate analysis with a p value <0.1. In addition, we also performed adjustment for differences in clinical,

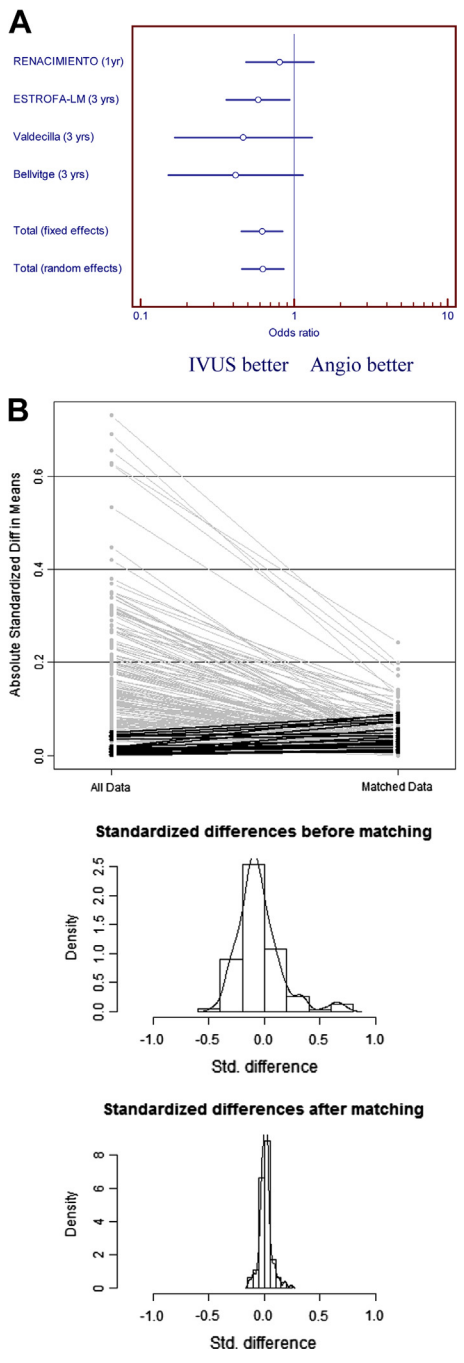


Figure 1. Propensity-Score Matching Procedure

(A) Forest plot showing the odds ratio for cardiac death, infarction, and target lesion revascularization in intravascular ultrasound (IVUS)-guided left main coronary artery percutaneous coronary intervention in the registries (test for heterogeneity: Q = 2, degrees of freedom [df] = 3, and p = 0.57). **(B)** Absolute standardized difference in means and density histograms before and after matching (overall balance test: chi-square = 13.4, df = 17.0, and p = 0.7). Angio = angiography; ESTROFA-LM = Grupo Español de Estudio de Stents Farmacoactivos: Left Main; RENACIMIENTO = Registro Nacional Sobre el Tratamiento del Tronco Común.

angiographic, and procedural characteristics by the use of propensity score matching.

The "psmatching" custom dialogue was used in conjunction with SPSS version 19 (IBM, Armonk, New York). The psmatching program performs all analyses in R (R Foundation for Statistical Computing, Vienna, Austria) though the SPSS R-Plugin (version 2.10.1). This procedure involved 3 stages:

1. The propensity scores were estimated using logistic regression in which the use of IVUS was used as the outcome variable and all covariates as predictors (registry, age, sex, smoker, diabetes, hypertension, hypercholesterolemia, chronic renal failure, left ventricular ejection fraction, previous MI, previous PCI, previous coronary artery bypass grafting, acute coronary syndrome, MI, number of diseased vessels, number of lesions treated, lesion location in LM, diffuse lesion in LM, LM ulceration or dissection, LM visual stenosis, LM stent length, LM stent diameter, 2-stents technique, side-branch stent length, side-branch stent diameter, rotational ablation, glycoprotein IIb/IIIa inhibitors, angiographic success).
2. Patients were matched using simple 1:1 nearest neighbor matching that is based on a "greedy" matching algorithm that sorts the observations in the IVUS group by their estimated propensity score. It then matches each unit sequentially to a unit in the no-IVUS group that has the closest propensity score. In order to exclude bad matches, we imposed a caliper of 0.2 of the SD of the logit of the propensity score. Units outside the area of common support (defined as the region of the distributions of estimated propensity scores in the IVUS and no-IVUS groups for which units in both groups are observed) were disregarded. This was done to improve the balance of the covariates.
3. A series of model adequacy checks were performed to check whether an adequate balance on the covariates was achieved through the matching procedure. This was done by computing the global imbalance measure and through the production of 5 diagnostic plots: 1) histograms of the propensity scores in both groups before and after matching; 2) a dot plot of individual propensity scores of units in the control and treatment group, either matched or unmatched; 3) histograms of the standardized differences of all terms (covariates, quadratic term, interactions) before and after matching; 4) a dot plot that displays the magnitude of the standardized differences before and after matching for each covariate; and 5) a line plot of standardized mean differences before and after matching. An overall imbalance chi-square test is provided. This test statistic, which is related to the well-known Hotelling's T2 statistic, assesses simultaneously whether any variable or any linear combination of variables is significantly

Table 1. Clinical Characteristics

	IVUS (n = 505)	No IVUS (n = 505)	p Value
Age, yrs	66.1 ± 11.6	66.9 ± 11.5	0.4
Women	101 (20.0)	108 (21.3)	0.7
Current smoker	148 (29.3)	161 (31.8)	0.4
Diabetes	183 (36.2)	175 (34.6)	0.6
Hypertension	342 (67.7)	325 (64.3)	0.3
Hypercholesterolemia	314 (62.2)	284 (56.2)	0.2
Chronic renal failure	35 (6.9)	31 (6.1)	0.7
LVEF, %	54.9 ± 12.5	55.3 ± 13.0	0.6
Previous MI	122 (24.1)	130 (25.7)	0.6
Previous PCI	111 (21.9)	107 (21.2)	0.8
Previous CABG	15 (2.9)	18 (3.5)	0.7
ACS	298 (59.0)	308 (61.0)	0.5
MI	121 (23.9)	115 (22.7)	0.7

Values are mean ± SD or n (%).

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; IVUS = intravascular ultrasound; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

unbalanced after matching. The test examines all covariates that were used to estimate the propensity score.

A p value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 19 for Windows.

Results

A total of 1,670 patients with LM disease treated with DES were eventually included in the pooled final database of the 4 registries. Among these, 505 patients (30.2%) underwent PCI of the LM under IVUS guidance (IVUS group). The use of IVUS was 27.7% in the RENACIMIENTO registry, 30.2% in the ESTROFA-LM registry (17), 21.7% in the Bellvitge registry (18), and 45.5% in Valdecilla registry. The odds ratio for major cardiac adverse events (cardiac death, MI, and TLR) in patients with IVUS guidance for the different registries is shown in Figure 1A. The use of IVUS was associated with better outcomes in all registries, without significant heterogeneity.

By means of the propensity score-matching method, a cohort of 505 patients treated without the use of IVUS during PCI were selected (no-IVUS group). The adequacy of propensity matching is illustrated in Figure 1B. The c-statistic was 0.78.

Clinical characteristics of both groups are shown in Table 1. The groups appeared well matched, and no significant differences were observed. Regarding angiographic and procedural details, these are described in Table 2. The only significant differences noted were in stent diameter in the LM and the side branch, most probably caused by the use of IVUS to select the most appropriate stent size to be implanted. All of the remaining characteristics were quite comparable.

Table 2. Angiographic and Procedural Characteristics

	IVUS (n = 505)	No IVUS (n = 505)	p Value
2-vessel disease	160 (31.7)	168 (33.2)	0.6
3-vessel disease	161 (31.9)	149 (29.5)	0.4
Lesions treated	1.47 ± 1.2	1.5 ± 1.1	0.7
Ostial LM lesion	151 (30.0)	145 (28.7)	0.9
Mid-shaft LM lesion	133 (26.3)	134 (26.5)	0.8
Distal LM lesion	221 (43.7)	226 (44.7)	0.6
Diffuse LM disease	92 (18.2)	88 (17.4)	0.8
LM ulceration or dissection	79 (15.6)	69 (13.6)	0.4
LM visual stenosis, %	70.5 ± 15.0	70.0 ± 16.0	0.6
LM stent length, mm	16.0 ± 5.4	16.8 ± 5.7	0.08
LM stent diameter, mm	3.8 ± 0.4	3.65 ± 0.4	0.0001
Complex technique (2 stents)	63 (12.5)	62 (12.2)	0.9
2 stents/distal lesion	28.5	27.4	0.7
SB stent length, mm	15.8 ± 5.0	16.2 ± 4.0	0.2
SB stent diameter, mm	3.1 ± 0.4	3.00 ± 0.36	0.0001
Rotational ablation	21 (4.1)	22 (4.3)	0.9
GP IIb/IIIa inhibitors	83 (16.4)	92 (18.2)	0.5
Angiographic success	498 (98.6)	495 (98.0)	0.6
DAPT for at least 12 months	505 (100)	505 (100)	1.0

Values are mean ± SD or n (%). Diseased vessel was defined as a vessel with angiographic stenosis ≥50% in a segment with a reference lumen diameter >2 mm. Lesion location in the LM could be ostial (at the aorto-ostial junction), mid-shaft (at the mid-portion, not affecting the ostium or bifurcation), or distal (lesion located at the bifurcation level of the LM).

DAPT = dual antiplatelet therapy; GP = glycoprotein; LM = left main coronary artery; SB = side branch; other abbreviations as in Table 1.

The use of IVUS was designed to assess basal lesion characteristics (severity, extension, calcification, and ostial involvement) and then to guide PCI in 12% of patients. In the remaining 88% of cases, IVUS was used to guide PCI, allowing stent size selection after dilation, assessment of stent coverage, expansion, and apposition, and evaluation of the side branch ostium when needed. Even though we included stent diameter and length in the propensity score-matching process, diameters for the main and side branch stents remained larger in the IVUS group. After IVUS examination, post-dilation (defined as dilation with higher pressure and/or larger balloon) was done in 40% of cases, and a new stent was implanted in 7.9% of patients. This information is not available for the angiography-guided group in all registries. In the ESTROFA-LM (17) and Valdecilla registries, post-dilation was significantly more frequently done in the IVUS-guided PCI group and was accomplished with larger balloons compared with angiography-guided PCI.

Curves for event-free survival in both groups are shown in Figures 2 to 4. The incidences of major adverse events are listed in Table 3. Survival free of the combined endpoint of cardiac death, infarction, and TLR was significantly better in the IVUS group. Patients with IVUS had significantly better

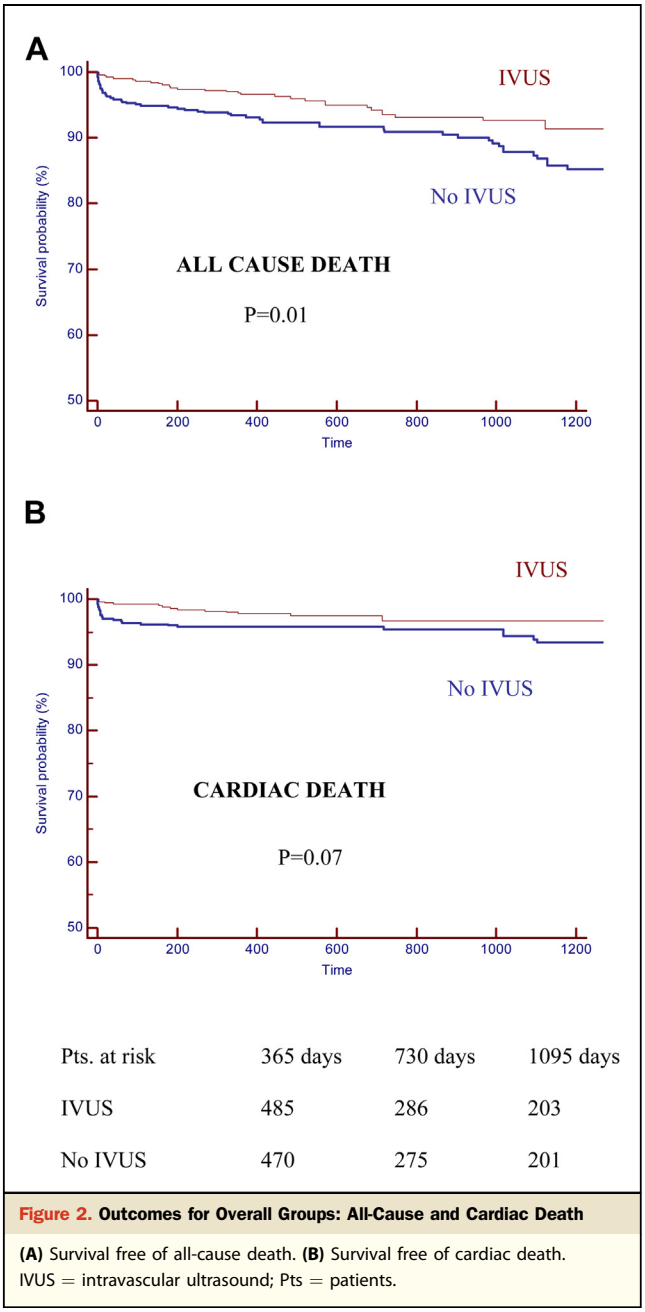


Figure 2. Outcomes for Overall Groups: All-Cause and Cardiac Death

(A) Survival free of all-cause death. **(B)** Survival free of cardiac death. IVUS = intravascular ultrasound; Pts = patients.

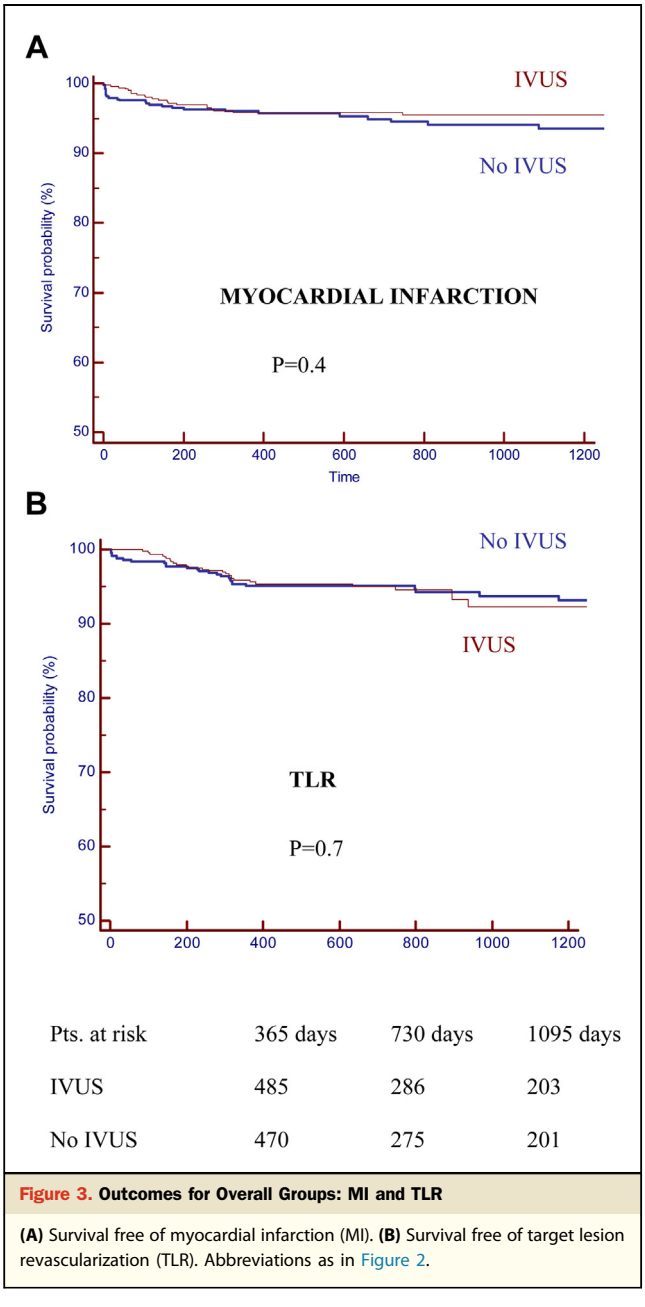


Figure 3. Outcomes for Overall Groups: MI and TLR

(A) Survival free of myocardial infarction (MI). **(B)** Survival free of target lesion revascularization (TLR). Abbreviations as in Figure 2.

survival, and they had lower all-cause mortality, but when considering only cardiac death, there was a trend in favor of IVUS guidance that did not reach significance. MI and TLR incidences were comparable in both groups. In addition, the incidence of definite and probable thrombosis was significantly lower in the IVUS group (0.6% vs. 2.2%; p = 0.04) (Fig. 5).

Subgroup analysis: distal lesions. In the subgroup of patients with distal lesions, survival free of major adverse events (cardiac death, MI, and TLR) was significantly better for the IVUS group (Fig. 6, Table 3). This benefit was driven by a reduction in death, but not in infarction or TLR. Among those patients treated with 2 stents, the use of IVUS was associated with a significantly better outcome, even despite the small numbers (Fig. 7, Table 3). However, in this particular subset, a trend for a decreased TLR rate in the IVUS group was observed.

Finally, independent predictors for major adverse events are listed in Table 4. Notably, IVUS emerged as an independent predictor for fewer adverse events in the overall patient population and especially in the subgroup of patients with distal LM disease.

In Figure 8, an illustrative case of definite stent thrombosis after DES implantation without IVUS guidance is shown.

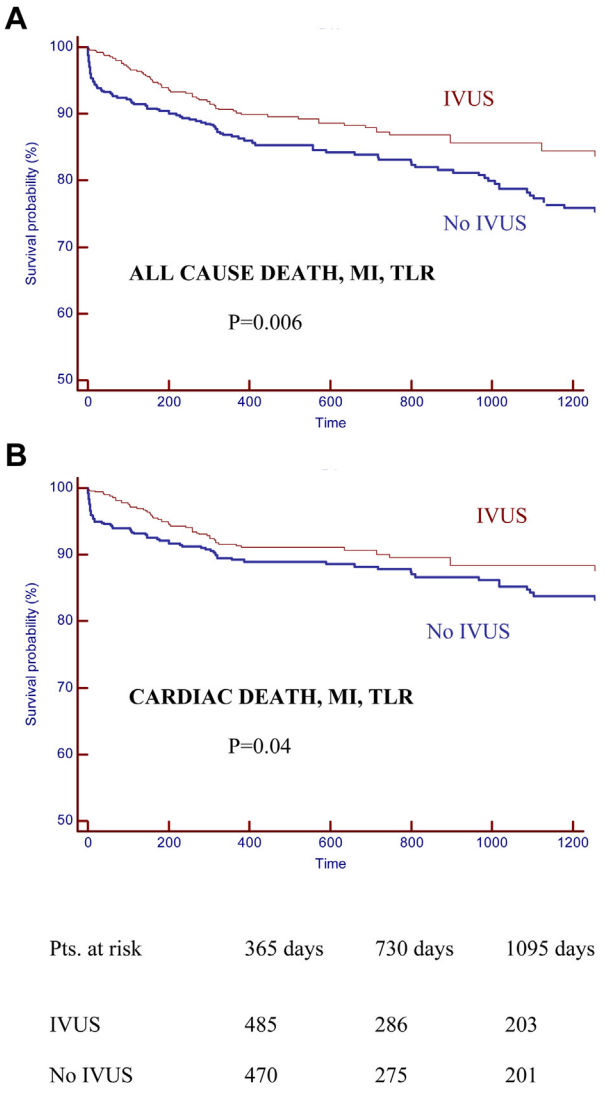


Figure 4. Outcomes for Overall Groups: MACE

(A) Survival free of all-cause death, MI, and TLR. **(B)** Survival free of cardiac death, MI, and TLR. MACE = major adverse cardiac events; other abbreviations as in Figures 2 and 3.

Findings in IVUS examination at the time of thrombosis (underexpansion and malapposition) could have been identified and corrected in the index procedure, probably avoiding stent thrombosis, a potentially fatal complication.

Discussion

The findings of this pooled analysis indicate that the use of IVUS guidance for PCI with DES in patients with LM lesions is associated with a better clinical outcome, especially in those cases with distal LM disease. Importantly, this benefit was driven by reduction in mortality. The use of IVUS was also associated with a lower risk of stent thrombosis. Finally, a trend for a lower TLR rate was observed with the use of IVUS in patients requiring the implantation of 2 stents.

Table 3. Incidence of Major Adverse Events

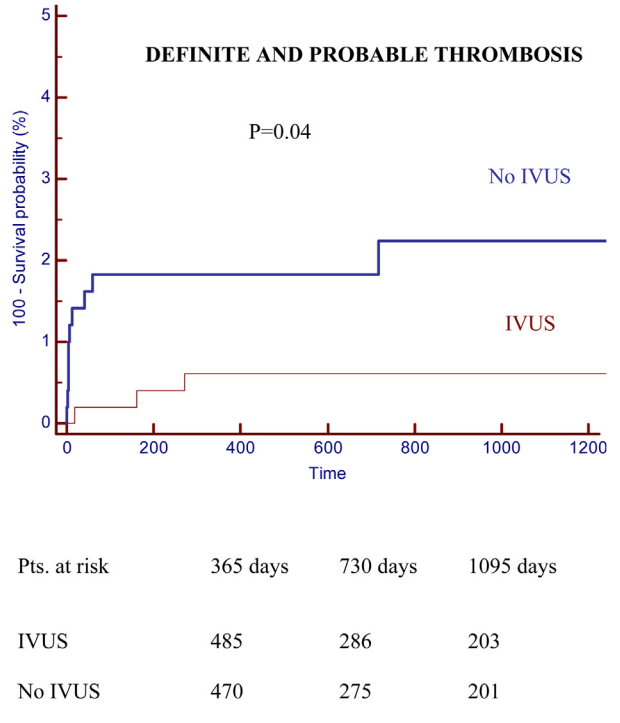
	IVUS	No IVUS	p Value
Overall, n	505	505	
Death	7.4	13.0	0.01
Cardiac death	3.3	6.0	0.07
MI	4.5	6.5	0.4
TLR	7.7	6.3	0.7
Death + MI + TLR	14.4	22.2	0.006
Cardiac death + MI + TLR	11.7	16.0	0.04
Definite or probable stent thrombosis	0.6	2.2	0.04
Subgroup with distal lesions, n	221	226	
Cardiac death + MI + TLR	11.0	19.0	0.03
Subgroup with distal lesions-2 stents, n	63	62	
Cardiac death + MI + TLR	16.7	41.0	0.02

Values are %, except where otherwise indicated.
IVUS = intravascular ultrasound; MI = myocardial infarction; TLR = target lesion revascularization.

We realize that the clinical benefit associated with the use of IVUS could have been partially explained by the effect of confounders. However, our results show that IVUS guidance allowed larger and more fully expanded stents. Differences in stent thrombosis rates and a clinical benefit focused in distal lesions are in agreement with a plausible IVUS-derived positive effect. Age, sex, diabetes, renal failure, ejection fraction, number of diseased vessels, number of lesions treated, and other variables with prognostic relevance were well matched. Patients selected for DES implantation, especially at the LM level, are considered to be suitable for long-term dual antiplatelet therapy. This criterion may have prevented the inclusion in these registries of patients with comorbidities related to a higher bleeding risk that may have great influence on outcomes. Patients with cardiogenic shock were excluded as well, because in these patients, the goal is an emergent restoration of flow at the LM level, and the use of IVUS is much less frequently done. Finally, the use of IVUS could be linked to a better operator's profile, being a marker of a higher-quality performance.

The use of IVUS was similar in the larger nation-wide registries (27.7% and 30.2%) and more different in the single-center registries (21.7% and 45.5%). Clinical outcomes in these registries were fairly comparable, with a rate of survival free of cardiac death, MI, and TLR at 1 year of 86% to 89%. Follow-up was shorter in the RENACIMIENTO registry (1 year). Nevertheless, the positive outcome associated with the use of IVUS was consistent across the 4 registries, with no significant heterogeneity.

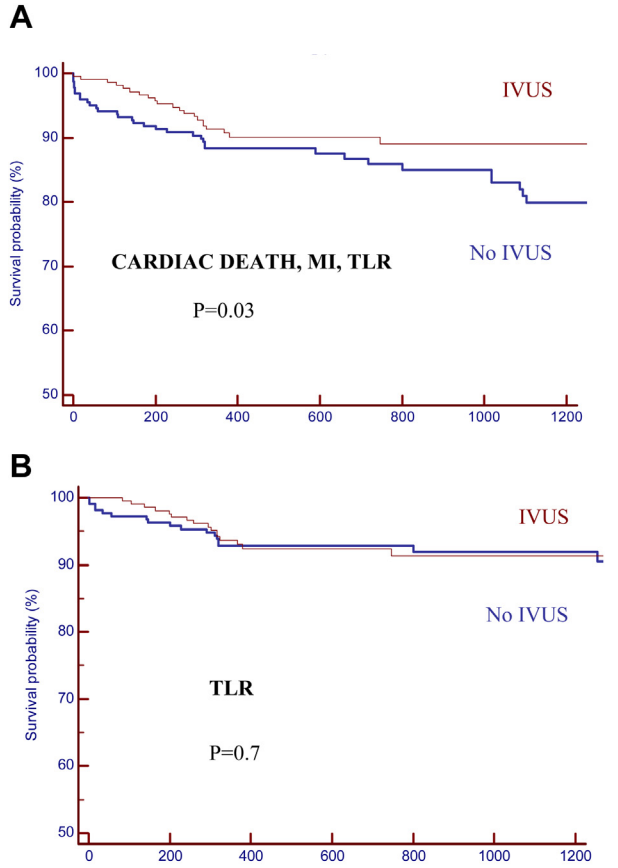
One of the most discussed issues in interventional cardiology has been the strategy for revascularization in patients



Pts. at risk	365 days	730 days	1095 days
IVUS	485	286	203
No IVUS	470	275	201

Figure 5. Outcomes for Overall Groups: Stent Thrombosis

Incidence of definite and probable thrombosis. Abbreviations as in Figure 2.



Pts. at risk	365 days	730 days	1095 days
IVUS	212	111	90
No IVUS	219	112	97

Figure 6. Outcomes for the Subgroups With Distal LM Disease

(A) Survival free of cardiac death, MI, and TLR. **(B)** Survival free of TLR. LM = left main coronary artery; other abbreviations as in Figures 2 and 3.

with LM lesions. This is a setting in which surgery still maintains its status as the first-option strategy. Multiple registries and 2 trials including patients treated with DES in LM disease have been overall positive, although these results depended to a great extent upon the type of lesion, and thus, outcomes were not as excellent in distal lesions as in cases of ostial or mid-shaft lesions (1–9). Thus, a Class IIb indication has been recently granted for percutaneous revascularization of the LM in patients with favorable anatomy (11).

On the other hand, the role of IVUS guidance in PCI of the LM has been highly controversial. In fact, the guidelines' recommendation for using IVUS guidance during LM PCI is Class IIb (11). The lack of specific randomized trials focused on answering this question implies that current evidence relies on retrospective analyses. In this regard, conflicting results were initially reported in small registries (13,20). However, significant differences in patient and procedural characteristics existed between these registries that could explain the observed different influence of IVUS guidance on clinical outcomes (5,21).

The most relevant contribution to this topic came from a post-hoc analysis of the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) study, which showed the outcome in 145 "comparable" well-matched pairs of patients with and without IVUS guidance during PCI with DES (14). In this analysis, the 3-year incidence of total mortality was lower in the IVUS-guided group (4.7% vs. 16%; p = 0.048) with survival curves diverging beyond the second year. The use of IVUS did not influence the incidence of MI or TLR. However, there are some important limitations worthy of discussion (16). In this registry, all baseline characteristics were clearly favorable for the IVUS-guided arm. Despite elegant, rigorous, and exhaustive adjustments (using propensity score-matching analyses), it remains possible that some unmeasured confounders could also be more favorable in the IVUS-guided arm, therefore explaining its better outcome. This is relevant because of the potential presence of

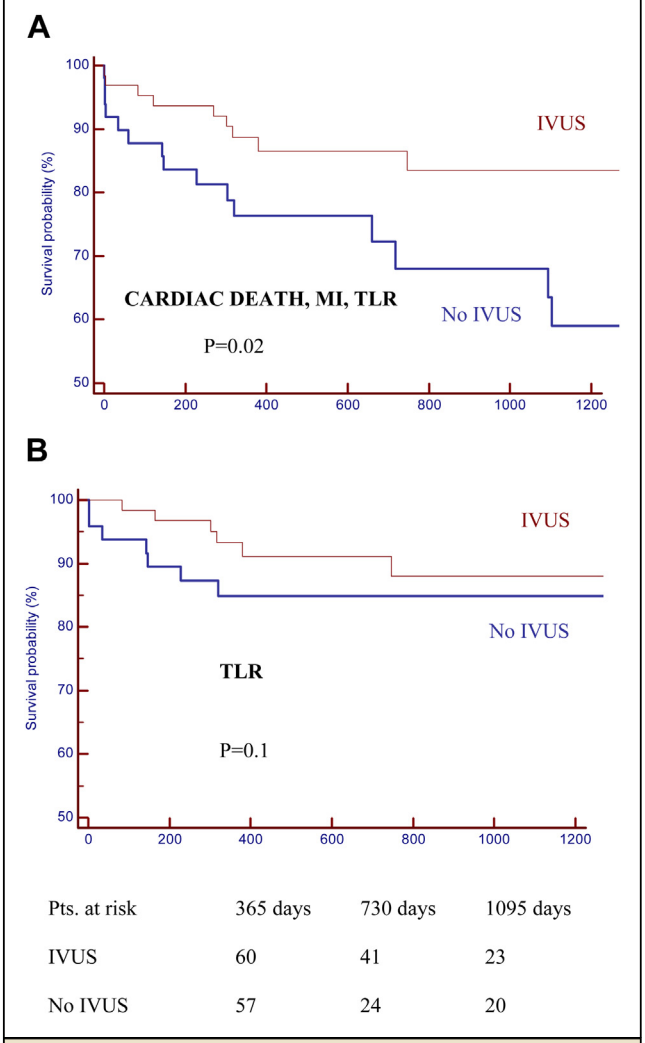


Figure 7. Outcomes for the Subgroups With Distal LM Disease Treated With 2 Stents

(A) Survival free of cardiac death, MI, and TLR. **(B)** Survival free of TLR. Abbreviations as in Figures 2, 3, and 6.

Table 4. Independent Predictors for Major Adverse Events

	HR	95% CI	p Value
Overall population			
IVUS	0.70	0.52–0.99	0.04
Age	1.03	1.01–1.05	0.0001
LVEF	0.98	0.97–0.99	0.01
Diabetes	1.81	1.32–2.47	0.0002
Distal LM with 2 stents	2.23	1.44–3.48	0.0004
ACS	1.84	1.30–2.60	0.0006
Subgroup with distal LM disease			
IVUS	0.54	0.34–0.90	0.02
Age	1.02	1.004–1.05	0.02
Diabetes	1.62	1.02–2.59	0.04
Distal LM with 2 stents	2.86	1.71–4.77	0.0001
ACS	1.95	1.14–3.31	0.01
Subgroup with ostial-mid LM disease			
Age	1.04	1.02–1.05	<0.0001
ACS	1.68	1.17–2.40	0.004
IVUS	0.85	0.55–1.15	0.2

Abbreviations as in Tables 1 and 2.

severe noncardiac comorbidities (difficult to adjust for) in the cohort of complex patients with angiographic-guidance alone. Data on "total mortality" favoring IVUS guidance are difficult to interpret in the absence of comparative data on cardiac mortality and stent thrombosis. The very late effect of IVUS on survival results is also intriguing.

There are notable differences between our current study and the MAIN-COMPARE study (14). After propensity score matching, our population, coming from multicenter nationwide registries, is significantly larger, therefore providing more statistical power and allowing subgroup analyses (distal LM lesions and 2-stent subgroups). Moreover, the proportion of patients undergoing IVUS examination during PCI in our registries is not that high (77.5% vs. 30.2%) and more comparable to the average reported in U.S. and European countries. Finally, data on cardiac mortality and stent thrombosis are only available from our study.

Our study shows similar results to the MAIN-COMPARE study, suggesting that IVUS guidance is associated with significantly lower mortality and similar TLR at follow-up. However, the present study provides further insights into these general findings. The difference in all-cause mortality is significant, but this is to some extent related to differences in cardiac causes. Interestingly, in our study the use of IVUS was associated with a lower thrombosis risk. However, despite the use of the Academic Research Consortium definitions for stent thrombosis, the incidence of this event may have been underestimated, because this complication at the LM location may easily present as sudden death. On the other hand, there seems to be an apparent disconnect between infarction and thrombosis rates; although there is a significant reduction in thrombosis rates with IVUS, the incidence of infarction is comparable. This is due to the fact that most of the infarctions occurring in follow-up were related to locations other than the LM. Another important finding is that most of the clinical benefit related to IVUS use occurs early after intervention (<60 days). This makes sense and would lend support to the contention that IVUS assists by improving acute outcomes.

In the subgroup of patients with distal lesions, and specifically in those treated with 2 stents, the differences between groups were even more evident and remained statistically significant despite the smaller numbers. It is well known that these patients have a higher risk for thrombotic

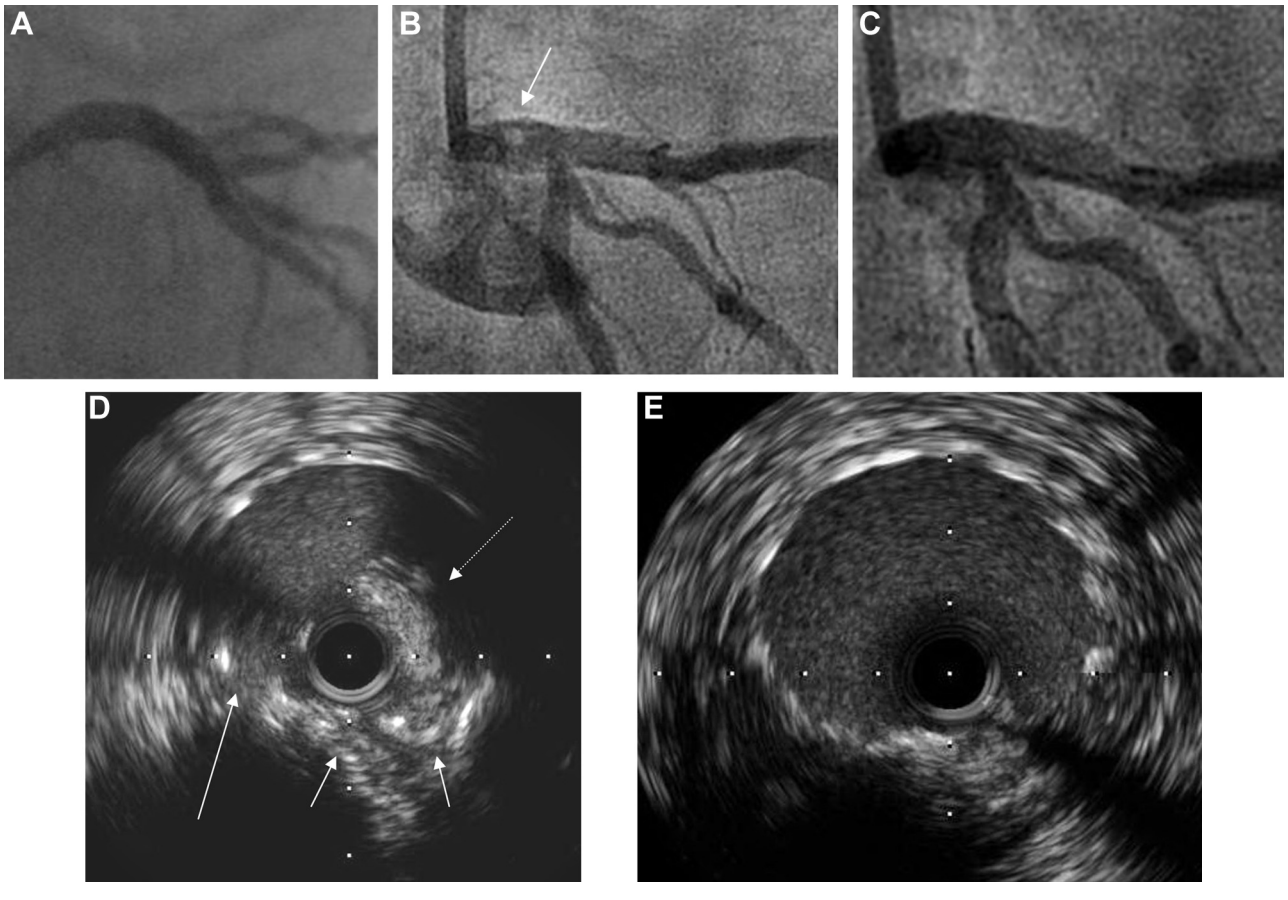


Figure 8. Case Corresponding to the No-IVUS Cohort

This patient underwent drug-eluting stent (DES) implantation (4/12 mm) in the LM without IVUS guidance; 20 days later, the patient was admitted with non–ST-segment elevation acute coronary syndrome. **(A)** Angiography with final result after DES implantation. **(B)** Angiography showing a nonocclusive thrombus within the stent **(arrow)**. **(C)** Angiography after post-dilation of the stent. **(D)** IVUS imaging revealed stent subexpansion and distortion **(short arrows)** that was due to an eccentric calcified plaque, stent malapposition **(long arrow)**, and thrombus **(dashed arrow)** at that level. **(E)** After dilation with a noncompliant balloon (4.5/8 mm) at high pressure (18 atm), stent expansion, geometry, and apposition were improved. Abbreviations as in Figures 1 and 6.

events and worse outcome compared with patients with nondistal LM lesions. It seems reasonable then to suggest that that the use of IVUS provides a greater benefit in this setting. We found that IVUS guidance did not reduce TLR. Only a trend in this regard was found in the subset of patients treated with 2 stents. This may be partially due to the low rate of TLR observed in these registries using DES and not mandating routine angiographic surveillance in asymptomatic patients. On the other hand, because the use of IVUS was at the discretion of the operator, the use of IVUS might be selected for more complex anatomy.

Study limitations. This is a retrospective comparative registry with baseline differences between groups. Registries entail limitations, particularly the problem of bias secondary to known and unknown confounding factors not always being sorted out even after careful adjustments with matched analyses such as the propensity score. Despite propensity score matching, it still remains possible that some unmeasured confounders could favor the IVUS-guided arm, explaining its better outcome.

None of the registries was specifically designed to evaluate the influence of IVUS on outcomes. Therefore, there were no specific IVUS criteria for device sizing or identification and treatment of malapposition and/or underexpansion. This is a limitation in order to know how IVUS affected the procedure, leading to improved outcomes. The decisions taken after IVUS examination were left up to the operator. The registries had different follow-up lengths and rate of IVUS usage; however, the use of IVUS guidance was associated homogenously with better outcomes in all the registries.

Characterization of distal LM disease could have been more detailed (e.g., Medina classification). The SYNTAX score was not recorded because this tool was not widely available when these registries started.

Conclusions

The results of this pooled analysis of multiple large registries suggest a positive clinical impact of the use of IVUS guidance during PCI of LM lesions with DES, especially when lesions affect the bifurcation.

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Key Words: drug-eluting stent(s) ■ intravascular ultrasound ■ left main coronary artery.