

# Impact of Coronary Anatomy and Stenting Technique on Long-Term Outcome After Drug-Eluting Stent Implantation for Unprotected Left Main Coronary Artery Disease

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**Objectives** This study sought to evaluate the impact of anatomic and procedural variables on the outcome of the unprotected left main coronary artery (uLMCA) itself after drug-eluting stent (DES) implantation.

**Background** There is a controversial debate regarding when and how to perform percutaneous coronary intervention (PCI) for an uLMCA stenosis.

**Methods** This analysis is based on a randomized study of 607 patients undergoing PCI for uLMCA, randomized 1:1 to receive paclitaxel- or sirolimus-eluting stents. We evaluated the impact of the SYNTAX score, uLMCA anatomy, and stenting technique on in-stent restenosis (ISR), target lesion revascularization (TLR), and the 3-year outcomes.

**Results** The 3-year cardiac mortality rate was 5.8%; 235 (39%) patients had a true bifurcation lesion (TBL), and the median SYNTAX score was 27. TBL was associated with a higher need for multiple stents (72% vs. 37%,  $p < 0.001$ ). TBL was a significant predictor of ISR (23% vs. 14%,  $p = 0.008$ ) and for TLR (18% vs. 9%,  $p < 0.001$ ). The need for multiple stents was a predictor of ISR (22% vs. 13%,  $p = 0.005$ ) and for TLR (16% vs. 9%,  $p = 0.005$ ). Culotte stenting showed better results compared with T-stenting for ISR (21% vs. 56%,  $p = 0.02$ ) and for TLR (15% vs. 56%,  $p < 0.001$ ). We observed a significant association between uLMCA-TLR and SYNTAX scores (9.2% for scores  $\leq 22$ , 14.9% for scores 23 to 32, and 13.0% for scores  $\geq 33$ ,  $p = 0.008$ ).

**Conclusions** PCI of uLMCA lesions with DES is safe and effective out to 3 years. TBL and multiple stents were independent predictors for ISR. In the multivariate analysis, independent predictors for TLR were TBL, age, and EuroSCORE (European System for Cardiac Operative Risk Evaluation). (Drug-Eluting-Stents for Unprotected Left Main Stem Disease [ISAR-LEFT-MAIN]; [NCT00133237](https://clinicaltrials.gov/ct2/show/study/NCT00133237)) (J Am Coll Cardiol Intv 2014;7:29–36) © 2014 by the American College of Cardiology Foundation

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Significant left main disease is observed with increasing incidence, given the progressively older patients with higher prevalence of cardiovascular risk factors (1). Left main disease has a significant impact on the symptomatic and prognostic outcome, with a controversial debate regarding the optimal treatment (1–3). Early studies using bare-metal stents have shown high restenosis rates, especially in the presence of left main bifurcation lesions, declaring elective left main percutaneous interventions to be almost a taboo or a palliative approach (1,2). Large randomized trials showed a reduction of restenosis rates in non-left main lesions by 60% to 80% using drug-eluting stents (DES) compared with bare-metal stents, reaching low single-digit rates with different DES (2–9).

See page 37

### Abbreviations and Acronyms

|              |   |
|--------------|---|
| <b>CABG</b>  | = coronary artery bypass graft surgery  |
| <b>DES</b>   | = drug-eluting stent(s)                 |
| <b>ISR</b>   | = in-stent restenosis                   |
| <b>LCX</b>   | = left circumflex coronary artery       |
| <b>LMCA</b>  | = left main coronary artery             |
| <b>MACE</b>  | = major adverse cardiac event(s)        |
| <b>MI</b>    | = myocardial infarction                 |
| <b>PCI</b>   | = percutaneous coronary intervention    |
| <b>TBL</b>   | = true bifurcation lesion               |
| <b>TLR</b>   | = target lesion revascularization       |
| <b>uLMCA</b> | = unprotected left main coronary artery |

In the last few years, different randomized and nonrandomized studies have addressed the percutaneous coronary intervention (PCI) of the unprotected left main coronary artery (uLMCA) with DES and compared it with aorto-coronary artery bypass graft surgery (CABG) (3,10–12). The largest trial to date, the SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) trial, randomized 1,800 patients with 3-vessel disease and/or left main lesions into 2 equally large groups, comparing PCI using the first-generation Taxus DES with CABG (3). In the overall population, major adverse cardiac or cerebrovascular events at 1 year were higher in the PCI group

because of an increased rate of repeat revascularization; the hard safety endpoint, including death and myocardial infarction (MI), was similar between the 2 groups, whereas stroke occurred significantly more often after CABG (3). Interestingly, within the subgroup of the 705 patients with left main stenosis, the primary endpoint major adverse cardiac or cerebrovascular events was not different between PCI and CABG ( $p = 0.44$ ), with a better outcome after PCI in the left main subgroup compared with the other patients (13). Despite these results, the worldwide proportion of patients treated with PCI compared with CABG is still higher for patients with 3-vessel disease compared with patients with left main disease, who are often still sent to CABG (14). This might be related to the frequent involvement of the challenging uLMCA bifurcation and concerns of restenosis requiring complex re-interventions, whereas restenosis in

the rest of the coronary tree is felt to be treated safely nowadays. But there is no systematic analysis on the basis of an adequate number of left main lesions treated with DES implantation regarding the impact of coronary anatomy, stenting technique, full DES coverage, need for final kissing balloon dilation, and overall coronary disease burden regarding the outcome of the important left main site. To our knowledge, this is the first analysis to systematically address these issues.

### Methods

**Patient population and analyzed variables.** This analysis is based on the previously published randomized ISAR-LEFT MAIN (Drug-Eluting-Stents for Unprotected Left Main Stem Disease) study including 607 symptomatic patients with uLMCA disease undergoing PCI (10); 302 patients were assigned to receive a paclitaxel-eluting stent (Taxus, Boston Scientific, Natick, Massachusetts) and 305 assigned to receive a sirolimus-eluting stent (Cypher, Cordis, East Bridgewater, New Jersey) (10). The primary trial focused on the comparison of the 2 different stent platforms and showed no significant difference in the outcome between paclitaxel-eluting stents and sirolimus-eluting stents, with an overall low MACE (major adverse cardiac events) rate, comparable to the SYNTAX trial (3,10). Given the similar outcome of the 2 stent platforms, this current analysis evaluated the prognostic impact of the overall coronary anatomy (reflected by the SYNTAX score), the left main anatomy, and the stenting technique on the angiographic restenosis rate (in-stent restenosis [ISR]) and target lesion revascularization (TLR) for the left main itself, independent of the DES used.

The methods of the randomized ISAR-Left Main trial have been published in detail (10). Written informed consent for participation in this trial has been obtained from all subjects (or their guardians). The study was conducted in accordance with the provisions of the Declaration of Helsinki and with the International Conference on Harmonisation's Good Clinical Practices, and protocol approval was obtained from the medical ethics committee for both participating centers, the Deutsches Herzzentrum and Medizinische Klinik I, Klinikum Rechts der Isar, Munich, Germany (10).

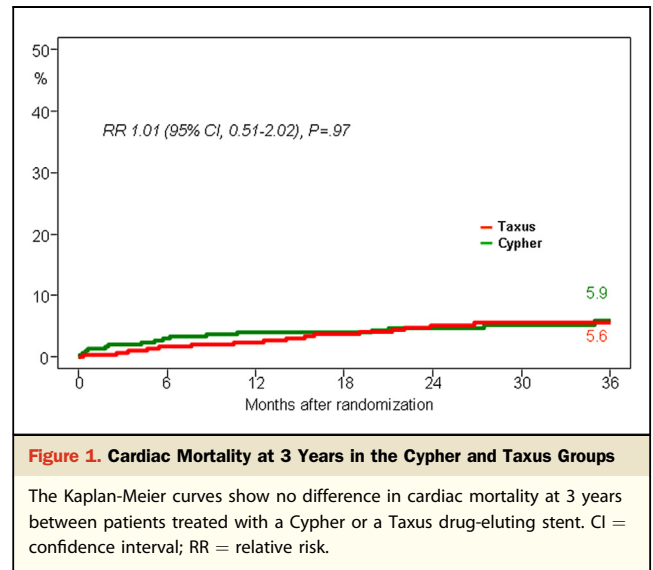
We assessed the Parsonnet score and EuroSCORE (European System for Cardiac Operative Risk Evaluation) to evaluate possible differences between the subgroups (15–17). Baseline, procedural, and follow-up coronary angiograms were digitally recorded and assessed off-line in the quantitative angiographic core laboratory (ISAR Center, Munich) with an automated edge-detection system (CMS version 7.1, Medis Medical Imaging Systems, Leiden, the Netherlands) by 2 independent experienced operators unaware of the treatment allocation and clinical characteristics. Quantitative analysis was performed on the left main area, which was considered the anatomic coronary region

from left main stem ostium to the end of the 5-mm proximal segments of the left anterior descending coronary artery, left circumflex coronary artery (LCX), as well as of the Ramus intermedius, if the latter had a vessel size of more than 2 mm in diameter (10). LMCA stenoses were classified as ostial (stenosis located within 3 mm of the LMCA ostium), midshaft (non-ostial and non-distal stenosis located in the medial part of the LMCA), and distal (stenosis within 5 mm of the distal part of the LMCA), and bifurcation/trifurcation with proximal left anterior descending coronary artery, proximal LCX, and proximal R. intermedius, if the latter was >2 mm in diameter). The Medina classification assigned a "1" for the presence of a ≥50% stenosis of each branch, as previously published (18). A trifurcation was present if both the LCX and the R. intermedius were >2 mm in size with significant myocardial territory. The SYNTAX score was calculated on the basis of the algorithm developed and presented in the SYNTAX trial using the calculator on their website, by 2 independent experienced operators blinded to other patients' characteristics (3,19,20).

**Statistical methods.** Baseline descriptive statistics are presented as frequencies and percentages for categorical variables, and mean ± SD or median (interquartile range) for continuous variables, depending on the type of distribution of the variable. The differences between the groups were assessed using the chi-square test or Fisher exact test for categorical data, and the Student *t* test or nonparametric Wilcoxon test for continuous data. Survival analysis was made by applying the Kaplan-Meier method. Differences in survival parameters were assessed for significance by means of the log-rank test. We used Cox proportional hazards models for the calculation of the risk estimates and for adjustment for potential confounders that showed significant difference in the univariate analysis. A 2-tailed *p* value <0.05 was considered to indicate statistical significance. Statistical software S-PLUS, version 4.5 (S-PLUS, Insightful Corporation, Seattle, Washington) was used for all analyses.

## Results

Clinical follow-up at 3 years was available for all patients, and 530 patients (87%) had re-angiography at 6 to 9 months. Three years after left main DES implantation, the cardiac mortality rate was 5.8%, and the overall mortality rate was 12.2%. Comparing the Taxus and Cypher stents at 3 years, there was no significant difference regarding cardiovascular mortality (5.6% in the Taxus group and 5.9% in the Cypher group, *p* = 0.97) (Fig. 1) or repeat revascularization (11.6% vs. 13.3%, *p* = 0.31) (Fig. 2), mostly repeat PCI. Similarly, there was no difference between Taxus and Cypher regarding overall mortality (11.7% vs. 12.4%, *p* = 0.93), MI (6.2% vs. 5.5%, *p* = 0.69), or stroke (2.0% vs. 1.4%, *p* = 0.52). The incidence of definite stent



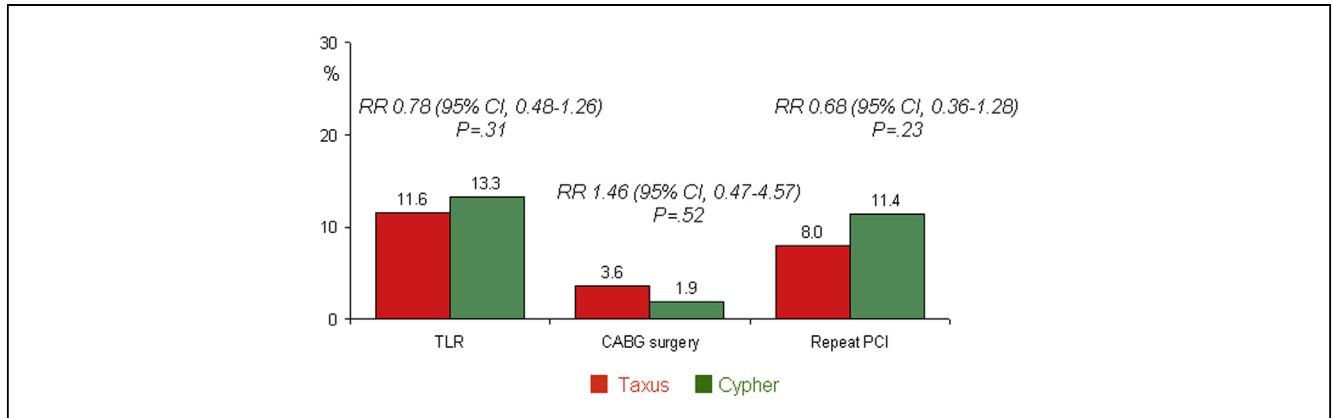
**Figure 1. Cardiac Mortality at 3 Years in the Cypher and Taxus Groups**

The Kaplan-Meier curves show no difference in cardiac mortality at 3 years between patients treated with a Cypher or a Taxus drug-eluting stent. CI = confidence interval; RR = relative risk.

thrombosis (21) was 0.3% in the Taxus group and 1.0% in Cypher group, *p* = 0.32. Given the similar results for the 2 DES platforms at 3 years, we assessed the entire population independent of the DES used and focused our detailed analysis on specific anatomic and technical factors and their impact on outcome.

The complex anatomy of uLMCA lesions was reflected by the majority of treated lesions involving the distal bifurcation, present in 384 (63%) patients; 235 (39%) patients had a true bifurcation lesion (TBL) (Medina 1,1,1) with ≥50% stenosis present in all 3 segments of the bifurcation.

Our first analysis focused on the impact of the local anatomy of the uLMCA and the stenting technique regarding the long-term outcome. The comparison of patients with and without TBL regarding baseline and procedural characteristics, is shown in Tables 1 and 2. Patients with TBL were older, and had higher Parsonnet scores and EuroSCOREs (Table 1). They also presented more often with reduced left ventricular function and 3-vessel disease (Table 2). Given its complexity, the presence of TBL was associated with a higher need for multiple stents (72% vs. 37%, *p* < 0.001) and final kissing balloon dilations (*p* < 0.001). When viewed separately, the presence of TBL was a significant predictor of ISR (23.4% vs. 14.3%, *p* = 0.008) and for TLR (17.8% vs. 9.1%, *p* < 0.001) (Fig. 3). Also, the need for multiple stents was a significant predictor of ISR (22.4% vs. 13.1%, *p* = 0.005) and TLR (16.2% vs. 8.5%, *p* = 0.005). Interestingly, even after correction for TBL, the need for multiple stents remained a significant predictor for ISR (*p* = 0.04), but not for TLR (*p* = 0.09). The predilection site for ISR was the proximal left coronary circumflex artery. Comparing techniques for multiple stenting, culotte stenting showed better results compared with T-stenting for ISR (21.3% vs. 55.6%,



**Figure 2. Repeat Revascularization Rates at 3 Years Depending on the DES Used**

The overall and specific (PCI or CABG) repeat revascularization rates were similar for the Cypher and Taxus groups. The majority of patients were treated with repeat percutaneous interventions (PCI). CABG = coronary artery bypass graft; DES = drug-eluting stent; TLR = target lesion revascularization; other abbreviations as in Figure 1.

$p = 0.02$ ) and for TLR (14.9% vs. 55.6%,  $p < 0.001$ ). When comparing left main bifurcations with and without angles  $\geq 90^\circ$ , there was no difference regarding ISR (16.4% vs. 18.2%,  $p = 0.63$ ). Final kissing balloon dilation was more often performed in the presence of TBL, severe calcification, and in lesions with pre-dilation of both branches, as well as after culotte stenting (Table 3). Final kissing balloon dilation was not associated with significant differences in ISR (22.1%

vs 25.0%,  $p = 0.73$ ) in patients with multiple stents, nor did it influence ISR in patients treated with a single stent (16.7% vs. 12.8%,  $p = 0.59$ ) (Fig. 4). Among patients with culotte stenting, kissing balloon dilation was associated with an ISR of 21.6% vs. 17.4% for patients without kissing balloon dilation ( $p = 0.63$ ) (Fig. 4). Among the few patients with T-stenting, the rate of ISR was high and not influenced by final kissing balloon dilation (50.0% vs. 60.0%,  $p = 0.76$ ) (Fig. 4).

Of the 149 patients (25% of the population) with trifurcation morphology, 62 patients had PCIs involving the R. intermedius. When stratified by number of stents, patients with a single stent had similar ISR and TLR rates ( $p > 0.21$ ), when comparing patients with and without relevant trifurcation. Patients with multiple stents had a trend for higher ISR and TLR rates ( $p = 0.06$  and  $p = 0.10$ , respectively), when comparing patients with and without trifurcation morphology. Therefore, a trifurcation morphology was a predictor for ISR only when multiple stents were needed.

In the second part of our analysis, we assessed the need for re-intervention of the left main itself, depending on the overall disease burden, reflected by the SYNTAX score; 428 patients (72%) had 3-vessel disease, 87 patients (14%) had an occluded right coronary artery, and 149 patients (25%) had a left main trifurcation, reflecting the complex coronary anatomy with a high median SYNTAX score of 27. After dividing the overall population of 607 patients depending on the SYNTAX score into the 3 categories according to the SYNTAX trial (3), the 3 groups were similarly sized in the overall population: 204 patients (34%) had a SYNTAX score  $\leq 22$ , 234 patients (39%) a score 23 to 32, and 169 patients (28%) had a score  $\geq 33$ , with a correlation with age ( $p = 0.02$ ) and presence of diabetes mellitus ( $p = 0.04$ ). There was a significantly lower TLR rate at 3 years in patients with SYNTAX scores  $\leq 22$  compared with patients with intermediate scores (23 to 32) and high scores  $\geq 33$ , (9.2% vs. 14.9% vs. 13.0%,  $p = 0.008$ ) (Fig. 5). Looking at

**Table 1. Baseline Characteristics and Therapy at Discharge**

| Characteristics                            | TBL<br>(n = 235) | No TBL<br>(n = 372) | p Value |
|--|------------------|---------------------|---------|
| Age, yrs                                   | 70.4 $\pm$ 9.8   | 68.3 $\pm$ 9.6      | 0.01    |
| Women                                      | 51 (22)          | 88 (24)             | 0.58    |
| Arterial hypertension                      | 164 (70)         | 255 (69)            | 0.75    |
| Hypercholesterolemia                       | 175 (75)         | 291 (78)            | 0.29    |
| Diabetes mellitus                          | 69 (29)          | 107 (29)            | 0.87    |
| Insulin-requiring                          | 24 (10)          | 30 (8)              | 0.37    |
| Current smoker                             | 22 (9)           | 39 (11)             | 0.65    |
| Body mass index, kg/m <sup>2</sup>         | 26.0 (24.4–28.6) | 26.5 (24.2–28.6)    | 0.80    |
| Acute coronary syndrome                    | 115 (49)         | 132 (35)            | 0.001   |
| History of myocardial infarction           | 68 (29)          | 93 (25)             | 0.28    |
| History of PCI                             | 100 (43)         | 192 (52)            | 0.03    |
| Creatinine serum level, mg/dl              | 1.0 (0.8–1.3)    | 0.9 (0.8–1.1)       | 0.14    |
| Malignancies                               | 22 (9)           | 39 (11)             | 0.65    |
| Parsonnet score                            | 11 (5–21)        | 9 (4–16)            | 0.02    |
| EuroSCORE                                  | 5 (3–8)          | 3 (2–6)             | <0.001  |
| Therapy at hospital discharge*             |                  |                     |         |
| Statins                                    | 223 (95)         | 356 (96)            | 0.64    |
| ACE inhibitors                             | 203 (86)         | 321 (86)            | 0.97    |
| Angiotensin II type<br>1 receptor blockers | 31 (13)          | 41 (11)             | 0.42    |
| Beta-blockers                              | 230 (98)         | 364 (98)            | 0.98    |

Values are mean  $\pm$  SD, n (%), or median (interquartile range). \*All patients received aspirin and clopidogrel at discharge.  
ACE = angiotensin-converting enzyme; PCI = percutaneous coronary intervention; TBL = true bifurcation lesion.

**Table 2. Angiographic and Procedural Characteristics**

|                                       | TBL<br>(n = 235) | No TBL<br>(n = 372) | p Value |
|---------------------------------------|------------------|---------------------|---------|
| Left ventricular ejection fraction, % | 57 (45-62)       | 59 (49-63)          | 0.01    |
| Vessel size of left main artery, mm   | 3.66 (3.36-4.03) | 3.83 (3.47-4.18)    | 0.001   |
| Coronary artery dominance             |                  |                     | 0.60    |
| Right                                 | 181 (77)         | 299 (80)            |         |
| Left                                  | 32 (14)          | 42 (11)             |         |
| Balanced                              | 22 (9)           | 31 (9)              |         |
| Three-vessel disease                  | 192 (76)         | 246 (70)            | <0.001  |
| Occluded right coronary artery        | 36 (15)          | 51 (14)             | 0.58    |
| Trifurcation morphology               | 36 (15)          | 20 (5)              | <0.001  |
| Stenting technique                    |                  |                     | <0.001  |
| Single stenting                       | 66 (28)          | 236 (63)            |         |
| T-stenting                            | 6 (3)            | 3 (1)               |         |
| Culotte-stenting                      | 163 (69)         | 133 (36)            |         |
| Kissing balloon technique             | 166 (71)         | 137 (37)            | <0.001  |
| Intra-aortic balloon pump             | 4 (2)            | 4 (1)               | 0.51    |
| Abciximab administration              | 16 (7)           | 43 (12)             | 0.05    |
| Bivalirudin administration            | 33 (14)          | 63 (17)             | 0.34    |

Values are n (%), or median (interquartile range).  
 TBL = true bifurcation lesion.

the entire coronary tree, there was also a correlation between the SYNTAX score group and the need for any additional intervention up to 3 years after the primary left main PCI (15.7% vs. 33.8% vs. 29.0%,  $p < 0.01$ ). Regarding the combined endpoint of death, MI, or stroke at 3 years, there was a better outcome for patients with lower SYNTAX scores (11.2% vs. 16.7% vs. 24.6% for patients with scores  $\leq 22$ , 23 to 32, and  $\geq 33$ , respectively,  $p = 0.006$ ). No interaction was observed between the SYNTAX score group and DES type used regarding adverse events.

In the multivariate analysis including relevant variables as potential confounders (Table 4), the significant predictors

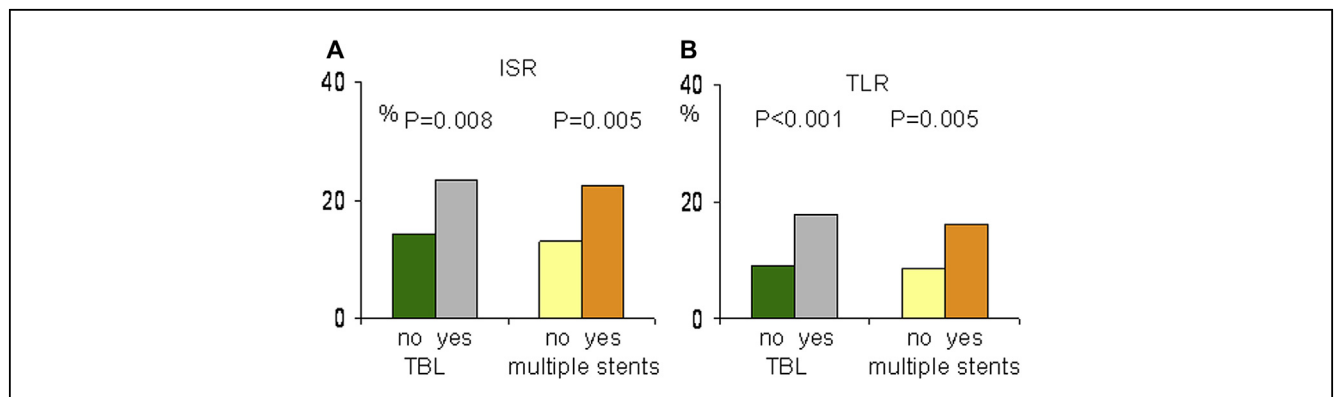
for death, MI, or TLR at 3 years were EuroSCORE, uLMCA vessel size, and TBL. The significant predictors for TLR up to 3 years were TBL, age, and EuroSCORE.

**Discussion**

Treatment of complex uLMCA with DES is safe and effective based on a complete long-term follow-up. The presence of TBL and need for multiple stents were independent predictors for ISR. The overall SYNTAX score was associated with the TLR rate and with the need for additional, non-left main interventions at 3 years. The only anatomic and procedural independent predictor for TLR was a TBL.

Our analysis has unique strengths: based on a randomized study in a large cohort of real-world patients with uLMCA disease and a detailed quantitative coronary angiography evaluation, this analysis focuses on anatomic and technical specifications not readily available in other left main trials. The complete 3-year follow-up combined with a high re-angiography rate of 87% enabled us to correlate the pre- and post-procedural data with the re-angiography data and the long-term outcome, and assess the different variables in the multivariate analyses. The highly experienced operators and the standardized pre-treatment of all patients, including clopidogrel loading with 600 mg followed by treatment for at least 12 months from the trial initialization in 2005, reduced potential bias through different operator skills and (21) medical therapies.

**Study limitations.** The secondary analysis regarding technical aspects has limitations. The different technical approaches were not randomized and might reflect the individual operator's preferences. Still, all operators performing the cases in this study had ample experience over many years in the 2 affiliated study centers, with similar interventional approaches on the basis of extensive case discussions during quality assurance conferences.



**Figure 3. Repeat Revascularization Rates Depending on the Presence of a TBL or the Number of Stents Used**

(A) shows in-stent restenosis (ISR), and (B) shows target lesion revascularization (TLR) rates, depending on the presence of a true bifurcation lesion (TBL) or the use of single or multiple stents.



**Table 3. Angiographic and Procedural Characteristics in Patients With and Without Kissing Balloon Technique**

|                               | Final Kissing<br>(n = 303) | No Final Kissing<br>(n = 304) | p Value |
|-------------------------------|----------------------------|-------------------------------|---------|
| True bifurcation lesion       | 166 (55)                   | 69 (23)                       | <0.001  |
| Angle <90°                    | 86 (28)                    | 84 (28)                       | 0.84    |
| Severe calcification          | 196 (65)                   | 221 (73)                      | 0.03    |
| Pre-dilation of both branches | 27 (9)                     | 12 (4)                        | 0.01    |
| Stenting technique            |                            |                               | <0.001  |
| Single stent                  | 28 (9)                     | 274 (90)                      |         |
| T-stenting                    | 4 (1)                      | 5 (2)                         |         |
| Culotte                       | 271 (89)                   | 25 (8)                        |         |

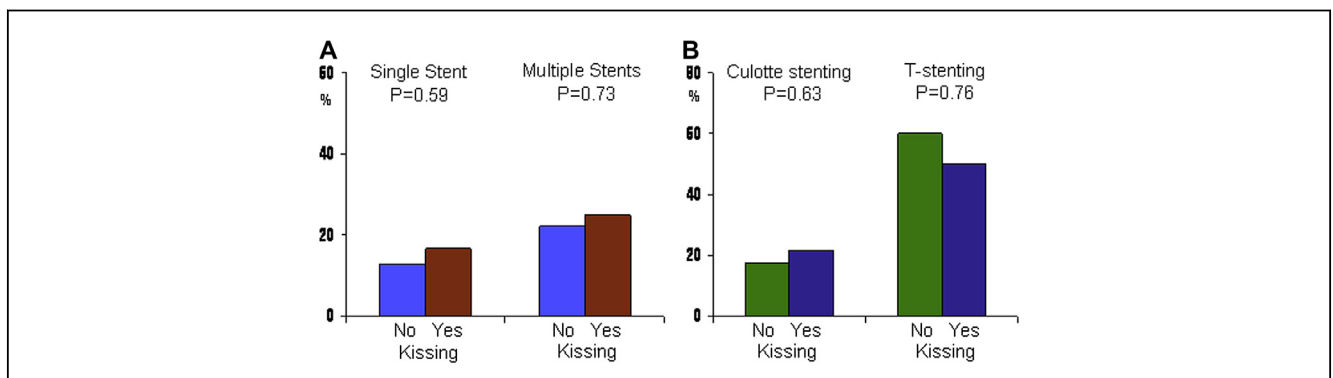
Values are n (%).  
PCI = percutaneous coronary intervention.

The 3-year cardiac mortality rate was 5.8% and the TLR rate was 12.5%, comparable to previous trial results (3,13,22). The somewhat higher TLR rate compared with the SYNTAX trial might be related to the high rate of angiographic follow-up, which always results in a higher rate of re-intervention. The complex left main anatomy, reflected by the high proportion of distal lesions (63%), including many trifurcation lesions (25%), and a high SYNTAX score, required challenging PCI strategies, often using multiple stents. The analysis of these PCI strategies led to interesting findings, directly transferable into everyday practice. Similar to the findings from the SYNTAX trial, where the left main subgroup treated with PCI had a better outcome compared with the overall PCI population and similar overall MACE rates as the LM patients treated with CABG, we found that DES implantation for uLMCA stenosis is safe and efficacious out to 3 years (3,13).

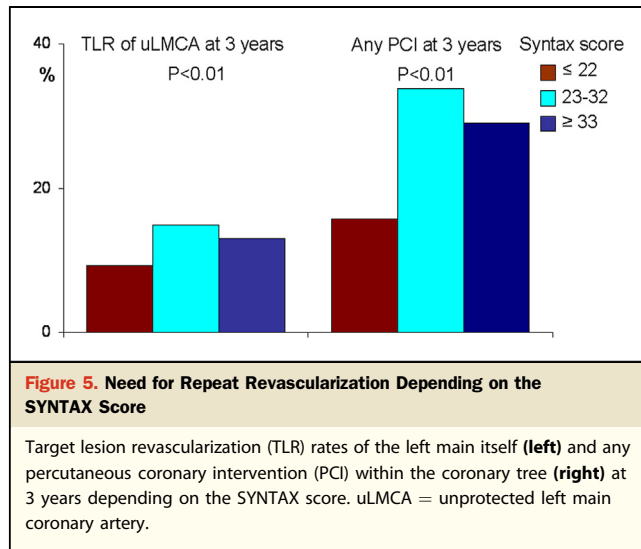
If a reasonable result was achieved with provisional DES implantation for the uLMCA, the long-term results were at least as good as with multiple stents, even in the presence of a TBL. These findings are similar to previous randomized trials evaluating non-uLMCA bifurcation lesions and favoring a 1-stent technique (23,24). The ongoing EXCEL

(Evaluation of Xience Prime or Xience V Versus CABG for Effectiveness of Left Main Revascularization) trial, comparing treatment of uLMCA with PCI using the Xience everolimus-eluting stent versus CABG surgery, is strongly recommending the provisional stenting technique unless the overstented side branch has a stenosis >70%, corresponding to our analysis (25). However, the strongest predictor of restenosis and subsequent TLR is the presence of a TBL. But even in the presence of a TBL, provisional DES implantation can result in quite low ISR and TLR rates. In our analysis, the only independent predictors of hard endpoints (death and MI) out to 3 years were EuroSCORE and uLMCA vessel size.

Neither the bifurcation angle nor the use of multiple stents had an influence on the long-term outcome if a reasonable result could be achieved during the intervention. With multiple stents, the culotte technique was mostly used, followed by T-stenting, thereby ensuring good DES coverage of the carina. The final kissing balloon dilation effectively reduced slow-flow, and therefore, creatine kinase and troponin elevations, similar to the CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) trial (26). Interestingly, we found no additional benefit of final kissing balloon regarding long-term outcome and 6-month restenosis rates in the presence of an unaffected side branch after 1-stent implantation, questioning the often performed “stent cell” dilation after provisional stenting. The inhibited neointimal proliferation with DES covering side branches led to minimal change of the side-branch stenosis, which was independent of final kissing, suggesting a protective effect by drug diffusion from the DES to the ostium of the side branch. In addition, kissing balloon did not affect the long-term angiographic and clinical outcome after multiple stent implantations in the presence of a good angiographic result after the last stent implantation. Similarly, the NORDIC-BALTIC Bifurcation Study III (27) and Brueck et al. (28) also found no improvement of the immediate or mid-term outcome

**Figure 4. Interventional Approach and Incidence of ISR**

In-stent restenosis (ISR) rates with and without kissing balloon dilation depending on number of stents used (A) or stenting technique (B).



compared with sequential dilations for non-uLMCA bifurcation lesions. On the other hand, by keeping stent struts open, final kissing might allow further access to new lesions during subsequent interventions.

The overall burden of coronary artery disease, reflected by the SYNTAX score, had a clear correlation with the need of additional PCI within the coronary tree, but also on the TLR rate and the clinical endpoint of the left main itself. This might be explained with the higher prevalence of TBL and diabetes mellitus in patients with higher SYNTAX scores, which are predictors of restenosis and clinical events. The increase of the incidence of hard endpoints with higher SYNTAX scores supports the current European recommendations regarding a restrictive approach for an interventional treatment of uLMCA in patients with SYNTAX scores >32. In concert with the recently published SYNTAX 3 Years, SYNTAX 5 Years, and Freedom results

(22,29,30), not the presence of a uLMCA stenosis, but diabetes mellitus and the SYNTAX score should be weighted higher regarding the decision for an interventional or a surgical treatment approach (30).

The DK CRUSH-III (Double-Kissing Crush better than Culotte Technique for left main bifurcation stenting) trial, presented recently at the American College of Cardiology meeting in March 2013, suggested a lower TLR rate with the crush technique followed by double-kissing balloon dilation. Still, we do not have enough information regarding the direct post-procedural results after the compared techniques, especially regarding the steps used in patients treated with the culotte technique (31). A detailed analysis similar to ours would help understand the very large differences in TLR observed in this trial. Obviously, an optimal interventional result is associated with good outcomes, as shown by both studies. In our study though, culotte stenting was performed more often and showed better results compared with T-stenting, with the crush technique being performed too rarely to allow reasonable comparisons.

The EXCEL trial (25) comparing PCI versus CABG in a specific population with uLMCA disease is expected to be completed in 2016. Systematic re-angiography is not required, so specific angiographic analyses, comparable to ours, will be limited. The results of the SYNTAX trial in the subgroup of patients with isolated left main disease already encourage cardiologists to pursue an often requested interventional approach.

### Conclusions

The good results and the low incidence of stent thrombosis in this and other studies (32), support the long-term safety of DES in uLMCA lesions. However, little scientific data

| Variable   | Model for MACE at 3 Yrs |         | Model for Death or MI at 3 Yrs |         | Model for TLR at 3 Yrs |         |
|--|-------------------------|---------|--------------------------------|---------|------------------------|---------|
|  | Hazard Ratio (95% CI)   | p Value | Hazard Ratio (95% CI)          | p Value | Hazard Ratio (95% CI)  | p Value |
| True bifurcation lesion                                | 1.66 (1.11-2.48)        | 0.01    | 1.23 (0.72-2.07)               | 0.448   | 2.12 (1.19-3.77)       | 0.011   |
| Age (per 10-yr increase)                               | 0.90 (0.66-1.22)        | 0.487   | 1.21 (0.81-1.81)               | 0.342   | 0.57 (0.37-0.86)       | 0.008   |
| Acute coronary syndrome                                | 1.01 (0.67-1.51)        | 0.962   | 1.03 (0.61-1.76)               | 0.909   | 0.86 (0.48-1.52)       | 0.593   |
| History of PCI   | 0.99 (0.68-1.44)        | 0.952   | 0.87 (0.53-1.44)               | 0.591   | 1.06 (0.63-1.80)       | 0.820   |
| EuroSCORE (per 1-U increase)                           | 1.69 (1.14-2.51)        | 0.009   | 1.73 (1.07-2.80)               | 0.026   | 2.18 (1.21-3.93)       | 0.010   |
| Left ventricular ejection fraction (per 10% reduction) | 0.98 (0.78-1.22)        | 0.860   | 0.82 (0.63-1.07)               | 0.138   | 1.39 (0.97-2.00)       | 0.075   |
| 3-vessel disease                                       | 0.98 (0.64-1.51)        | 0.943   | 1.28 (0.69-2.34)               | 0.433   | 0.89 (0.49-1.59)       | 0.683   |
| Vessel size of the left main artery (per mm decrease)  | 1.42 (1.00-2.01)        | 0.049   | 1.57 (1.01-2.45)               | 0.044   | 1.17 (0.70-1.95)       | 0.560   |
| Trifurcation lesion                                    | 1.04 (0.58-1.87)        | 0.890   | 1.20 (0.56-2.56)               | 0.632   | 0.77 (0.33-1.84)       | 0.564   |
| Multiple stents  | 1.54 (0.82-2.89)        | 0.184   | 1.13 (0.51-2.52)               | 0.757   | 1.64 (0.66-4.10)       | 0.288   |
| Final kissing balloon dilation                         | 0.95 (0.51-1.77)        | 0.867   | 1.03 (0.47-2.25)               | 0.938   | 1.21 (0.49-2.99)       | 0.688   |

CI = confidence interval; MACE = major adverse cardiac events (death, myocardial infarction, or target lesion revascularization); MI = myocardial infarction; PCI = percutaneous coronary intervention; TLR = target lesion revascularization.

are available to guide the approach for this high-risk intervention. Our analysis may provide guidance for the different strategies for this challenging intervention.

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**Key Words:** left main ■ stenting technique ■ SYNTAX score.