Impact of Final Kissing Balloon and of Imaging on Patients Treated on Unprotected Left Main Coronary Artery With Thin-Strut Stents (From the RAIN-CARDIOGROUP VII Study)

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Few data are available about the impact on outcomes of procedural strategies for percutaneous coronary intervention with thin-struts stents on unprotected left main (ULM): 792 patients with an ULM stenosis treated with percutaneous coronary intervention with thin-strut stents were enrolled in the present multicenter registry. Target lesion revascularization (TLR) was the primary end point. MACE (a composite of all-cause death, myocardial infarction, TLR, and stent thrombosis) and its single components, along with target vessel revascularization were the secondary end points. Subgroup analyses were performed according to complex versus noncomplex bifurcation lesions. After 16 months, 5.5% of patients experienced a TLR. At multivariate analysis, provisional stenting (odds ratio [OR] 0.46: 0.85 to 0.23, p = 0.006), use of imaging (OR 0.45: 0.23 to 0.98, p = 0.003) and final kissing balloon (FKB) (OR 0.41: 0.83 to 0.21, p = 0.001) reduced risk of TLR. FKB reduced risk of overall TLR only for 2 stents-strategy (6.2% vs 32.4%, p <0.05), but not for provisional strategy (3.8% vs 3.7%, p = 0.67). Intracoronary imaging reduced risk of overall TLR both for provisional (2.2% vs 5.4%) and for 2-stents strategy (7.3% vs 14.1% p <0.05 for both, all confidence interval 95%). In conclusion, TLR for ULM patients treated with thin-strut stents is infrequent. Provisional stenting was noninferior compared with 2-stents apart from complex lesions. Benefit from intracoronary imaging is consistent for different strategies, whereas that from FKB persists only for 2-stents. **(Am J Cardiol 2019;123:1610−1619)**

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The optimization of permanent coronary stents, along with the development of ancillary technologies like intracoronary imaging, allowed percutaneous coronary intervention (PCI) to gain a role over surgical revascularization for patients with unprotected left main (ULM) coronary artery disease.[1−6] In particular, the continued reduction of stent struts thickness is linked to a decreased flow disturbance in coronary vessels, with a consequent reduction of activation of atherosclerotic pathways[7,8] and of thrombotic sequelae, translating clinically in lower rates of revascularization and stent thrombosis.[4,9] In coronary stents with thickness of struts inferior to 81 μm, only the Synergy (Boston) and the XIENCE (Abbott) have been tested in patients with ULM.[10,11] Other very thin strut stent models have been recently compared in the BIORESORT trail, with satisfactory results, but patients with ULM (2%) and bifurcation lesions (35%), were under-represented.[12] In another large series,[13] final kissing balloon (FKB) was performed in about 30% of patients, and intracoronary imaging in 70%, however without evaluation of their impact on the risk of restenosis. We designed the RAIN study (veRy thin stents for patients with left mAIn or bifurcatioN in real life) to appraise the incidence of target lesion revascularization (TLR) in patients with ULM in real life, and potential strategies to reduce subsequent adverse events.

Methods

The RAIN study is a multicenter study (see Appendix web only for sites of enrollement, NCT03622203) that recruited patients prospectively from June 2015 to January 2017.

All consecutive patients presenting with a critical lesion of an ULM (see supplementary appendix for definitions) in our Centers were included, if treated with one of the following stents:

- Platinum-chromium stent coated with a permanent polymer loading everolimus with strut thickness of 81 μm for diameters from 2.25 to 3.5 mm (Promus Element, Boston Scientific);
- Cobalt-chromium stent coated with a permanent polymer loading everolimus with a strut thickness of 80 μm (Xience Alpine, Abbott);
- Cobalt-chromium stent coated with a biodegradable polymer abluminal coating loading sirolimus with strut thickness of 80 μm (Ultimaster, Terumo Corporation);
- Platinum-chromium stent coated with a biodegradable polymer loading everolimus with strut thickness of 74 μm for diameters in the range 2.25 to 2.75 mm, 79 μm for diameters in the range 3.00 to 3.50 mm, and 81 μm for diameter equal to 4.0 mm (Synergy, Boston Scientific);
- Platinum-chromium stent coated with a biodegradable polymer loading zotarolimus with a strut thickness of 74 μm for diameters $\leq 2 \cdot 5$ mm, (2) 79 μm for diameters in the range 3.0 to 3.50 mm, and (3) 81 μm for diameter equal to 4.0 mm (Resolute Onyx, Medtronic).

Data about cardiovascular risk factors, clinical presentation, angiographic features, use of IntraVascular UltraSound (IVUS), optical coherence tomography (OCT), and fractional flow reserve were derived from electronic charts at each Center on prespecified forms and recorded online (http://www.cardiogroup.org/RAIN/index.php?cat=home). IVUS or OCT was applied before stent implantation to assess the severity of the stenosis and side branch involvement, and after stent implantation to evaluate dissection, and to drive postdilatation. The decision of applying postdilatation, FKB, use of imaging and choice of stenting strategies (provisional vs 2-stents, defined as "as treated"), were left to the physician. Follow up was performed through dedicated clinical assessment, telephonic follow-up or formal query to primary care physicians. Rate of target lesion revascularization (TLR, defined as critical restenosis [angiographic or with instrumental imaging or with functional evaluation] according to operators' choice) was the primary end point. MACE (a composite endpoint of all cause death, myocardial infarction, TLR and stent thrombosis) and its single components, along with target vessel revascularization (TVR) were the secondary end points. The analysis was performed according to stenting strategy (provisional vs 2-stents), to use of FKB and imaging. Subgroup analysis was performed according to complex vs noncomplex bifurcation lesions, as defined in the DEFINITION trial.[14] When available, lesions were classified according to MADS classification.[15,16] The study was implemented with subanalysis for the primary and secondary outcomes according to the kind of drug eluted by drug eluting stents (DES) (everolimus vs zotarolimus vs sirolimus), the kind of polymer (permanent vs biodegradable) and length of dual antiplatelet therapy (DAPT) (more or less than 12 months).

The recent DELTA registry observed a rate of TLR of 7.8% at 17 months.[9] According to Peduzzi et al,[17] at least 500 patients were needed, to test at least 5 independent variables in a multivariate model (diabetes mellitus, use of imaging, FKB, postdilatation, and provisional stenting) with TLR as dependent variable.

Categorical variables were reported as count and percentages, continuous variables as mean and standard deviations, or interquartile range. The hypothesis of normal distribution was verified by Kolmogorov-Smirnoff test. The *t* Test was used to assess differences between parametric continuous variables and Man-Whitney U-test for nonparametric variables, the chi-square test for categorical variables, and Fisher exact test for 2×2 tables. Cox multivariate analysis was performed to assess the independent predictors of TLR. Survival analysis was performed for provisional versus 2-stents strategy, FKB, and use of imaging. A 2-sided p value <0.05 was considered statistically significant. All analyses were performed with SPSS 21.0 (IBM, Armonk, New York).

Results

After 16 (12 to 22) months, 44 (5.5%) of 792 patients experienced a TLR. Patients with TLR did not differ from the others regarding burden of cardiovascular risk factors and admission diagnosis (see Table 1).

Table 1
Baseline features of included patients

Variable	Target lesion revascularization		p Value
	YES n = 44 (5.6%)	NO n = 748 (94.4%)	
Age (years)	70.82 ± 9	70.76 ± 10.6	0.974
Women	8 (18.2%)	164 (21.9%)	0.733
Hypertension	38 (86.4%)	568 (77.1%)	0.308
Hyperlipidemia	25 (56.8%)	463 (62.8%)	0.317
Noninsulin-treated diabetes mellitus	9 (20.5%)	186 (25.2%)	0.174
Insulin-treated diabetes mellitus	2 (4.7%)	50 (7.1%)	0.796
Previous smoker	16 (36.4%)	214 (29.2%)	0.753
Current smoker	5 (11.4%)	106 (14.5%)	0.753
Renal disease (estimated glomerular filtration rate <60 ml/min/m^2)	11 (25%)	154 (20.5%)	0.889
Previous percutaneous coronary intervention	15 (34.1%)	255 (34.7%)	0.764
Previous coronary artery bypass graft	6 (13.6%)	81 (11.1%)	0.819
Previous myocardial infarction	9 (20.5%)	233 (31.9%)	0.224
Indication for percutaneous coronary intervention:			0.211
ST-elevation myocardial infarction	0	98 (13.1%)	
Non ST-elevation myocardial infarction	14 (32.1%)	167 (22.3%)	
Unstable angina	10 (23.3%)	110 (14.7%)	
Stable angina	16 (36%)	325 (40%)	
Planned angiographic follow up	4 (7.5%)	48 (6.4%)	

Most of TLR patients presented complex lesions (32% vs 18%, p = 0.817) involving mid shaft or of distal left main (17.9% vs 18.5%, and 69.2% vs 65.8%, p = 0.939). Provisional strategy was less frequently used in patients with TLR (43.9% vs 74.9%, p = 0.001), as use of imaging, though the last one did not reach statistical significance (29.5% vs 42.1% for IVUS, p = 0.07, see Table 2 and Table 3).

At multivariate analysis (see Figure 1; see supplementary appendix, supplementary Table 1), provisional stenting (odds ratio [OR] 0.46: 0.23 to 0.85, p = 0.006), use of imaging (OR 0.45: 0.23 to 0.98, p = 0.003), along with FKB (OR 0.41: 0.21 to 0.83, p = 0.001) reduced risk of TLR. Independently from the strategy, LM was the most frequent site of restenosis, followed by ostial or proximal left circumflex and by ostial or proximal left anterior descending coronary artery segments (see Figure 2).

When evaluating provisional vs 2-stents strategies, the provisional strategy reduced risk of TLR (4.0 vs 11.4%, p <0.001, confirmed also by the survival analysis) and TVR. This result was significant for simple (TLR: 2.3% vs 8.2%, p = 0.003; TVR: 2.3% vs 9.8%, p <0.001; stent thrombosis (ST): 1.4% vs 3.6% p 0.003), but not for complex lesions (TLR: 11.0% vs 9.0%, p = 0.56; see Table 4 and Figures 3 to 5).

At survival analysis, FKB and use of imaging reduced risk of TLR (see Figure 5, respectively p 0.038 and p = 0.002). When stratified for provisional *vs.* 2-stenting strategy:

- FKB reduced risk of overall TLR only for a 2 stent-strategy (6.2% vs 32.4%, p <0.05), mainly for restenosis within the LM (2.5% vs 20.0%, p <0.005) while this benefit disappeared for provisional strategy (3.8% vs 3.7%, p = 0.67), see Figure 6.
- Use of imaging reduced risk of overall TLR both for provisional (2.2% vs 5.4%, p <0.05) and for 2 stents-strategy (7.3% vs 14.1%, p <0.05), again mainly driven by restenosis within the ULM, see Figure 7.

Results of the subanalysis regarding TLR occurrence according to the drug eluted by the DES, the kind of polymer and the length of DAPT are reported in supplementary appendix (see also supplementary Figure 1 and 2). The impact of FKB and imaging on definite ST occurrence is reported as supplementary results as well.

Discussion

This is one of the largest registries of patients treated with thin-strut stents on ULM with highly documented details about procedural features. The main results of the present paper are:(1) TLR is an infrequent event at mid-term follow-up for ULM treated with PCI using thin-strut last generation stents; (2) a provisional strategy offers satisfactory results for patients without complex lesions; (3) the use of intracoronary imaging improves outcomes, irrespective of the stenting strategy; (4) FKB remains of benefit only for patients treated with a 2 stents strategy; (5) TLR and MACE occurrence was not significantly influenced by the kind of polymer (biodegradable vs permanent), neither by the drug eluted by the DES.

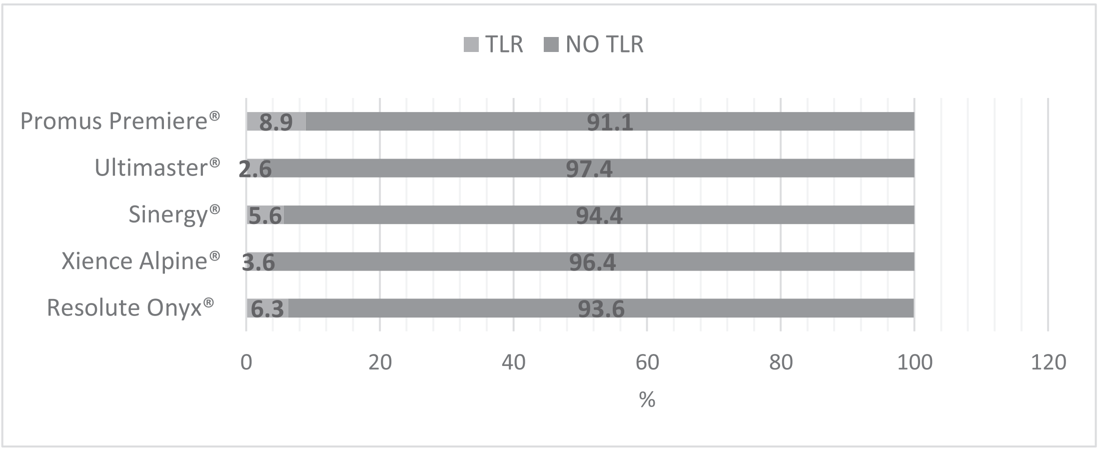
In patients who underwent PCI for ULM with thin-strut stents, TLR represents an infrequent event at mid-term follow-up, with better results than those offered by first generation DESs. Moreover, LM was the most frequent site of restenosis rather than the ostial left anterior descending or Cx. Our results are the clinical counterpart of the autopsy study of Mori et al, showing that most of the area of malapposition and uncovered struts occurred in the LM.[18] Compared with other studies, in the NOBLE trial rates of TLR were about 11% at 5 years,[19] whereas in the EXCEL (Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease) they were

Table 2
Interventional features

Variable	Target lesion revascularization		p Value
	YES n = 44 (5.6%)	NO n = 748 (94.4%)	
Radial access	18 (40.9%)	419 (56.1%)	0.310
Site of lesion:			0.939
Ostial left main	5 (12.8%)	104 (15.8%)	
Mid shaft of left main	7 (17.9%)	122 (18.5%)	
Distal left main	27 (69.2%)	434 (65.8%)	
Type c lesion	22 (52.4%)	259 (41.4%)	0.264
Severe calcification	7 (21.2%)	110 (19%)	0.846
Diffuse disease	15 (40.5%)	285 (40%)	0.715
Medina class			0.113
0,0,1	0	1 (0.1%)	
0,1,0	0	4 (0.5%)	
0,1,1	3 (6.8%)	7 (0.9%)	
1,0,0	1 (2.3%)	45 (6%)	
1,0,1	0	23 (3.1%)	
1,1,0	4 (9.1%)	200 (26.6%)	
1,1,1	12 (27.3%)	149 (19.8%)	
Bifurcation with side branch disease	16 (36.4%)	227 (30.2%)	0.079
Angle <45̄	0	35 (4.4%)	0.224
Length of side branch lesion >10 mm	7 (16%)	101 (13%)	0.962
Complex lesions according to DEFINITION	14 (32%)	142 (18%)	0.817
Provisional strategy	18 (43.9%)	521 (74.9%)	0.001
2 stents technique strategy	19 (43.6%)	148 (21.3%)	0.001
Culotte	3 (6.8%)	12 (1.6%)	
Mini crush	1 (2.3%)	24 (3.2%)	
Crush	2 (4.5%)	2 (0.3%)	
DK-crush	0	1 (0.1%)	
T stent	5 (11.4%)	50 (6.7%)	
TAP stent	3 (6.8%)	28 (3.7%)	
V stenting	4 (9.1%)	1 (0.1%)	
MADS classification:			0.01
M	0	0	
A	29 (65%)	601 (81%)	
D	4 (9.1%)	1 (0.1%)	
S	3 (7%)	27 (3.6%)	
Use of imaging:			0.07
IVUS	13 (29.5%)	314 (42.1%)	
OCT	0	10 (1.3%)	
Predilatation	40 (91%)	670 (89.5%)	0.96
Conventional balloon	38 (86%)	640 (85.5%)	
AngioSculpt	2 (4.6%)	16 (2.1%)	
Scoring Balloon	0	14 (1.7%)	
Stent on main branch:			0.680
Promus Premiere®	10 (22.7%)	102 (13.6%)	
Xience Alpine®	6 (13.6%)	162 (21.6%)	
Sinergy®	8 (18.2%)	136 (8.1%)	
Ultimaster®	2 (4.5%)	75 (10%)	
Resolute Onyx®	18 (40.9%)	269 (35.7%)	
Main branch diameter (mm)	3.2 (2.9-3.8)	3.5 (3.5−4)	0.345
Main branch Length (mm)	16.57 ± 6.60	18.48 ± 7.18	0.503
Stent on SB:			0.498
Promus Premiere®	11 (5.0%)	1 (6.2%)	
Xience Alpine®	34 (15.6%)	5 (31.2%)	
Sinergy®	31 (14.2%)	0	
Ultimaster®	12 (5.5%)	1 (6.2%)	
Resolute Onyx® on SB	64 (29.4%)	7 (43.8%)	
Side branch diameter (mm)	3.17 ± 1.49	2.86 ± 0.43	0.44
Side branch length (mm)	18.5 ± 7.2	16.6 ± 6.6	0.50
Postdilatation	33 (82.5%)	536 (84.5%)	0.730
Final kissing balloon	19 (46.3%)	410 (57.6%)	0.157

Table 3
Rates of target lesion revascularization according to stent type

Kind of stent	Target lesion revascularization		p Value
	YES n = 44 (5.6%)	NO n = 748 (94.4%)	
Resolute Onyx®	18 (6.3%)	269 (93.6%)	0.68
Xience Alpine®	6 (3.6%)	162 (96.4%)	
Sinergy®	8 (5.6%)	136 (94.4%)	
Ultimaster®	2 (2.6%)	75 (97.4%)	
Promus Premiere®	10 (8.9%)	102 (91.1%)	



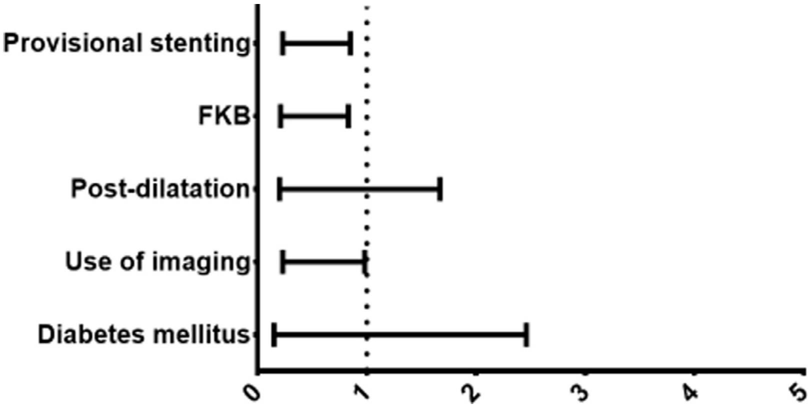


Figure 1. Independent predictors of target lesion revascularization at follow up.
FKB = final kissing balloon.

9.5% after 3 years.[11] In a recent study[10] enrolling patients with ULM treated with thin-strut stents, target vessel failure (a composite of TVR, target vessel myocardial infacrtion, and cardiac death) ranged from 13.2% to 16.7% at 3 years. The lower rate of TLR reported in our study compared with EXCEL could be due to a shorter follow-up (16 months vs 36 months), although our population was significantly older and with higher prevalence of hypertension, chronic kidney disease, previous PCI and acute coronary syndrome as admission diagnosis. These high-risk features could also account for the relevant rate of ST. Data from randomized conttrolled trials (RCT) as the EXCEL[11] and the NOBLE[19] report an incidence of definite ST ranging from 0.6% to 1%, whereas Chen et al[20] described a rate of 0.8% and 0.4% of definite ST in patients treated with provisional stenting (PS) and Double-Kissing crush respectively. In a recent meta-analysis including both RCT and observational trials, the incidence of ST was 2.13%.[21] However, the suboptimal results about freedom from ST shown in the present analysis could also reflect the not extensive use of intracoronary imaging and the effect of confounders as the adherence to DAPT in a real-life cohort. Interestingly, use of imaging reduced

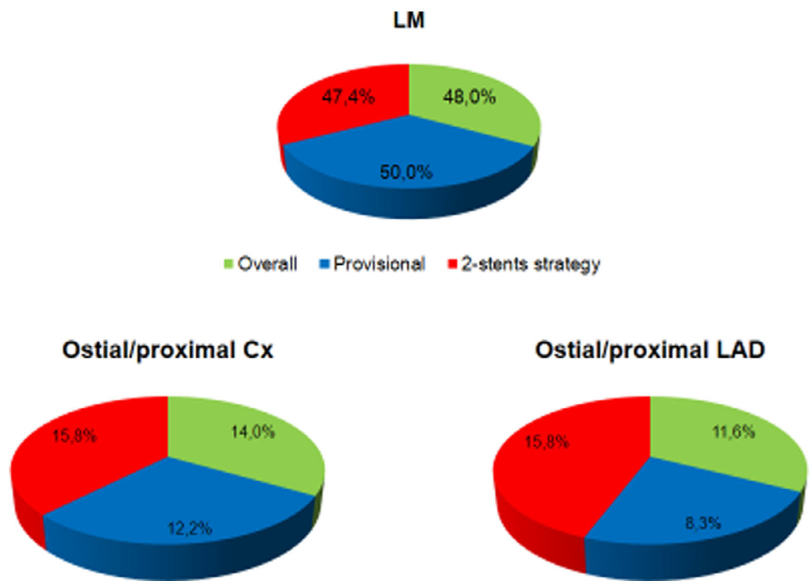


Figure 2. Site of restenosis according to stenting strategy. C =: circumflex artery; LAD = left anterior descending artery; LM = left main artery.

Table 4
Mid-term outcome according to stent strategy

Variable	Provisional strategy (n = 632)	2 stents technique strategy (n = 167)	p Value
Major adverse cardiovascular events	109 (17.3%)	39 (23.4%)	0.078
All cause death	66 (11.4%)	13 (8.1%)	0.238
Myocardial infarction	35 (5.6%)	9 (5.4%)	0.292
Target vessel revascularization	32 (5.1%)	23 (13.8%)	0.0001
Target lesion revascularization	25 (4%)	19 (11.4%)	0.0001
*Stent thrombosis**	12 (1.9%)	10 (6%)	0.005
Acute	0	2 (20%)	0.245
Subacute	3 (27.3%)	3 (30%)	
Late	2 (18.2%)	3 (30%)	
Very late	6 (54.5%)	2 (20%)	
Definite stent thrombosis	9 (1.8%)	8 (5.2%)	0.067
Probable stent thrombosis	1 (0.2%)	1 (0.6%)	
Possible stent thrombosis	2 (0.4%)	1 (0.6%)	

* Not all ST were classified according to occurrence due to lack of data.

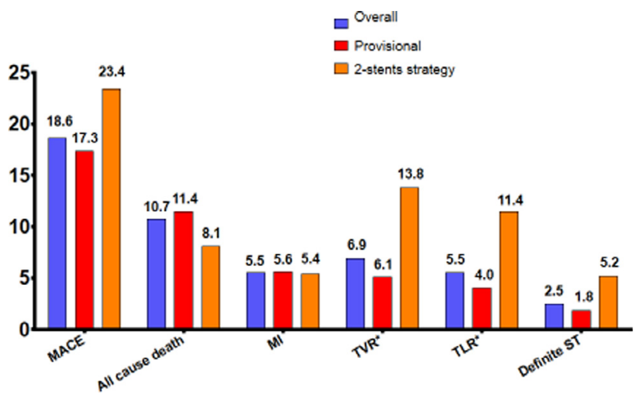


Figure 3. Long-term outcomes according to stenting strategy after 16 (12 to 22) months. MACE = major adverse cardiovascular events; MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization; ST = stent thrombosis.

risk of TLR and ST consistently for patients treated with provisional and 2-stents strategy, whereas FKB was beneficial only for the double stenting strategy, resulting in a significant reduction of TLR and a trend for reduction of definite ST.

The benefit of a provisional strategy was confirmed, apart from complex lesions in which, however, one stent strategy was not inferior to 2-stents. These results are in contrast with those of recent RCTs: actually, the DK-CRUSH V[20] reported a lower rate of target lesion failure for patients treated with DK crush on true distal LM lesions compared with provisional stenting. In our registry, less than 70% of patients had a disease of distal ULM, and most of patients underwent a T stent or a culotte technique, which were proved inferior to DK crush in the recent DKCRUSH III.[22] In our registry, the benefit of provisional stenting disappeared in complex lesions, stressing the

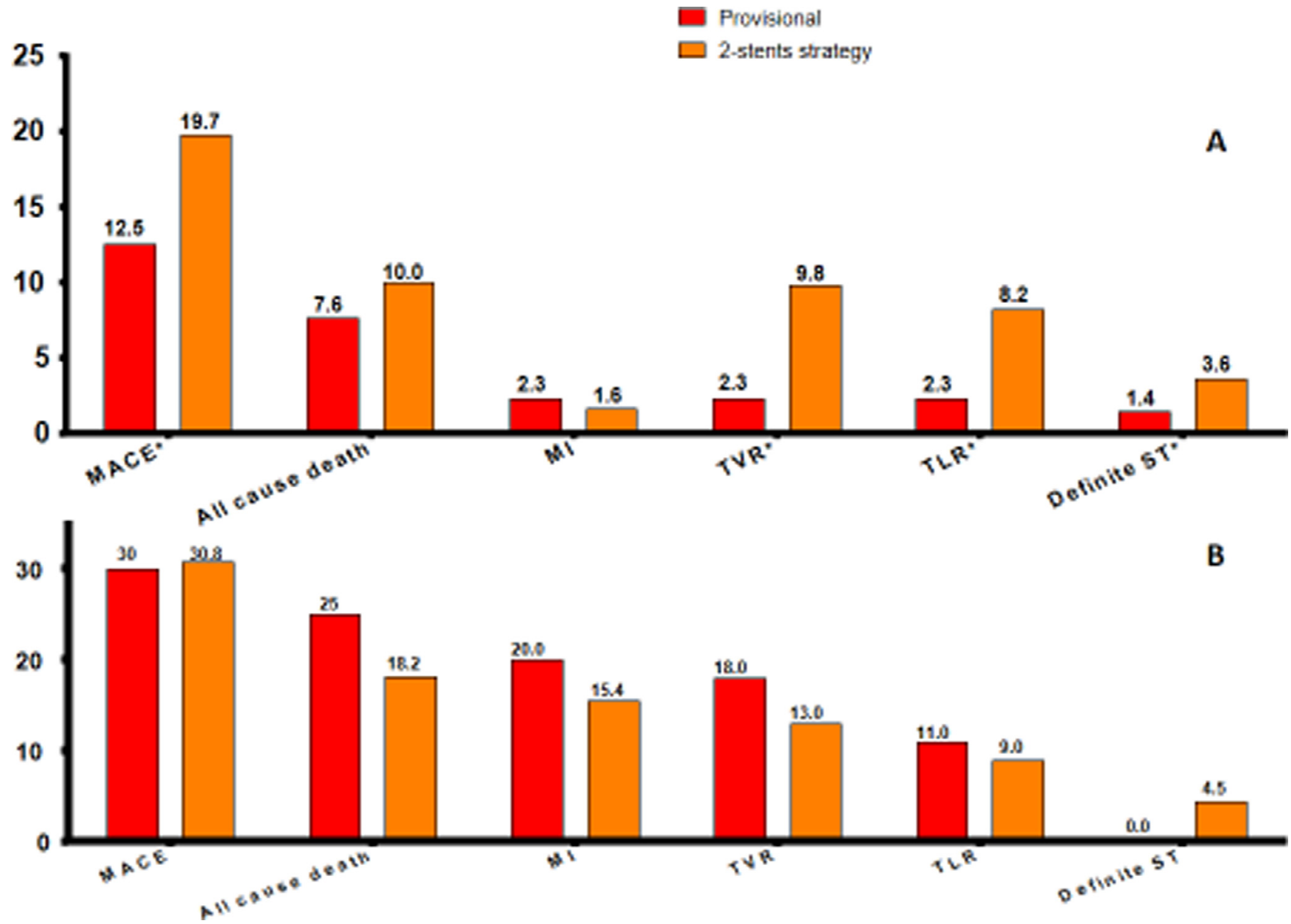


Figure 4. Long term outcomes according to stenting strategy after 16 (12 to 22) months for simple lesions (panel A) and complex (panel B). MACE = major adverse cardiovascular events; MI = myocardial infarction; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization.

concept that a tailored approach should be reserved to these patients. Moreover, the DEFINITION study[14] demonstrated that for complex ULM lesions double stenting was associated with improved clinical outcomes compared with a provisional strategy. The ongoing *European Bifurcation Club Left Main* (EBC MAIN)[23] randomized trial will compare one versus 2-stents (DK crush or Culotte) and will provide more definitive information on the optimal treatment of LM bifurcation lesions.

The importance of FKB in reducing restenosis after double stenting was previously stressed by several studies.[24,25] For patients with provisional stenting, the long-term effect of a jailed strut remains unclear, although opening the jailed strut and relieving the side branch ostium might decrease the shear stress at this site.[26] With a provisional strategy, FKB induces an expansion of the main stented segment which commonly leads to a loss of the circular proximal diameter and toward an oblong or elliptical shape of the side branch with an increase in local shear stress as suggested by in vitro study.[27] Recently Kumar et al reported that high coronary shear stress in proximal segments of atherosclerotic lesions predicts occurrence of myocardial infarction.[28] This could explain the absence of clinical benefit of FKB with this strategy, and it could be speculated that this consequence is even more relevant for thin-strut stents, which may be more prone to elliptical deformation. However, since there are no explicit data to indicate a direct correlation between asymmetry in metal stent and adverse outcomes, these observations should be considered as hypothesis generating.

Our paper has several limitations. First, it is not an RCT, consequently the results have to be interpreted with caution. Second, data about complex lesions and on the double stenting strategy were limited to a smaller sample size of patients than the overall group, and data about potential benefit of proximal optimization technique (POT) were not collected. Despite intracoronary imaging globally resulted to be a protective strategy against TLR occurrence at follow-up, only ten patients underwent OCT use and none of these experienced a TLR, so that additional comparison distinguishing imaging type (IVUS vs OCT) could not be performed. Moreover, data about length of DAPT showed a selection bias toward high-risk patients discharge with short DAPT, probably due to noncardiac co-morbidity like cancer requiring surgery. Finally, we acknowledge that data about fractional flow reserve-guided procedures and drug eluting balloons were not consistently available for the majority of patients.

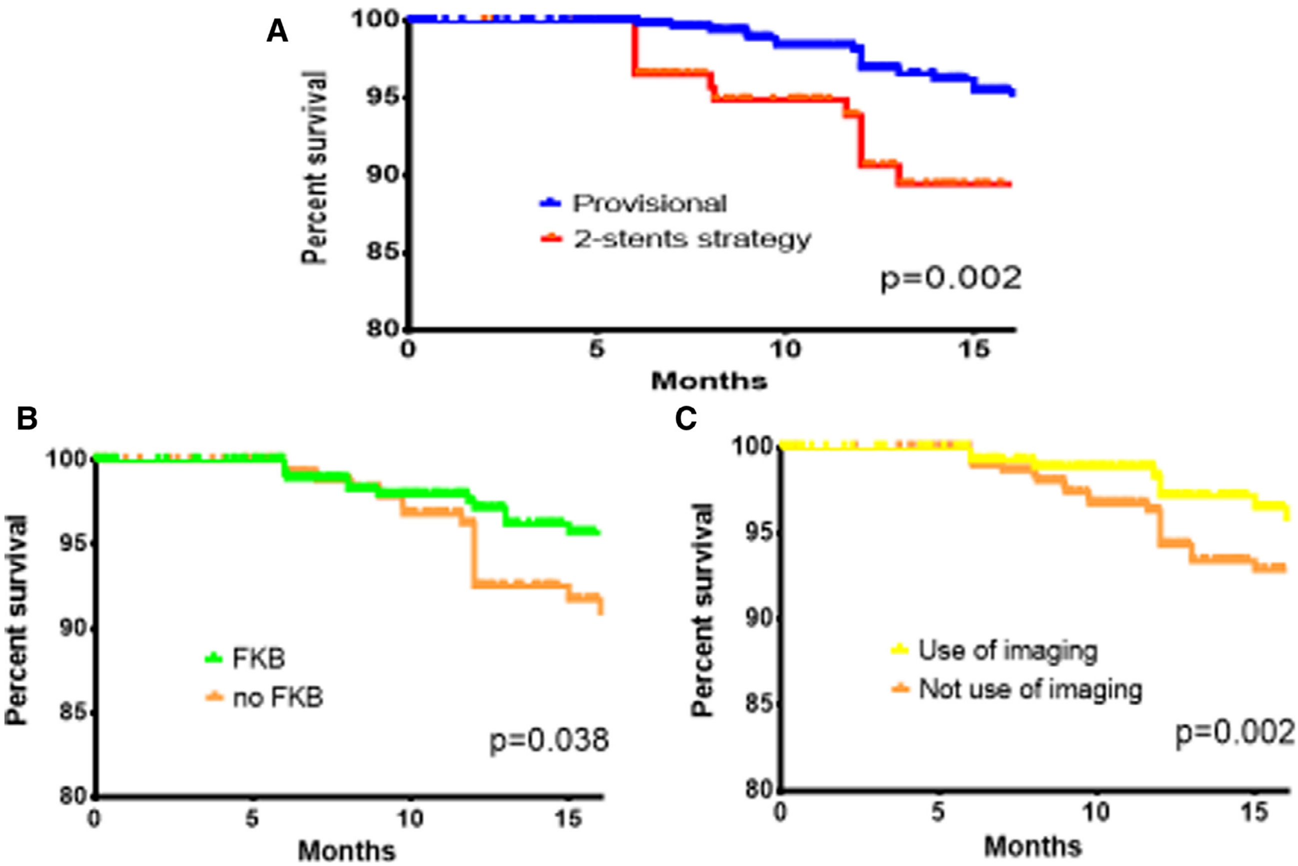


Figure 5. Freedom from TLR at follow up according to stenting strategy (panel A), final kissing balloon (panel B) and use of imaging (panel C). FKB = final kissing balloon.

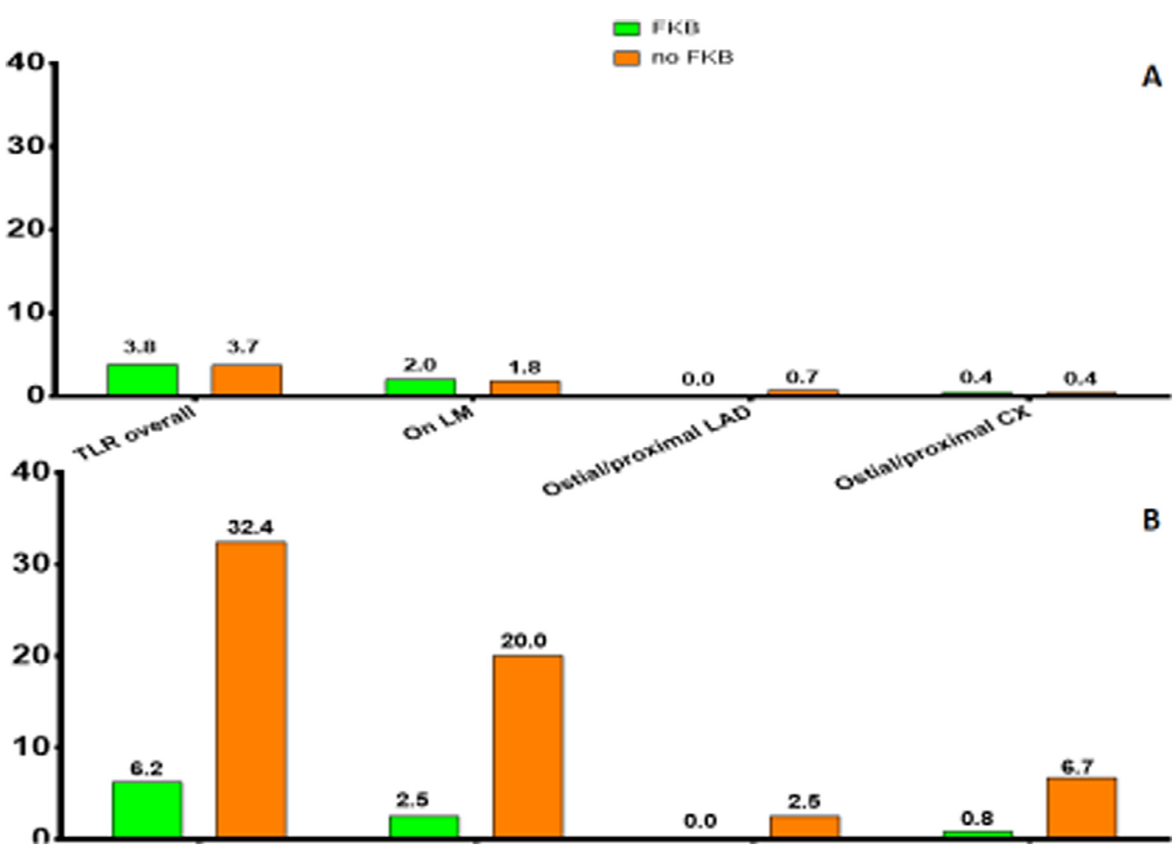


Figure 6. Site of restenosis according to use of final kissing balloon. Panel A: provisional stenting; Panel B: 2-stent strategy. Cx = circumflex artery; FKB = final kissing ballon; LAD = left anterior desceding artery; LM = left main artery; TLR = target lesion revascularization. *Significance: p < 0.005 for TLR overall and TLR on LM for 2-stent strategy*

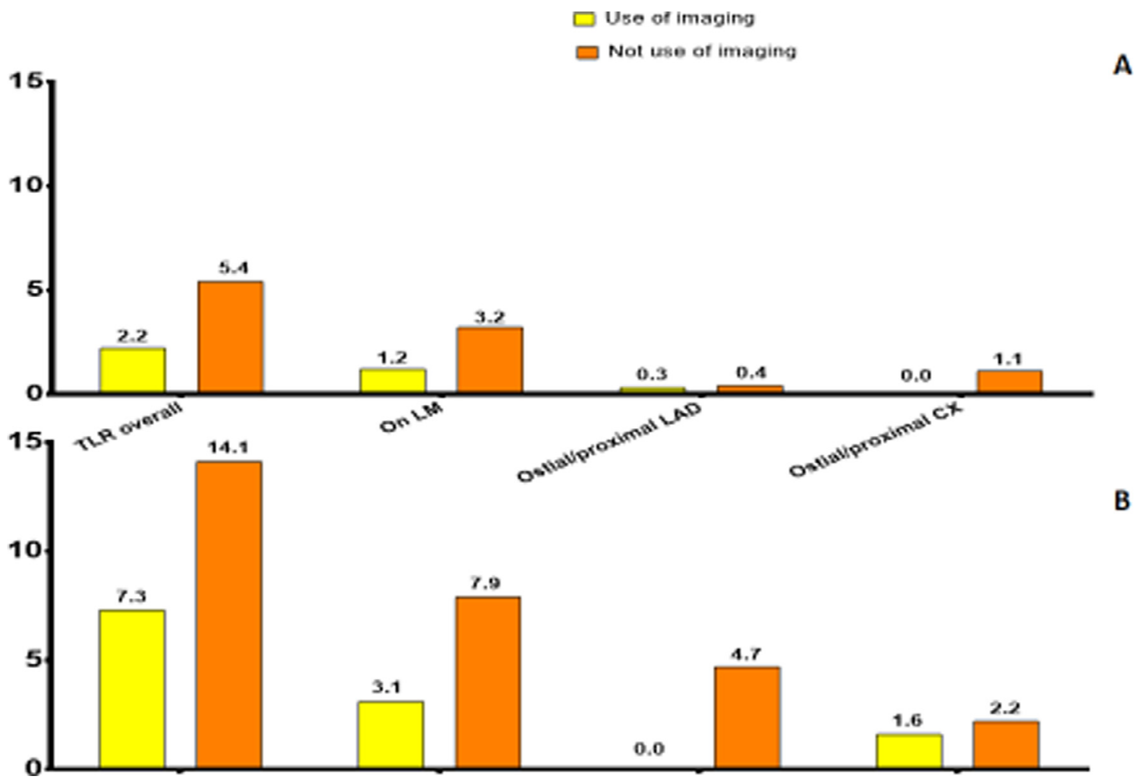


Figure 7. Site of restenosis according to use of imaging. Panel A: provisional stenting; Panel B: 2-stents strategy. Cx = circumflex artery; FKB = final kissing balloon; LAD = left anterior descending artery; LM = left main artery; TLR = target lesion revascularization. *Significance: p<0.005 for TLR overall and TLR on LM for both provisional stenting and 2-stents strategy.*

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.02.013.

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