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Impact of Kissing Balloon in Patients Treated With Ultrathin Stents for Left Main Lesions and Bifurcations: an Analysis From the RAIN-CARDIOGROUP VII Study

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Abstract

Background

There are limited data regarding the impact of final kissing balloon (FKI) in patients treated with percutaneous coronary intervention using ultrathin stents in left main or bifurcations.

Methods

All patients undergoing left main or bifurcations percutaneous coronary intervention enrolled in the RAIN registry (Very Thin Stents for Patients With MAIN or BiF in Real Life: The RAIN, a Multicenter

Study) evaluating ultrathin stents were included. Major adverse cardiac event (a composite of all-cause death, myocardial infarction, target lesion revascularization, and stent thrombosis) was the primary end point, while its components, along with target vessel revascularization, were the secondary end points. The main analysis was performed comparing patients with and without FKI after adjustment with inverse probability of treatment weighting. Subgroup analyses were performed according to FKI (short [<3 mm] versus long overlap), strategy (provisional versus 2-stent), routine versus bail-out FKI, and the use of imaging and proximal optimization technique.

Results

Two thousand seven hundred forty-two patients were included. At 16 months (8–20) follow-up, inverse probability of treatment weighting adjusted rates of major adverse cardiac event were similar between FKI and no-FKI group (15.1% versus 15.5%; *P*=0.967), this result did not change with use of imaging, proximal optimization technique, or routine versus bail-out FKI. In the 2-stent subgroup, FKI was associated with lower rates of target vessel revascularization (7.8% versus 15.9%; *P*=0.030) and target lesion revascularization (7.3% versus 15.2%; *P*=0.032). Short overlap FKI was associated with a lower rate of target lesion revascularization compared with no FKI (2.6% versus 5.4%; *P*=0.034), while long overlap was not (6.8% versus 5.4%; *P*=0.567).

Conclusions

In patients with bifurcations or unprotected left main treated with ultrathin stents, short overlap FKI is associated with less restenosis. In a 2-stent strategy, FKI was associated with less target vessel revascularization and restenosis.

What Is Known

- The ultrathin struts of new drug eluting stents are associated with shorter re-endothelialization times, a reduction in shear stress and coronary wall inflammation.
- Data regarding their safety and efficacy in left main or coronary bifurcations are limited.

What the Study Adds

- The use of new generation ultrathin strut stents for complex coronary lesions (left main and non-left main) is associated with good clinical and angiographic results.
- Final kissing balloon plays a fundamental role in this setting when a 2-stent strategy is chosen.
- Patients treated with short overlap final kissing balloon (<3 mm) experienced less restenosis independent of strategy and use of proximal optimization techniq

Footnote

Nonstandard Abbreviations and Acronyms

FKI - final kissing balloon inflation
LM - left main
MACE - major adverse cardiac event
MB - main branch
POT - proximal optimization technique
SB - side branch
ST - stent thrombosis
TLR - target lesion revascularization

Introduction

The reduction of coronary stent strut thickness was one of the main innovations in interventional cardiology, ensuring greater maneuverability, a lower risk of stent thrombosis (ST), and a lower rate of repeat revascularization. Coronary bifurcation lesions are regarded as one of the most challenging lesions and are known to be associated with lower angiographic success rates, due to both procedural complications and higher restenosis rates compared with non-bifurcation lesions.[1,2] The BIORESORT trial (Comparison of Biodegradable Polymer and Durable Polymer Drug-Eluting Stents in an All Comers Population), the largest randomized controlled clinical study presently available, examining the efficacy of ultrathin (100 µm) stents (Synergy, Orsiro, and Resolute) provided very encouraging results, highlighting, at 1 year, a revascularization rate of 2% and ST rates of 0.5%.[3] However, it is important to emphasize that, due to the design of the study, only 29% of the patients enrolled had a bifurcation lesion and a left main (LM) was treated in <2% of cases.[3] Therefore, BIORESORT did not have sufficient power to identify any statistically significant difference between the excellent results in the general population and those in these specific subgroups of patients with complex coronary lesions which strongly influence prognosis.[4–6] In light of the intrinsic limitations of the BIORESORT study, the RAIN study (Very Thin Stents for Patients With Main or Bifurcation in Real Life: The RAIN, a Multicenter Study) was designed to evaluate the clinical performance of ultrathin stents in everyday clinical practice. Furthermore, the potential benefits of final kissing balloon inflation (FKI) in bifurcation lesions is still debated, particularly following single stent treatment. Several recent retrospective trials, comparing the FKI strategy with the no-FKI strategy in patients treated with a 1-stent technique using first-generation drug-eluting stents, did not detect any difference in clinical outcomes.[7–10] A recent meta-analysis found similar clinical outcomes between the FKI and no-FKI groups; however, the FKI strategy was associated with lower incidence of side branch (SB) restenosis and increased risk of main branch (MB) restenosis in the 1-stent approach.[11] In contrast, when a 2-stent technique is chosen, FKI is standard. Importantly, these studies only included first- and second-generation drug-eluting stents, omitting the newer ultrathin stents.[12–14] In light of these limitations, we aimed to investigate the potential benefits of FKI in bifurcations treated with new generation ultrathin stents using a 1- or 2-stent technique, applying a propensity score adjustment to determine the independent impact of FKI in this cohort.

Methods

RAIN (NCT03544294) is a large multicenter retrospective observational registry (see www.Clinicaltrial.gov records and the Data Supplement for more details).[15] The data that support the findings of this study are available from the corresponding author upon reasonable request.

Inclusion Criteria

The RAIN registry included all consecutive patients undergoing complex percutaneous coronary interventions involving LM and/or bifurcation with ultrathin stents (Promus Element, Xience Alpine, Ultimaster, Synergy, and Resolute Onyx; see the Data Supplement).
The study enrolled patients from January 2015 to December 2017.

Baseline and Procedural Data

Cardiovascular risk factors, clinical presentation, angiographic features, use of intravascular ultrasound, optical coherence tomography, and fractional flow reserve were recorded, along with the characteristics of the implanted stents. intravascular ultrasound or optical coherence tomography was used before stent implantation to assess the severity of the stenosis and SB involvement, and poststent implantation to detect dissections and determine if stent optimization was required. The decision to use post-dilatation, FKI, proximal optimization technique (POT), intracoronary imaging and technique (provisional versus 2-stent), was at the discretion of the treating physician. The current European Bifurcation Club consensus and most recent evidence from the literature guided the use of FKI, POT, and complex sequential technique (eg, double-kissing double crush).[16–18] Follow-up data were obtained from clinical assessment, telephonic consultations, and/or via primary care physicians. The study was approved by an institutional review committee, and all patients provided informed consent.

End Points

Major adverse cardiac events (MACEs; a composite end point of all-cause death, myocardial infarction, target lesion revascularization [TLR], and stent thrombosis [ST]) were the primary end point, while its components, along with target vessel revascularization, were the secondary end points. Prespecified clinical end points are listed and defined in the Data Supplement. Subgroup analyses were performed for: short versus long FKI (defined as an overlap <3 mm between the 2 balloons, evaluated by at least 2 physicians),[19] provisional versus 2-stent strategy; use of POT; intracoronary imaging and routine versus bailout FKI.

Statistical Analysis

Categorical variables are reported as count and percentages, whereas continuous variables as mean and SDs or interquartile range. Gaussian or nongaussian distribution was evaluated by Kolmogorov-Smirnov test. The *t*-test was used to assess differences between normally distributed continuous variables, Mann-Whitney *U* test for nongaussian variables, the χ^2 test for categorical variables and Fisher exact test for 2×2 tables. The a priori statistical significance level was set at $\alpha=0.05$.
The first step of the adjusted analysis[20] was the management of missing data: we used predictive mean matching[21] as imputation techniques to fill in missing values, according to a multiple imputation treatment of missing values (see the Data Supplement for percentages of missing data). We imputed 5 different datasets and from a logistic regression model, we derived the propensity score (PS), defined as the probability of being treated with FKI, conditional on the individual's baseline characteristics (listed in Tables 1 and 2) for each imputed dataset. Inverse Probability of Treatment Weighting (IPTW) techniques involves assigning each patient a weight $(1-p)/(1-PS)$ if a control, or weight p/PS if a treated patient, where p is the probability of treatment without any covariate and PS is the value of the PS for that patient. The choice of stabilized weights allowed us to work with a pseudo-sample (as large as the sum of the weights) that has approximately the same size of the actual one. After that, Rubin rule[22] was used to get pooled IPTW-adjusted incidences of outcomes.[21–26] Standardized mean difference for each variable was imputed before and after propensity score to appraise the performance of the model. The adjusted statistical analysis was performed with R 3.5.1 software.[27]

Results

At univariate analysis, 3055 patients from the RAIN registry were assessed for eligibility. After careful evaluation, 313 patients were excluded due to missing data regarding their baseline and/or procedural characteristics (see the Data Supplement). The remaining 2742 patients were included in the study: 1619 were treated with no-FKI and 1123 with FKI. The patients' baseline characteristics are listed in Table 1.
Patients in the no-FKI group had higher rates of noninsulin-dependent diabetes mellitus (27.2% versus 22.7%; *P*=0.004), renal disease (GFR <60 mL/minute; 22.2% versus 19.1%; *P*=0.027), previous coronary artery bypass surgery (5.9% versus 3.9%; *P*=0.011), and previous myocardial infarction (31.6% versus 27.7%; *P*=0.017). Patients in the no-FKI group more commonly presented with ST-Elevation myocardial infarction (18.8% versus 15.1%; *P*=0.007).
There was a higher prevalence of LM in the FKI group (20.5% versus 39.1%; *P*<0.001) and of left anterior descending artery in the no-FKI group (49.4% versus 42.8%; *P*<0.001). The 2-stent technique

(29.1% versus 7.7%; *P*<0.001), predilatation (91.6% versus 87.2%; *P*<0.001), and post-dilation (86.0% versus 65.7%; *P*<0.001) were more common in the FKI group (Table 2).

Main Analysis With IPTW Adjustment

At a median follow-up of 16 (8–20) months, after adjustment with IPTW, no significant differences were reported in terms of MACE (15.1% versus 15.2%; *P*=0.967), or secondary end points, including myocardial infarction (5.3% versus 7.0%; *P*=0.408), target vessel revascularization (6.3% versus 6.3%; *P*=0.996), TLR (5.4% versus 5.6%; *P*=0.932), and ST (2.5% versus 3.6%; *P*=0.545; Figure 1; Table II in the Data Supplement).

Subgroup Analysis

In the provisional group, there were no statistically significant differences in MACE rates (12.4% versus 15%; *P*=0.311; 26.6% versus 21.9%; *P*=0.260; 10.8% versus 12.9%; *P*=0.452, respectively) or secondary end points between FKI and no-FKI (Figure 2A; Table II in the Data Supplement). In the 2-stent strategy group, FKI reduced the incidence of MACE (16.6% versus 24.9%; *P*=0.083), target vessel revascularization (7.8% versus 15.9%; *P*=0.030), and TLR (7.3% versus 15.2%; *P*=0.032), independent of the overlap length (Figure 2B; Table II in the Data Supplement). In this subgroup, FKI was associated with more freedom from TLR (*P*=0.01; Figure 3B), and no difference in terms of survival was found in the provisional subgroup (*P*=0.92; Figure 3A).

The use of POT was similar in the FKI and no-FKI groups (47.1% versus 46.5% respectively; *P*=0.238; Table 2). The effect of FKI did not vary in either patients treated with and without POT (Table II in the Data Supplement) or treated patients with and without imaging-guided intervention (Table II in the Data Supplement). Overall imaging reduced rates of TLR and ST (Table III in the Data Supplement). Finally, the use of bail-out FKI (25.7% of the FKI group; Table 2) was not associated with an increased risk of adverse events (Table II in the Data Supplement).
When evaluating the overlap between the balloons, short overlap was associated with lower rates of target vessel revascularization (3.2% versus 6.3%; *P*=0.037) and TLR (2.6% versus 5.4%; *P*=0.034) compared with no-FKI (Figure 4A; Table II in the Data Supplement). On the contrary, long overlap did not reduce TLR compared with no FKI (6.8% versus 5.4%; *P*=0.592; Figure 4A; Table II in the Data Supplement). The benefit of short overlap compared with no-FKI in terms of TLR was also found in the POT subgroup (1.4% versus 4.9%; *P*=0.014; Figure 4B; Table II in the Data Supplement).

Discussion

To the best of our knowledge, this is the first real world, observational registry in patients treated with ultrathin stents (struts thinner than 81 µm) for complex percutaneous coronary intervention, including LM and bifurcation stenosis, evaluating the impact of FKI, in both provisional and 2-stent strategies, on long-term follow-up.
The main findings of the present study are:
1.Overall, the adjusted MACE rates were similar between the FKI and no-FKI groups, independent of the use of imaging, POT, or routine versus bail-out FKI.
2.In the 2-stent subgroup, FKI was associated with less restenosis.
3.Compared with no FKI, final kissing balloon with a short overlap (<3 mm) reduced TLR, while a long overlap did not.
Bifurcation lesions, due to their anatomic nature, expose the patient to the risk of side branch compromise, defined as worsening of the stenosis, and in some cases complete SB occlusion.[28–30] Final kissing balloon inflation was the first technique specifically designed for percutaneous bifurcation interventions. However, it remains unclear whether FKI should be routinely performed. FKI has been advocated to preserve access to the SB, prevent narrowing and restenosis of the SB, enlarge the lumen of the proximal main vessel, optimize stent apposition, and minimize stent deformation.[13] In the MB, FKI expands the main stented segment, commonly leading to a reduction

in the circular proximal diameter and a more oblong or elliptical shape of the side branch, accompanied by an increase in local shear stress as suggested by one in-silico study.[31]

In the present registry, patients treated with a 2-stent strategy experienced less restenosis when FKI was performed. Although FKI has not been evaluated in randomized control trials of 2-stent techniques, patients with no FKI had consistently worse outcomes in both the Nordic III trial[32] and registries.[9,12] Therefore, FKI is currently recommended in all 2-stent techniques.[33] Our results confirm the fundamental role of FKI in 2-stent techniques, with lower rates of TLR.[34]

In the overall population, FKI is beneficial in reducing restenosis only if performed with a short overlap. Indeed, the benefit of FKI in the overall population, and in particular in a 1-stent approach, remains uncertain due to lack of data.[35,36] Several recent retrospective studies comparing FKI with no-FKI strategy in patients undergoing a 1-stent technique with first- and second-generation drug-eluting stents have not shown any difference in clinical outcomes.[5,7–9,32,35–37] A recent meta-analysis evaluating the role of FKI for a 1-stent approach found similar clinical outcomes between the FKI and no-FKI groups.[11] However, the FKI strategy reduced the incidence of SB restenosis and increased the risk of MB restenosis. In our study, the efficacy of FKI is restricted to cases in which it was performed with a short overlap between the balloons. Preliminary studies have shown that minimal balloon overlapping (<3 mm) yields an ideal spherical stent dilation in the MB, while overexpansion or elliptical deformation by a long overlap may increase the exposure to low shear stress,[19] especially in high-degree angle bifurcations. Our results represent the clinical counterpart to these bench findings, underlining the importance of performing FKI with short balloons (to minimize overlap <3 mm) to reduce clinically significant restenosis.

The impact of FKI did not seem to depend on POT or the use of imaging. The POT has been proposed as a strategy to improve the results of stent scaffolding in bifurcation lesions. It is a straightforward technique where a short, appropriately sized balloon is inflated in the main vessel just proximal to the carina. This technique changes the tubular stent to a tapered device fitting both the distal and proximal diameters of the MB and potentially expanding the stent struts toward the SB, respecting the anatomy of the bifurcation core segment.[38,39] In addition, the POT facilitates re-crossing into the side branch to optimize the final result if required.[15] While POT is recommended by the European Bifurcation Club, data regarding its clinical relevance are limited.[39] Recently, the COBIS II registry,[40] comparing 665 patients without and 204 patients with POT, showed a significant difference in terms of a combined end point (MACE) at 36 months follow-up, in favor of the POT group. In our study, POT did not impact patient outcomes, perhaps due to the advantages of ultrathin strut DES.

Limitations

There are several limitations to this study. First, this was not a randomized controlled study and although there was the use of propensity score, we could not adjust for variables which were not collected, such as the experience of the physicians performing PCI. Furthermore, cases where FKI was not feasible were infrequent (1.6% mostly in patients treated with a 2-stent strategy) and due to the small sample size, no subgroup analysis was performed. Finally, in the overall population, the use of imaging was associated with lower rates of TLR and of ST at unadjusted analysis, while significance was lost after stratification for FKI probably due to reduced sample size. Due to absence of adjustment for use of imaging in the present article, both these results should be seen as merely descriptive, without an inferential aim. Regarding the statistical analysis, standardized mean difference between and after propensity score (see the Data Supplement) demonstrated an overall good performance of IPTW.

Conclusions

In conclusion, FKI confers a significant benefit in terms of clinical and angiographic outcomes for complex coronary lesions (non-LM and LM) treated with ultrathin stents using a 2-stent technique. Patients treated with a short overlap (<3 mm) FKI experienced less restenosis.

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Table 1. Baseline Characteristics

	NO FKI (1619)	**FKI (1123)**	***P* Value**
Age	68.57±11.472	68.44±10.861	0.769
Male	1215 (75.3)	852 (76.1)	0.334
Hypertension	1179 (75.7)	826 (74.3)	0.219
Hyperlipidemia	1002 (61.9)	650 (57.9)	0.019
Diabetes mellitus non-ID	441 (27.2)	255 (22.7)	0.004*
Previous smoker	454 (29.8)	328 (29.5)	0.155
Current Smoker	334 (21.9)	220 (19.8)	0.155
Renal disease (GFR <60 mL/min)	359 (22.2)	214 (19.1)	0.027*
Previous PCI	519 (32.1)	354 (31.5)	0.4
Previous CABG	94 (5.9)	43 (3.9)	0.011*
Previous MI	484 (31.6)	301 (27.7)	0.017*
EF at admission or discharge (%)	52.24±9.702	52.12±9.633	0.614
STEMI	301 (18.8)	168 (15.1)	0.007*
ACS	911 (56.9)	599 (53.8)	0.06

ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; EF, ejection fraction; FKI, final kissing balloon inflation; GFR, glomerular filtration rate; ID, insulin dependent; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.
*****Statistically significant difference.

Table 2. Procedural Characteristics

	NO FKI (1619)	**FKI (1123)**	***P* Value**
LM			
Overall	311 (19.2)	421 (37.5)	<0.001*
Ostial	71 (22.8)	41 (9.7)	
Mid	71 (22.8)	65 (15.4)	
Distal	169 (54.3)	315 (74.8)	
Access			
Radial	1088 (69.0)	735 (67.4)	0.453
Femoral	489 (31.0)	354 (32.5)	
First lesion vessel			
LM	324 (20.5)	428 (39.1)	<0.001*
LAD	782 (49.4)	469 (42.8)	

	NO FKI (1619)	FKI (1123)	*P* Value
CxOM	302 (19.1)	156 (14.2)	
RCA	136 (8.6)	36 (3.3)	
Intermediate	38 (2.4)	6 (0.5)	
Lesion localization			
Ostial	109 (7.2)	81 (7.7)	<0.001*
Proximal	502 (33)	267 (25.3)	
Mid	561 (36.9)	350 (33.1)	
Distal	346 (22.8)	359 (34.0)	
Type C lesion	544 (33.6)	498 (43.3)	<0.001*
Severe calcification	244 (13.8)	150 (13.4)	0.382
Diffuse disease	573 (38.6)	375 (36.3)	0.138
BiF strategy			
Provisional	1344 (87.7)	755 (70.2)	<0.001*
2-stent	118 (7.7)	321 (29.1)	
Use of imaging			
No imaging	1086 (67.2)	759 (67.7)	0.618
IVUS	508 (31.5)	353 (31.5)	
OCT	21 (1.3)	9 (0.8)	
Predilatation	1412 (87.2)	1029 (91.6)	<0.001*
Main branch stent			
Resolute onyx	449 (27.8)	360 (32.3)	0.866
Xience alpine	419 (26)	209 (18.8)	
Synergy	335 (20.8)	240 (21.5)	
Ultimaster	123 (7.6)	109 (9.8)	
Biomatrix alpha	1 (0.1)	2 (0.2)	
Promus	268 (16.6)	180 (16.2)	
Post-dilatation	1063 (65.7)	966 (86)	<0.001*
POT	792 (46.5)	543 (47.1)	0.238*
Type of FKI			
Correct (short overlap, <3 mm)	…	377 (32.7)	
Incorrect (long overlap, >3 mm)	…	775 (67.3)	
Routine FKI	…	856 (74.3)	
Bailout FKI	…	297 (25.7)	
DAPT (ASA+ …)			
Clopidogrel	1002 (66.5)	621 (61.5)	0.045*
Ticagrelor	382 (25.4)	310 (30.7)	
Prasugrel	120 (8.0)	76 (7.5)	

ASA indicates acetylsalicylic acid; BiF, bifurcation; CxOM, circumflex-obtuse marginal artery; DAPT, dual antiplatelet therapy; FKI, final kissing balloon inflation; IVUS, intravascular ultrasound; LAD, left anterior descending; LM, left main; OCT, optical coherence tomography; POT, proximal optimization technique; and RCA, right coronary artery.
*Statistically significant difference.

Graphical abstract

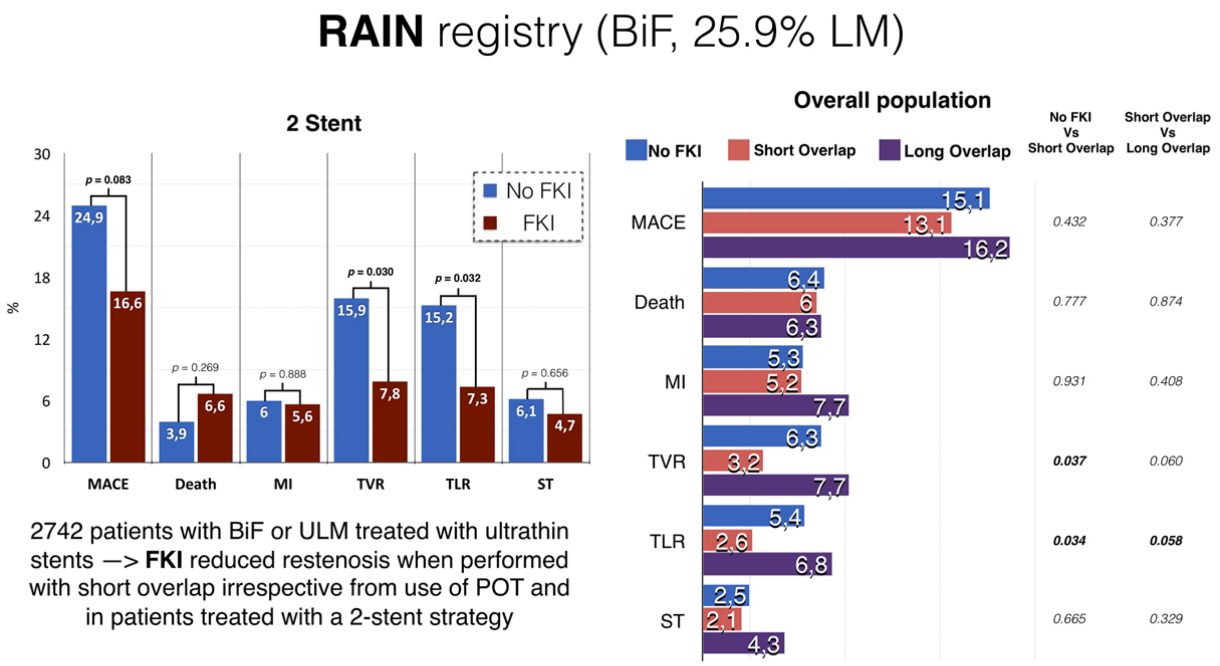

Figure 1. **Follow-up in the overall population, stratified by final kissing balloon inflation (FKI).** MACE indicates major adverse cardiac event; MI, myocardial infarction; ST, stent thrombosis; TLR, target lesion revascularization; and TVR, target vessel revascularization.

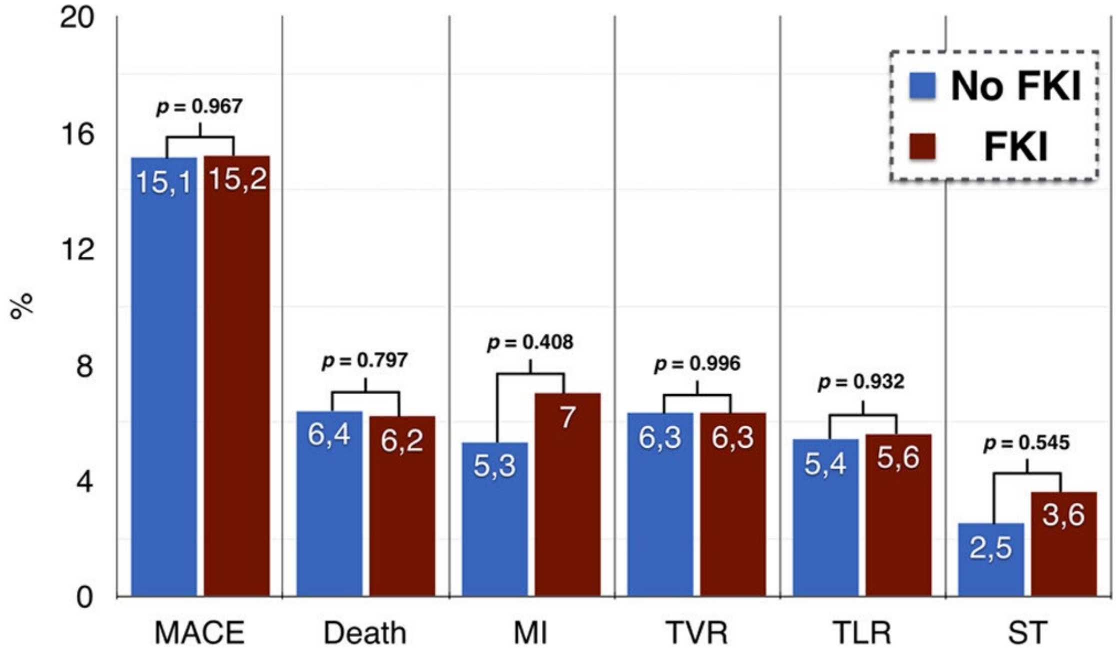

Figure 2. **Follow-up according to bifurcation techinique**. **A**, Provisional; (**B**) 2-stent technique. FKI indicates final kissing balloon inflation; MACE, major adverse cardiac event; MI, myocardial infarction; ST, stent thrombosis; TLR, target lesion revascularization; and TVR, target vessel revascularization.

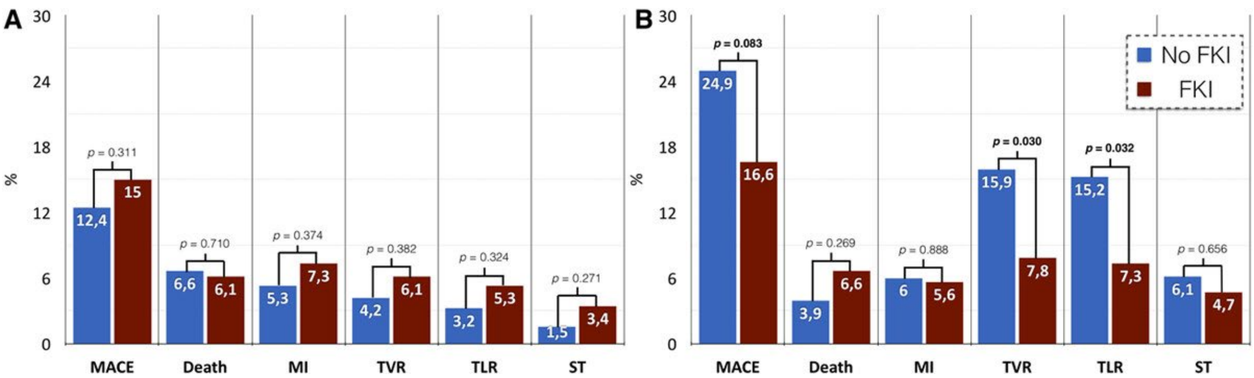

Figure 3. **Kaplan-Meier curves for freedom from target lesion revascularization according to bifurcation technique**. **A**, Provisional; (**B**) 2-stent technique. FKI indicates final kissing balloon inflation.

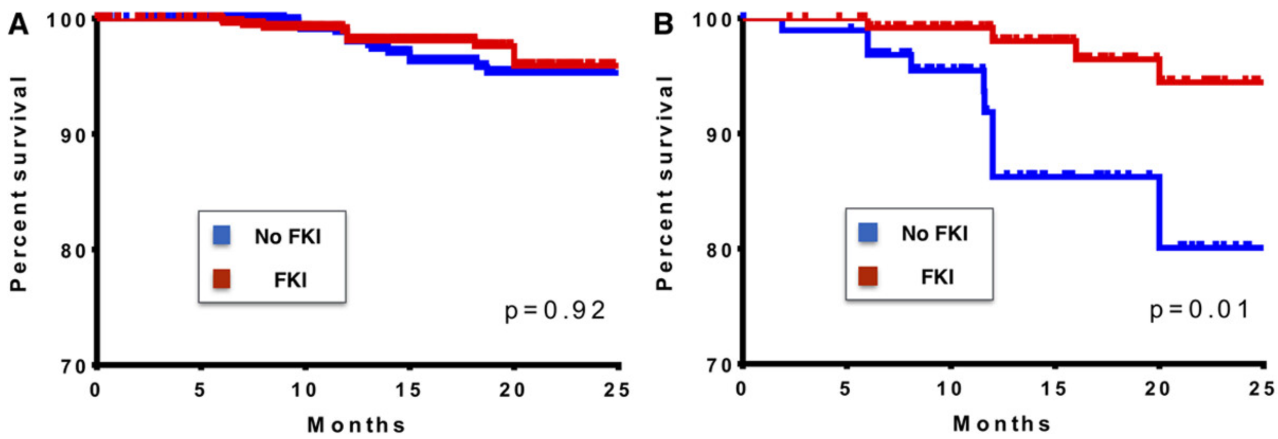

Figure 4. **Follow-up according to different use of final kissing balloon inflation (FKI).** No FKI versus short overlap (correct, <3 mm), FKI versus long overlap (incorrect, >3 mm), FKI in the overall population (**A**) and in the proximal optimization technique (POT) subgroup (**B**). MACE indicates major adverse cardiac event; MI, myocardial infarction; ST, stent thrombosis; TLR, target lesion revascularization; and TVR, target vessel revascularization.