

## Randomized Study of the Crush Technique Versus Provisional Side-Branch Stenting in True Coronary Bifurcations

### The CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) Study

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**Background**—Sirolimus-eluting stents have been reported to be effective in the treatment of coronary bifurcations. Still, it has not been fully clarified which strategy would provide the best results with true bifurcation lesions.

**Methods and Results**—The CACTUS trial (Coronary bifurcations: Application of the Crushing Technique Using Sirolimus-eluting stents) is a prospective, randomized, multicenter study comparing 2 different techniques of stenting, with mandatory final kissing-balloon inflation, in true bifurcations: (1) elective “crush” stenting and (2) stenting of only the main branch, with provisional side-branch T-stenting. From August 2004 to June 2007, 350 patients were enrolled in 12 European centers. The primary angiographic end point was the in-segment restenosis rate, and the primary clinical end point was the occurrence of major adverse cardiac events (cardiac death, myocardial infarction, or target-vessel revascularization) at 6 months. At 6 months, angiographic restenosis rates were not different between the crush group (4.6% and 13.2% in the main branch and side branch, respectively) and the provisional stenting group (6.7% and 14.7% in the main branch and side branch, respectively;  $P=NS$ ). Additional stenting on the side branch in the provisional stenting group was required in 31% of lesions. Rates of major adverse cardiac events were also similar in the 2 groups (15.8% in the crush group versus 15% in the provisional stenting group,  $P=NS$ ).

**Conclusions**—In most bifurcations with a significant stenosis in both branches, a provisional strategy of stenting the main branch only is effective, with the need to implant a second stent on the side branch occurring in approximately one third of cases. The implantation of 2 stents does not appear to be associated with a higher incidence of adverse events at 6 months. (*Circulation*. 2009;119:71-78.)

**Key Words:** angioplasty ■ restenosis ■ follow-up studies ■ drug-eluting stents

Percutaneous interventions on lesions located on coronary bifurcations have been considered a challenging task for interventionists. Before drug-eluting stents became available, the restenosis rate was unacceptably high on both branches regardless of the technique used.<sup>1-3</sup> The effectiveness of sirolimus- and paclitaxel-eluting stents in bifurcations has been confirmed both by prospective analysis and by dedi-

cated prospective studies<sup>4-8</sup>; however, it still has not been fully clarified which stenting strategy should be adopted when a drug-eluting stent is implanted in bifurcation lesions. This issue is even more relevant in the case of true bifurcations, in which the angiographic stenosis is >50% of the lumen of both branches. The unanswered question is whether elective stenting of both branches, which can be more

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technically demanding, provides greater benefits than the simpler approach of stenting only the main branch (MB), with additional stenting on the side branch (SB) only in the case of an unsatisfactory result at that site.

### Clinical Perspective p 78

To address the above question, we designed the CACTUS trial (Coronary bifurcations: Application of the Crushing Technique Using Sirolimus-eluting stents). We prospectively and randomly compared 2 different approaches for the treatment of de novo true coronary bifurcation lesions with sirolimus-eluting stents (SES): (1) elective double stenting by use of the crush technique and (2) elective stenting of the MB and provisional T-stenting of the SB.

## Methods

### Patient Selection

The CACTUS study was conducted in 12 Italian and German centers. The protocol was approved by ethics committees of the participating centers, and signed informed consent was obtained from all patients. Male and nonpregnant female patients  $\geq 18$  years of age with a diagnosis of stable or unstable angina (Braunwald classification B and C I-II) or documented silent ischemia were considered eligible for enrollment. Additional eligibility criteria were the presence of a de novo true coronary bifurcation lesion, defined as a stenosis  $>50\%$  in both the MB and the ostium of the SB. Both branches had to have at least Thrombolysis In Myocardial Infarction flow 1, with a maximum treatable lesion length  $\leq 28$  mm by visual estimation for each individual branch, as well as a reference vessel between 2.5 and 3.5 mm in diameter for the MB and between 2.25 and 3.5 mm for the SB. Exclusion criteria were myocardial infarction (MI) in the 24 hours preceding the treatment (elevation of total creatine kinase [CK]  $>2$  times normal or creatine kinase myocardial band isoenzyme (CK-MB) levels  $>3$  times normal within the preceding 24 hours); lesion location in the left main trunk unprotected by a graft; angiographically visible thrombus within the target lesion; chronic total occlusion; left ventricular ejection fraction  $<35\%$ ; serum creatinine  $\geq 2.65$   $\mu\text{mol/L}$ ; and contraindication or suspected intolerance to 1 of the study drugs.

### Procedure

After baseline angiograms had been obtained, patients were randomly assigned in a 1:1 ratio to 1 of the 2 treatment strategies: (1) elective stenting of both branches with SES (Cypher, Johnson & Johnson, Miami Lakes, Fla) with the "crush" technique (crush group) or (2) SES implantation in the MB with balloon angioplasty and provisional stenting for the SB (provisional group). In the crush group, stenting was performed by a technique described previously.<sup>9–11</sup> Predilation of both branches before stenting and final kissing-balloon inflation (FKI) were mandatory steps of the procedure. In the provisional group, FKI was also considered a necessary final step of the procedure, and stent implantation in the SB was allowed by the T-stenting technique only when at least 1 of the following conditions was met: residual stenosis  $\geq 50\%$ ; dissection of type B or worse<sup>12</sup>; or Thrombolysis in Myocardial Infarction flow  $\leq 2$ . Additional stent implantation in any of the 2 branches was allowed to obtain whole-lesion coverage or in case of dissection.

All patients were pretreated with aspirin and either ticlopidine or clopidogrel. A 300-mg loading dose of clopidogrel before the index procedure was administered if patients were not pretreated. During the procedure, patients received intravenous unfractionated heparin to maintain an activated clotting time between 250 and 300 seconds. The administration of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. Total CK and CK-MB isoform cardiac enzymes were measured at 6 hours, at 18 to 24 hours, and at discharge. After discharge, aspirin therapy was continued indefinitely, and clopidogrel or ticlopidine was continued for at least 6 months.

### Follow-Up

Clinical follow-up was performed with visits or telephone contact at 1, 6, and 12 months. Adverse events were monitored throughout the entire study period. Follow-up coronary angiography was scheduled at 6 months after the procedure for all patients unless necessary at an earlier time for clinical reasons. No patients were lost to follow-up.

### Quantitative Coronary Angiographic Measurements

Matched orthogonal views were used for quantitative coronary analysis before and after treatment. Angiography was performed after intracoronary injection of nitroglycerine (100 to 200  $\mu\text{g}$ ) or isosorbide dinitrate (1 to 3 mg). Angiograms were analyzed offline with a validated automated edge-detection system (QCA-CMS version 5.2, Medis Medical Imaging Systems, Leiden, Netherlands). Quantitative coronary analysis measurements were performed at baseline and after stent implantation both on the parent vessel and on the SB. At follow-up, all parameters were calculated for the 5 mm proximal and distal to the stented segment. In-segment restenosis was defined as lumen diameter stenosis  $\geq 50\%$  at any of the following sites: (1) inside the stent; (2) within 5 mm proximal or distal to the stent; (3) within the proximal 5 mm of the nonstented SB; or (4) at the site of balloon inflation in the SB. In-stent late luminal loss was defined as the difference between minimal lumen diameter immediately after the procedure and at 6 months. Angiographic measurements were performed by an independent core laboratory (MCR [Mediolanum Cardio Research], Milan, Italy).

### Study End Points and Definitions

The primary end point of the study was angiographic in-segment restenosis at 6 months. The primary clinical end point of the study was the occurrence of major adverse cardiac events (MACE), defined as the composite of cardiac death, Q-wave or non-Q-wave MI, or target-vessel revascularization, at 6 and 12 months. Secondary angiographic end points were minimal lumen diameter and percent diameter stenosis in the MB and SB of both groups as measured by quantitative coronary analysis at 6 months. Q-wave MI was defined as the development of new, pathological Q waves in 2 or more contiguous leads with postprocedure CK or CK-MB levels above normal. Non-Q-wave MI was defined as an elevation of postprocedural CK levels  $>2$  times normal levels with elevated CK-MB in the absence of pathological Q waves. Stent thrombosis (ST) was defined as a MI attributable to the target vessel with angiographic documentation of thrombus or total occlusion at the target site. The timing of ST was classified as subacute if ST occurred within 30 days of the index procedure and as late if it occurred after 30 days. ST was also classified according to the Academic Research Consortium (ARC) definition.<sup>13</sup> The protocol definition of ST in the CACTUS study corresponds with the ARC definition of definite ST. Angiographic success was defined as achievement of a final residual diameter stenosis  $<50\%$  (by quantitative coronary analysis) in both branches of the coronary bifurcation with the assigned bifurcation stenting technique. Procedural success was defined as angiographic success without the occurrence of death, MI, or repeat revascularization of the target lesion during the hospital stay. Independent study monitors verified all data from case report forms on site. The clinical study end points were adjudicated by an independent committee blinded to treatment allocation after review of original source documentation.

### Statistical Analysis

The study tested the hypothesis that in-segment restenosis rates in the 2 arms would be significantly different, favoring the crush versus provisional stenting. A sample size of 100 subjects per group was estimated to have 80% power to detect a 60% difference in restenosis rate (25% restenosis rate for provisional stenting compared with 10% in the crush group) with a 0.05 2-sided significance level. To accommodate a 20% loss in angiographic follow-up and because of considerable uncertainty about expected end-point rates, it was decided to extend the enrollment to 350 patients. The treatment-group differences were evaluated with ANOVA or Wilcoxon rank

**Table 1. Baseline Clinical Characteristics**

	Crush Group (n=177)	Provisional-Stenting Group (n=173)	P
Age, y	65±10	67±10	0.12
Gender, male/female	142/35	132/41	0.37
Diabetes mellitus	42 (23.7)	38 (22.0)	0.69
Hypercholesterolemia	113 (63.8)	122 (70.5)	0.18
Hypertension	125 (70.6)	138 (79.8)	0.05
Current smokers	36 (20.3)	29 (16.8)	0.67
LVEF	55±9	57±8	0.08
Previous MI	79 (44.6)	61 (35.3)	0.07
Previous PCI	55 (31.1)	46 (26.6)	0.35
Previous CABG	8 (4.5)	10 (5.8)	0.59
Family history of CAD	83 (46.9)	62 (35.8)	0.11
Unstable angina	78 (44.0)	63 (47.4)	0.15
Stable angina	55 (31.1)	63 (36.4)	0.78
Silent ischemia	31 (17.5)	23 (13.3)	0.08

LVEF indicates left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; and CAD, coronary artery disease.

Values are mean±SD or n (%).

sum scores for continuous variables. The conventional  $\chi^2$  test or Fisher exact test was used for the analysis of categorical variables. Statistical significance was declared if the 2-sided *P* value was <0.05. All analyses were performed with the use of the statistical program SAS version 9.1.3 (SAS Institute Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

### Baseline Characteristics

From August 2004 to June 2007, 350 patients were enrolled in the study and randomly assigned to either elective crush stenting (crush group, n=177) or provisional stenting (provisional group, n=173). Baseline clinical characteristics are reported in Table 1. The 2 groups were well matched for all clinical characteristics except hypertension, which was more prevalent in the provisional group. Bifurcation lesions were located as follows in the crush and provisional groups, respectively, with no difference between the 2 groups: left anterior descending/diagonal artery, 131 (74%) versus 121 (70%); left circumflex/obtuse marginal artery, 34 (19%)

versus 43 (25%); and distal right coronary/posterior descending artery, 12 (7%) versus 9 (5%). Among all 350 treated bifurcations, 328 (94%) were true bifurcation lesions, categorized according to the Medina classification<sup>14</sup> as type 1.1.1 (262 lesions, 75%), type 1.0.1 (10 lesions, 3%), and type 0.1.1 (56 lesions, 16%). No differences were found between the 2 groups in the distribution of true and nontrue bifurcations.

### Procedural Characteristics

Table 2 shows the procedural characteristics for the 2 groups. In the provisional group, an additional stent on the SB was implanted in 54 (31%) of 173 patients. Reasons for additional stenting were Thrombolysis in Myocardial Infarction flow grade <3 in 1 (1.9%) of 54 cases, residual stenosis >50% in 39 (72%), and dissection of type B or worse in 21 (39%). Angiographic success was attained in 175 cases (98.9%) in the crush group and 169 (97.7%) in the provisional group, and procedural success was attained in 90.4% and 91.3% of cases, respectively. All cases without angiographic success were unsuccessful because of residual stenosis  $\geq$ 50% in the

**Table 2. Procedural Characteristics**

	Predilation	Intravascular Ultrasound	No. of Stents per Lesion	Total Stent Length, mm	Maximal Inflation Pressure, atm	FKI	Glycoprotein IIb/IIIa Inhibitors
Crush group (n=177)						163 (92.1)	40 (22.6)
MB	159 (89.8)	6 (3.4)	1.23±0.44	23.8±5.9*	15.7±4.3	...	...
SB	159 (89.8)	5 (2.8)	1.02±0.15	17.9±5.0	13.4±3.4*	...	...
Provisional stenting group (n=173)						156 (90.2)	30 (17.3)
MB	157 (90.8)	7 (4.1)	1.14±0.43	22.2±5.7*	16.4±4.1	...	...
SB	157 (90.8)	4 (2.3)	1.07±0.26 (54 lesions)	18.1±6.2 (54 lesions)	12.0±2.4*	...	...

Values are mean±SD or n (%).

\**P*<0.05 for comparisons between crush and provisional-stenting groups. All other comparisons were not significant.

**Table 3. Clinical Outcomes**

	Crush Group (n=177)	Provisional-Stenting Group (n=173)	P
<b>30-day MACE (days 0–30)</b>			
Q-wave MI	3 (1.7)	2 (1.1)	1.00
Non-Q-wave MI	15 (8.5)	12 (6.9)	0.69
TLR	3 (1.7)	1 (0.5)	0.63
TVR (including TLR)	3 (1.7)	1 (0.5)	0.63
Death	0	0	...
<b>6-month MACE (days 31–180)</b>			
MI	1 (0.5)	1 (0.5)	1.00
TLR	10 (5.6)	10 (5.8)	1.00
TVR (including TLR)	11 (6.2)	12 (6.8)	0.83
Death	0	1* (0.5)	0.49
<b>Cumulative MACE (days 0–180)</b>			
MI	19 (10.7)	15 (8.6)	0.59
TLR	13 (7.3)	11 (6.3)	0.83
TVR (including TLR)	14 (7.9)	13 (7.5)	1.00
Death	0	1* (0.5)	0.49

TLR indicates target-lesion revascularization; TVR, target-vessel revascularization. Values are mean±SD or n (%).

\*Noncardiac death (ischemic stroke confirmed by autopsy).

SB. Two cases of complete SB occlusion during the procedure were encountered in the provisional group but none in the crush group. The in-hospital MACE in the crush group included Q-wave MI in 2 cases (1.1%), non-Q-wave MI in 14 (7.9%), and target-vessel revascularization in 1 (0.5%), whereas in the provisional group, MACE consisted of Q-wave MI in 1 case (0.5%) and non-Q-wave MI in 12 (6.9%), with no target-vessel revascularizations. No in-hospital deaths occurred in either group.

### Clinical Outcome

The primary clinical end point of the study, cumulative MACE at 6-month follow-up, occurred in 28 patients in the crush group (15.8%) and 26 in the provisional group (15.0%;  $P=0.95$ ). The individual adverse events at 30 days and 6 months are shown in Table 3; no significant differences were found between groups. At 6 months, 85% of patients in the crush group and 84% of those in the provisional group were still taking dual-antiplatelet therapy. The rate of protocol-defined and ARC-definite ST at 6 months was 1.7% in the crush group and 1.1% in the provisional group. The timing of

ST is presented in Table 4, and the baseline clinical and procedural characteristics of patients in whom ST occurred are summarized in Table 5. No cases of ARC-defined probable or possible ST were found. The performance of FKI compared with no FKI was associated in the crush and provisional groups with a lower incidence of in-hospital and follow-up MI (7.5% with FKI versus 29.0% without,  $P<0.001$ ), a lower incidence of target-lesion revascularization (6.3% with FKI versus 12.9% without,  $P=0.25$ ), and a lower incidence of angiographic restenosis in the MB (4.7% with FKI versus 16.0% without,  $P=0.03$ ) and the SB (11.9% with FKI versus 36.0% without,  $P=0.001$ ), as well as a lower incidence of ST (0.9% with FKI versus 6.5% without,  $P=0.06$ ). The main reasons for not performing FKI in 14 cases in the crush group and 17 cases in the provisional groups, respectively, included operator decision (7/14 versus 12/17) and technical difficulties, such as rewiring the SB or inability to advance the balloons (7/14 versus 5/17).

### Quantitative Coronary Angiographic Measurements

Angiographic follow-up was performed in 86% of patients in both groups, and the results of the quantitative coronary angiographic analysis are shown in Table 6. No difference was found in the primary angiographic end point of binary in-segment restenosis in the MB and SB between the crush and provisional stenting groups (Figure). The reference-vessel diameter of both the MB and SB before and after stenting tended to be larger in the crush group, but these differences were lost at follow-up. Crush stenting was associated with a significantly larger final minimal lumen diameter at the SB ( $1.94\pm 0.39$  versus  $1.65\pm 0.39$  mm,  $P<0.001$ ), which was even more pronounced when SB lesions in the provisional group treated only with balloon angioplasty were considered ( $1.94\pm 0.39$  versus  $1.58\pm 0.39$  mm,  $P<0.001$ ). When restenosis rates were analyzed by actual treatment implemented, the rate of restenosis was similar in both the MB (4.0% versus 8.7%,  $P=0.09$ ) and the SB (14.6% versus 12.5%,  $P=0.61$ ) for the double-stenting (ie, crush plus crossover from provisional) and MB-only-stenting groups, respectively.

### Discussion

The main findings of the CACTUS trial are as follows: (1) The strategy of electively stenting both branches with the crush technique does not provide better outcomes than the strategy of provisional T-stenting. (2) When the strategy of provisional T-stenting is adopted, an additional stent on the SB is required in 31% of lesions. (3) Regardless of the

**Table 4. Timing of ST**

Group	Total	Acute (First Day)	Subacute (Days 2–30)	Late (Days 31–180)
Crush (n=177), n (%)	3 (1.7)	1 (0.5)	2* (1.1)	0
Provisional stenting (n=173), n (%)	2 (1.1)	0	1 (0.5)	1 (0.5)

All cases of ST were definite according to the ARC definitions; no "probable" or "possible" ST occurred.  $P=0.62$  for comparisons between groups.

\*One patient did not take thienopyridine therapy after discharge.

**Table 5. Patients With ST**

	1	2	3	4	5
Technique	Crush	Crush	Crush	Prov.-T	Prov.-T
Days from procedure	1	7	6	7	72
Thienopyridine at time of ST	Yes	Yes	No, stopped on day 1*	Yes	Yes
No. of stents	2+1	1+1	2+1	1	1+1
Total stent length, mm	83	65	72	13	41
FKI	Yes	No	Yes	Yes	No
Diabetes mellitus	No	No	Yes	Yes	No
Lesion location	LAD-Diag	LAD-Diag	LAD-Diag	LAD-Diag	RCA
Clinical consequences	Q-wave MI and TLR	Non-Q-wave MI and TLR	Q-wave MI and TLR	Q-wave MI and TLR	Q-wave MI and TLR

Prov.-T indicates provisional T-stenting; LAD, left anterior descending coronary artery; Diag, diagonal artery; RCA, right coronary artery; and TLR, target-lesion revascularization.

All cases of ST were definite according to the ARC definitions; no "probable" or "possible" ST occurred.

\*One patient did not take thienopyridine therapy after discharge.

technique used, SES implantation in true bifurcation lesions provides good clinical and angiographic results with an acceptable midterm safety profile.

Several authors have proposed the hypothesis that the simplest approach of electively stenting the MB, with provisional stenting on the SB only when required (provisional T-stenting), should be preferred to the more complex and demanding strategy of elective stenting of both branches.<sup>4-6,15,16</sup> The provisional strategy is certainly preferable when dealing with relatively simple bifurcations in which the plaque involves predominantly the MB, or in the presence of small SBs. However, little information is available about which strategy should be preferred when dealing with bifurcations when significant narrowing is present in the MB and

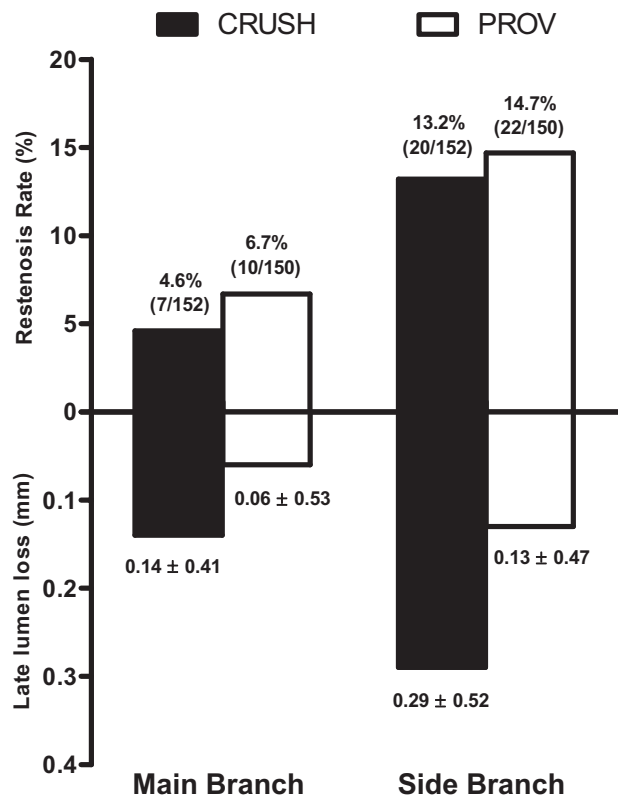
SB. Two studies randomly compared the 2 strategies in true bifurcations.<sup>4,6</sup> Both studies were limited by the relatively small number of patients enrolled and by the technique used in the double-stent arm: modified T-stenting in the study by Colombo et al<sup>4</sup> and traditional T-stenting in the study by Pan et al.<sup>6</sup> In the Nordic study, no mention is made of the prevalence of true bifurcations in the study groups.<sup>5</sup> The CACTUS study is the first large-scale study in which a single technique specifically conceived to fully cover the bifurcation carina was used, and the inclusion criteria demanded a significant stenosis on the MB and SB (92% of the lesions included were true bifurcations). The study failed to prove the hypothesis of the superiority of crush stenting in reducing the restenosis rate compared with provisional T-stenting. The

**Table 6. Quantitative Coronary Angiography Measurements**

	Crush Group (n=177)		Provisional-Stenting Group (n=173)	
	MB	SB	MB	SB
<b>Baseline</b>				
RVD, mm	2.85±0.33	2.30±0.31	2.74±0.35*	2.16±0.33*
MLD, mm	0.90±0.38	0.84±0.32	0.83±0.33	0.83±0.30
Diameter stenosis, %	68±12	63±12	69±12	61±13
Length, mm	15.8±8.7	5.9±4.7	14.7±8.2	5.7±4.2
<b>Final</b>				
RVD, mm	2.99±0.47	2.43±0.36	2.87±0.42*	2.24±0.35*
Final MLD, mm	2.71±0.32	1.94±0.39	2.58±0.33*	1.65±0.39*
Diameter stenosis, %	12±6	16±11	13±6	27±14*
Acute gain, mm	1.47±0.56	1.41±0.54	1.1±0.46	0.81±0.42*
<b>Follow-up at 6 months</b>				
RVD, mm	2.98±0.43	2.37±0.34	2.91±0.48	2.36±0.35
MLD, mm	2.24±0.52	1.66±0.51	2.19±0.58	1.52±0.54*
Diameter stenosis, %	25±14	30±19	25±16	31±22
Late lumen loss, mm	0.14±0.41	0.29±0.52	0.06±0.53	0.13±0.47
Net gain, mm	1.34±0.58	1.35±0.62	0.82±0.54	0.76±0.61
Restenosis, n (%)	7/152 (4.6)	20/152 (13.2)	10/150 (6.7)	22/150 (14.7)

RVD indicates reference-vessel diameter; MLD, minimum lumen diameter. Values are mean±SD or n (%).

\* $P<0.05$  for comparisons between crush and provisional-stenting groups.



**Figure.** Restenosis rates and late lumen loss in the MB and SB of the crush stenting (CRUSH) and provisional T-stenting (PROV) groups.

clinical implication of this finding is that in most cases, provisional rather than elective stenting of the SB should be performed. Provisional stenting appears less expensive and simpler and can be performed with less contrast and in a shorter procedural time.<sup>5</sup> At the same time, the evidence of equivalent results in the 2 arms does not contradict the choice of crush stenting in selected cases with complex anatomy or with diffuse disease on the SB.

SB stenting may be required in approximately one third of bifurcations. Previous studies evaluating drug-eluting stents in this setting have shown that the rate of crossover from a provisional SB strategy to stenting of the SB may vary from 2% to 51%.<sup>4,6</sup> This wide range of SB stenting rates in different studies mirrors relevant differences in study design, type of lesions included, and criteria for stenting the SB. The low incidence of SB stenting in the study by Pan et al<sup>6</sup> (2%) and in the Nordic trial<sup>5</sup> (4%) may be the consequence of the very strict study criteria, which limited the use of stenting on the SB to cases of complete absence of flow<sup>5</sup> or impaired flow and severe residual stenosis.<sup>6</sup> This attitude seems reasonable when dealing with small SBs, but it may provide unsatisfactory clinical results when the SB has a larger diameter. The acceptance of a suboptimal result on the SB after MB stenting (ie, residual stenosis >50%, Thrombolysis in Myocardial Infarction flow grade 1 to 2), as in these studies, derives from the lack of confidence in alternative treatments. Similar results rarely have been considered acceptable in any other lesion subset since stents became available.<sup>17,18</sup> Another likely reason for the higher percentage

of SB stenting in the CACTUS trial than in the above studies is the different lesion selection, because SBs with diffuse disease were not excluded, and only true bifurcations were considered. Compared with the Nordic trial,<sup>5</sup> lesions included in the CACTUS trial had a significantly higher baseline percentage stenosis on the SB ( $61 \pm 13\%$  in the CACTUS study versus  $46 \pm 26\%$  in the Nordic study,  $P < 0.001$ ) and a smaller baseline SB minimal lumen diameter ( $0.83 \pm 0.30$  mm in the CACTUS study versus  $1.21 \pm 0.61$  mm in the Nordic study,  $P < 0.001$ ). Similar to CACTUS, the percentage of double-SES implantation in true bifurcation lesions in a large registry such as the ARTS II study (Arterial Revascularization Therapies Study Part II) was 22%.<sup>8</sup>

### Adverse Events

The overall outcomes of the present study show a good safety profile for SES implantation in coronary bifurcations. Regardless of the strategy adopted, the incidence of MACE was lower than that reported in studies from the bare-metal stent era.<sup>1-3</sup> This finding further supports the hypothesis that SES implantation can be considered a viable treatment in most bifurcation lesions.<sup>5</sup> It should also be recognized that the MACE rates in the CACTUS study are not comparable with those in other bifurcation studies such as the Nordic study<sup>5</sup> because of the inclusion of periprocedural MI in MACE reported in the present study.

Bifurcation lesions have been identified as independent predictors of ST.<sup>19</sup> Moreover, in the first study evaluating SES implantation on both branches using the T-stenting technique, a 3.5% rate of ST was reported, and similar results were obtained from the initial experience with crush stenting in Milan, Italy (4.5%),<sup>10</sup> and in a multicenter experience (4.3%).<sup>11</sup> These findings raised concerns about the safety of stenting both branches and discouraged the use of crush or other techniques that result in overlapping stent struts. It was somewhat surprising to observe lower rates of ST in the more recent studies evaluating SES implantation in bifurcations, ie, Nordic 1/413 (0.2%; 1.2% including cardiac death)<sup>5</sup>; CACTUS 5/350 (1.4%), with no difference between the 2 arms; and ARTS II 5/324 (1.5%),<sup>8</sup> with no difference between those treated with double stenting (1/61, 1.6%) and those treated with 1 stent (4/263, 1.5%). In the CACTUS study, all cases of ST were adjudicated as ARC-definite ST, because the high angiographic surveillance in the present study made any ARC-probable ST become ARC-definite ST. The reduction of ST in contemporary studies may be a consequence of a multifactorial improvement in stent implantation and patient management. In addition, the crush technique has evolved and is now performed with less stent protrusion into the MB and with mandatory 2-step FKI (ie, high-pressure SB balloon dilation followed by simultaneous kissing-balloon inflation).<sup>15,20</sup> Unfortunately, in the CACTUS study, no emphasis was put on the 2-step FKI in patients treated with the crush technique.<sup>10,15,20-22</sup> This may explain the relatively small final minimal lumen diameter ( $1.94 \pm 0.39$  mm) obtained in the SB in patients randomized to the crush technique. It is conceivable that the rate of angiographic restenosis in this group of lesions would have been lower if a more aggressive technique had been used. Finally,

and keeping in mind all of the limitations associated with a post hoc analysis, it is interesting to see that the lack of FKI was associated with adverse angiographic and clinical events.

### Study Limitations

The CACTUS study enrolled patients with very focal stenosis on the SB, and we do not know what the best strategy would be in patients with disease in the SB that is as diffuse as that present in the MB. No specific functional studies were performed at the time of follow-up to evaluate whether the angiographic restenosis was clinically relevant, a problem frequently outlined in bifurcation lesions.<sup>23</sup> Little can be stated about the long-term safety of either approach used in the CACTUS study, because we are reporting only the 6-month results.

### Conclusions

In most bifurcation lesions with a significant stenosis in both branches, a strategy to stent the MB is effective, with the need to implant a second stent in the SB occurring approximately one third of the time. The implantation of 2 stents does not appear to be associated with a higher incidence of adverse events, taking into account that the follow-up was limited to 6 months and that most patients were still on dual-antiplatelet therapy.

## Appendix

### Steering Committee

Antonio Colombo and Flavio Airoldi.

### Clinical Events Committee

Giuseppe Biondi-Zoccai, Carlo Briguori, John Cosgrave.

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### Statistical Support

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## Disclosures

None.

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### CLINICAL PERSPECTIVE

The optimal strategy in the percutaneous treatment of true coronary bifurcation lesions has not been fully clarified. In this 350-patient randomized multicenter trial, we compared the “crush” technique of electively stenting both branches versus stenting only the main branch, with provisional side-branch stenting if needed, with sirolimus-eluting stents. Regardless of the technique used, sirolimus-eluting stent implantation in true bifurcation lesions results in good clinical and angiographic results with acceptable midterm safety. The rates of angiographic restenosis, stent thrombosis, and major adverse cardiovascular events at 6 months were similar in both groups. Thus, in most bifurcations with a significant stenosis in both branches, a provisional strategy of stenting the main branch only is effective, with the need to implant a second stent on the side branch occurring in approximately one third of cases. However, if 2 stents are required and are implanted with the crush technique, there appears to be no increased risk of adverse events at 6 months.