Randomized trial on routine vs. provisional T-stenting in the treatment of *de novo* coronary bifurcation lesions

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Aims	We investigated whether routine T-stenting reduces restenosis of the side branch as compared with provisional T-stenting in patients with *de novo* coronary bifurcation lesions.
Methods and results	Our randomized study assigned 101 patients with a coronary bifurcation lesion to routine T-stenting with sirolimus-eluting stents (SES) in both branches and 101 patients to provisional T-stenting with SES placement in the main branch followed by kissing-balloon angioplasty and provisional SES placement in the side branch only for inadequate results. Primary endpoint was per cent diameter stenosis of the side branch at 9 month angiographic follow-up. Angiographic follow-up in 192 (95%) patients revealed a per cent stenosis of the side branch of $23.0 \pm 20.2\%$ after provisional T-stenting (19% with side-branch stent) and of $27.7 \pm 24.8\%$ ($P = 0.15$) after routine T-stenting (98.2% with side-branch stent). The corresponding binary restenosis rates were 9.4 and 12.5% ($P = 0.32$), prompting re-intervention in 5.0 and 7.9% ($P = 0.39$), respectively. In the main branch, binary restenosis rates were 7.3% after provisional and 3.1% after routine T-stenting ($P = 0.17$). The overall 1 year incidence of target lesion re-intervention was 10.9% after provisional and 8.9% after routine T-stenting ($P = 0.64$).
Conclusions	Routine T-stenting with SES did not improve the angiographic outcome of percutaneous coronary intervention of coronary bifurcation lesions as compared with stenting of the main branch followed by kissing-balloon angioplasty and provisional side-branch stenting.
Keywords	Coronary disease • Bifurcations • Stents • Sirolimus • Restenosis

Introduction

The optimal technical approach to catheter-based treatment of coronary bifurcation lesions is still a matter of debate. Compared with plain balloon angioplasty, stents improved the primary result of catheter treatment of bifurcation lesions and reduced the risk of abrupt closure.[1–4] Nevertheless, in the era of bare-metal stents, the need for re-intervention continued to be high.[2–4] Specifically, recurrences in the side branch constituted a major problem. Although the analysis of registry data revealed better outcome, if stent placement in the side branch could be avoided, restenosis rates in non-stented side branches were still in the range of 30%.[2–4]

Drug-eluting stents held promise to solve this issue. The first randomized study on drug-eluting stents for bifurcation lesions

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revealed restenosis rates as low as 4% in the main branch.[5] In the side branch, however, the results were disappointing with restenosis rates of 20%, irrespective of whether the operators intended to avoid the side-branch stent or pursued routine side-branch stenting.[5] In addition, the incidence of 6.3% for stent thrombosis among patients with a side-branch stent was worrisome.[5] The authors highlighted the problem that conventional T-stenting results in incomplete coverage of the origin of the side branch. They suggested that this may impair outcome.[5] Interpretation of their study was, however, hampered by a large number of patients with side-branch stents in the provisional side-branch stenting arm and by the diversity of techniques for stenting of the side branch.

We hypothesized that stenting of the side branch with sirolimus-eluting stents (SES) can reduce side-branch restenosis, if a stenting technique is applied that avoids non-stented gaps at the orifice of the side branch with minimal stent distortion. To test this hypothesis we performed the 'Bifurcations Bad Krozingen' (BBK) study to assess the effect of routine T-stenting on restenosis of the side branch as compared with provisional T-stenting.

Methods

Study population

The study included patients with stable angina pectoris or a positive stress test, attributable to a *de novo* bifurcation lesion of a native coronary artery with >50% diameter stenosis of the main branch or the side branch, as defined by Lefevre *et al.*[6] Patients were not eligible, if on visual estimation the vessel size of the side branch was <2.25 mm or if the main branch was >4 mm in diameter or <2.5 mm. Other major exclusion criteria were left main stenosis, intraluminal thrombus, heavy calcification, severe tortuosity, contraindication to aspirin, heparin, clopidogrel, stainless steel, or sirolimus, and a history of bleeding diathesis or coagulopathy. The study, carried out according to the Declaration of Helsinki, was approved by the ethics committee of the medical faculty of the University of Freiburg, Germany. All patients gave written informed consent before enrolment.

Randomization, stenting procedure, and follow-up

The study was designed as a non-blinded, randomized, single-centre trial. We allocated patients to provisional or routine T-stenting using a computer-generated random sequence, set in blocks of 20. The size of the block and the random sequence were selected by the statistician and were unknown to the investigators and medical staff caring for the patients. Randomization was performed immediately before catheter treatment of the bifurcation.

At least 2 h before the intervention, all patients received a loading dose of 600 mg of clopidogrel. In the catheterization laboratory, we administered an intra-arterial dose of 100−140 U/kg heparin plus i.v. aspirin, 500 mg, if the patient was not on chronic treatment with aspirin. We did not administer glycoprotein IIb/IIIa inhibitors, except for bail out. For the stenting procedure, we exclusively used SES (Cypher™, Cordis Corporation).

After placement of the stent in the main branch, rewiring and pre-dilatation of the side branch, we advanced the second stent in the side branch and placed a balloon in the main branch at the orifice of the side branch. Then, the stent in the side branch was meticulously positioned, taking care that the marker band and about the first half

millimetre of the stent were within the main branch stent. When the optimal position of the side-branch stent was achieved, we deployed the side-branch stent by a kissing balloon manoeuvre, first inflating the side-branch balloon with the stent and immediately afterwards the main branch balloon. Among the many approaches to bifurcation stenting, we specifically chose our technique with the intention to avoid non-stented gaps at the orifice of the side branch with minimal stent distortion or stent overlap in the carina region. In the provisional T-stenting group, the main branch was stented and final kissing-balloon dilatation with a balloon matching the size of the vessel was performed in all patients, even if there was no relevant side-branch stenosis. This was done to adapt the main branch stent to the orifice of the side branch and to facilitate access to the side branch, in case it will be needed in the future. Thus, final 'kissing-balloon' dilatation was performed in both groups irrespective of whether they were assigned to routine or provisional T-stenting. In the provisional T-stent arm, crossover to side-branch stenting was mandated in case of a flow limiting dissection or residual stenosis of ≥75%. After percutaneous coronary intervention, we recommended lifelong aspirin (≥100 mg/day) and clopidogrel (≥75 mg/day) for 6 months.

Plasma concentrations of creatine kinase and its MB isoenzyme were systematically determined for 48 h after the intervention. In addition, we obtained at least three ECG recordings during that time. Patients returned to the hospital for routine angiographic re-study and clinical evaluation at 9 months. We also conducted an interview at 30 days, at 1 year, and at 2 years. For patients reporting cardiac symptoms, at least one clinical and electrocardiographic examination was performed in the outpatient clinic or by the referring physician. At 1 year and at 2 years, all information derived from contingent hospital re-admission records or provided by the referring physician or by the outpatient clinic were entered into the computer database.

Quantitative coronary angiography

By visual assessment, bifurcation lesions were characterized according to the Medina classification.[7] For quantitative coronary angiography, angiograms obtained at baseline, at completion of the intervention, and at 9 month follow-up were analysed with the use of a computer-based system dedicated to bifurcation analysis (Qangio XA, version 7.0, Medis, Leiden, Netherlands), according to the standard operating procedure of our angiographic core laboratory.[8] We obtained quantitative angiographic measurements of the three segments of the bifurcation lesion: the proximal and distal segment of the main branch and the side branch. We always performed measurements in the stented or balloon-treated portion of the vessel (in-stent) and in the distal or proximal 5 mm margin (edge). In-segment analyses comprised the in-stent and the edge area. In addition, we obtained the bifurcation angle from the analysis system.

Study endpoints and definitions

Primary endpoint of the study was the in-segment per cent diameter stenosis of the side branch at 9 month follow-up. In addition, we assessed various other variables of 9 month angiographic outcome, both in the side branch and in the main branch.

We also assessed 1 and 2 year clinical outcome. We monitored the incidences of death from any cause and myocardial infarction. Myocardial infarction was defined as the presence of new Q waves in two or more contiguous electrocardiographic leads or an elevation of creatine kinase or its MB isoenzyme to at least three times the upper limit of normal in two samples during hospitalization. After discharge, the diagnosis of myocardial infarction was made according to the European

Society of Cardiology/American College of Cardiology consensus document and based on new rise in troponin T $\geq$0.03 mg/L associated with either typical symptoms and/or typical ECG changes and/or typical angiographic findings.[9] We determined the incidence of stent thrombosis according to the Academic Research Consortium (ARC) criteria.[10] In addition, we assessed target lesion revascularization (TLR) defined as coronary artery bypass surgery or repeat percutaneous angioplasty involving the stented segment and performed for symptoms or signs of ischaemia in the presence of angiographic restenosis. All events were classified and adjudicated by two physicians not involved in the follow-up process. Clinical data entry and quantitative coronary angiography were double-checked by a trained study personnel.

Statistical methods

On the basis of previously published data,[5] we assumed a per cent diameter stenosis of 32 $\pm$ 22% in the side branch after provisional T-stenting. To achieve 80% power, to detect a 33% reduction in per cent diameter stenosis of the side branch by routine T-stenting as compared with provisional T-stenting at a level of significance of 5%, we needed a sample size of 160 patients. To allow for potential losses to angiographic follow-up, we aimed for 200 patients. All analyses were performed according to the 'intention to treat' principle. Hence, patients in the provisional T-stenting arm who received a side-branch stent and patients in the routine T-stenting arm in whom the side-branch stent could not be placed were analysed as randomized and not according to the treatment they were actually given. The analysis of angiographic outcome measures, including the primary end-point, was restricted to patients with follow-up angiography, whereas the analysis of clinical outcome was based on all patients as randomized.

For all statistical analyses, we used the SPSS software package (version 15, SPSS Inc., Chicago, IL, USA). Discrete variables are reported as counts (percentages), and continuous variables are reported as mean $\pm$ standard deviation. For discrete variables, we tested differences between groups with the χ^2 test or Fisher's exact test when expected cell sizes were <5. We used the two-tailed t-test to compare continuous variables. Where appropriate, we also performed ANCOVA with the baseline measurement as covariate, to corroborate our primary analysis. ANCOVA always confirmed the result of the t-test. All tests were two-sided and statistical significance was set at 5%.

Results

Study cohort and procedural outcome

The trial profile is shown in *Figure 1*. From April 2005 to August 2006, we enrolled 202 consecutive patients; 101 were assigned to the provisional T-stenting and 101 to routine T-stenting.
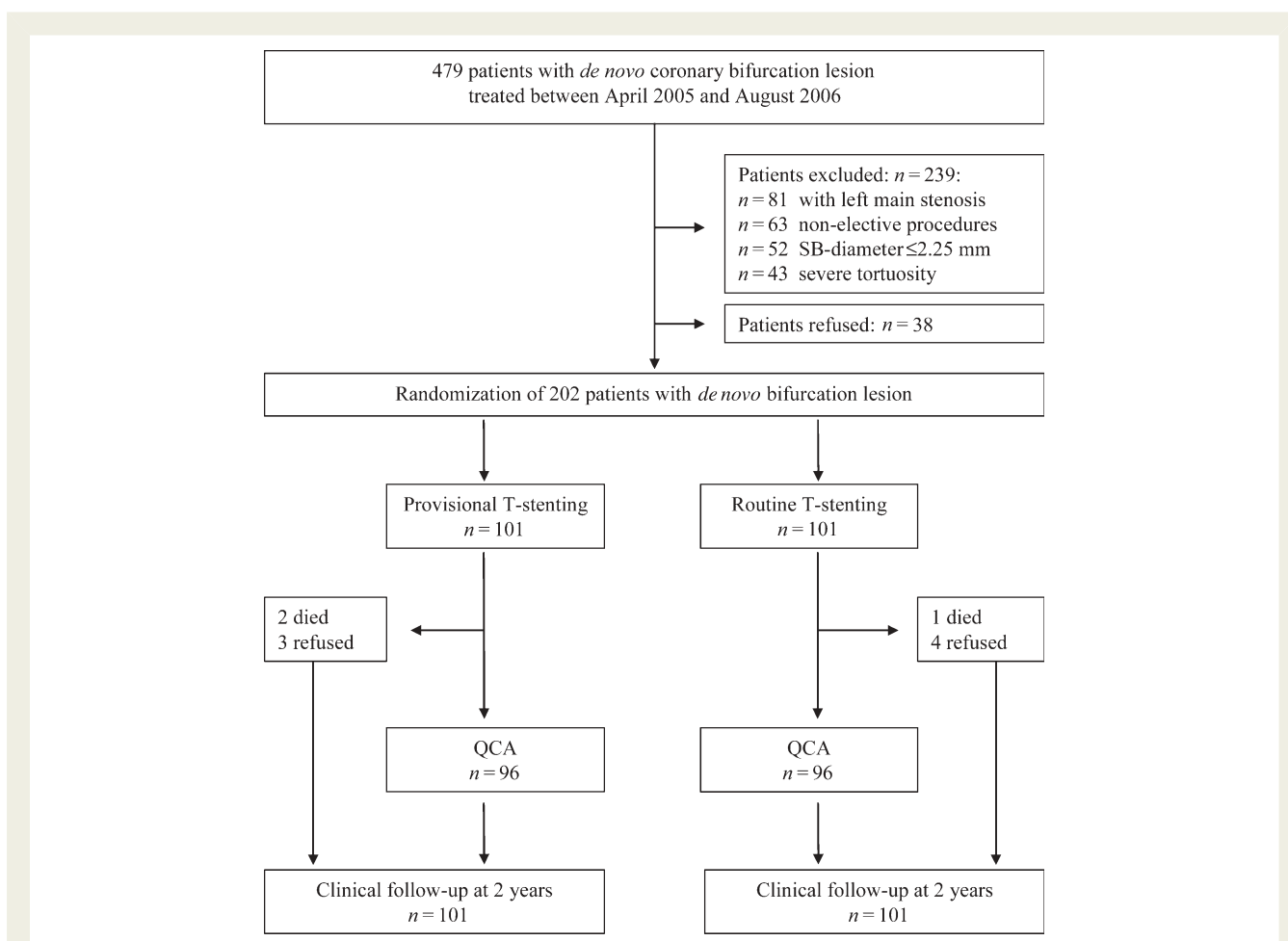

Figure 1 Flow diagram of the Bad Krozingen Bifurcation Study. QCA, quantitative coronary angiography.

Table 1 Baseline clinical characteristics

	Provisional T-stenting (*n* = 101)	Routine T-stenting (*n* = 101)	*P*-value
Age (years)	66.7 ± 9.2	66.9 ± 10.5	0.92
Male (%)	80 (79.4)	79 (78.2)	0.50
Diabetes mellitus (%)	26 (25.7)	19 (18.8)	0.16
Current smoker (%)	10 (9.9)	14 (13.9)	0.26
LDL-cholesterol (mg/dL)	130 ± 44	126 ± 40	0.52
Hypertension (%)	93 (92.1)	90 (89.1)	0.32
Renal dysfunction (%)	21 (20.8)	24 (23.7)	0.61
Previous MI (%)	19 (18.8)	21 (20.8)	0.43
History of PCI (%)	45 (44.6)	52 (51.5)	0.20
History of CABG (%)	4 (4.0)	3 (3.0)	0.50
Ejection fraction (%)	59 ± 12	61 ± 12	0.30

CABG, coronary artery bypass grafting; LDL, low-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention.

We obtained 9 month angiographic follow-up in 192 patients (96 patients of each group); reasons for missing follow-up angiography were death in three patients and patient refusal in seven. Two-year clinical follow-up was complete in all surviving patients.

With respect to baseline demographic and clinical characteristics (*Table 1*), there were no significant differences between the two study groups. The mean age of our study population was 67 years, and 79% were male. Diabetes mellitus was prevalent in 22%. The two groups were well balanced with respect to angiographic characteristics, including the distribution of the Medina classification (*Table 2*). In both groups, 68% of the bifurcation lesions involved both the side branch and the main branch, and the majority was located in the territory of the left anterior descending coronary artery. On average, vessel sizes were 3.1 mm in the proximal main branch and 2.4 mm in the side branch with lesion lengths of 21 and 10 mm, respectively. The mean angle between side branch and main branch was 49°.

In 19 patients assigned to provisional T-stenting, a stent was placed in the side branch because of a relevant residual stenosis after the kissing-balloon manoeuvre in 14 patients and because of a flow-limiting dissection in five patients. In three patients assigned to routine T-stenting, the main-branch stent could not be crossed with the side-branch stent, despite multiple kissing-balloon pre-dilatations. Two patients received abciximab periinterventionally.

Angiographic results

We did not find any significant differences between the two study groups in any of the angiographic variables for restenosis assessed at 9 month follow-up (*Table 3*). As shown in *Figure 2*, the cumulative distribution of in-segment per cent diameter stenosis of the side branch at angiographic follow-up, our primary study endpoint, did not differ significantly between the two study groups (*P* = 0.15). On average, it was of 23.0 ± 20.2% after provisional T-stenting and 27.7 ± 24.8% after routine T-stenting [mean difference 4.7; 95% confidence interval (CI) −11.1 to 1.7]. The

Table 2 Baseline angiographic and procedural characteristics

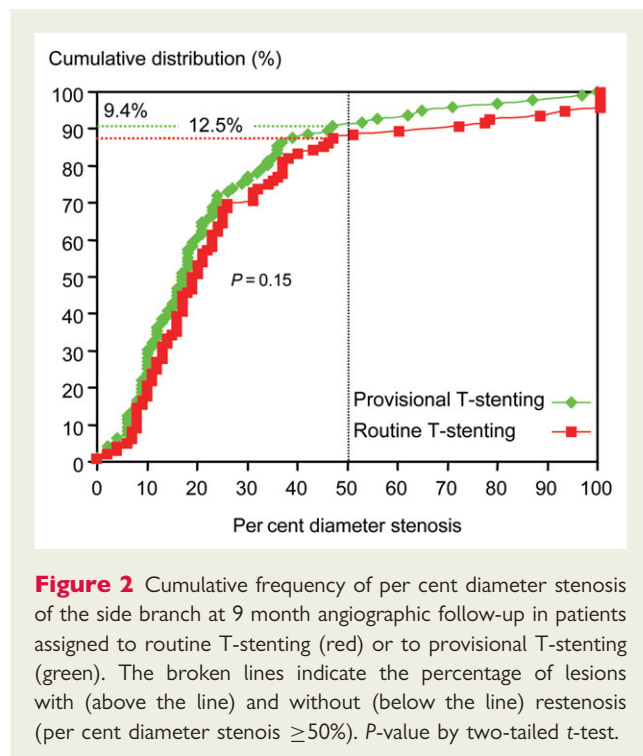|	Provisional T-stenting (*n* = 101)	Routine T-stenting (*n* = 101)	*P*-value
Number of vessels affected (%)			
One vessel	35 (34.7)	26 (25.8)	0.45
Two vessels	28 (27.7)	27 (26.7)	
Three vessels	38 (37.6)	48 (47.5)	
Location of bifurcation (%)			
LAD territory	76 (75.2)	74 (73.3)	0.52
LCX territory	16 (15.8)	21 (20.8)	
RCA territory	9 (8.9)	6 (5.9)	
Medina classification (%)			
111	36 (35.6)	31 (30.7)	0.91
110	12 (11.9)	10 (9.9)	
101	8 (7.9)	6 (5.9)	
100	3 (3.0)	2 (2.0)	
011	25 (24.8)	32 (31.7)	
010	12 (11.9)	14 (13.9)	
001	5 (5.0)	6 (5.9)	
Vessel size (mm)			
Main branch	3.08 ± 0.40	3.08 ± 0.38	0.10
Side branch	2.39 ± 0.31	2.38 ± 0.37	0.87
Lesion length (mm)			
Main branch	21.7 ± 7.5	20.9 ± 8.2	0.48
Side branch	10.4 ± 4.1	9.9 ± 4.2	0.36
Bifurcation angle (°)	49.9 ± 59.9	47.6 ± 17.6	0.71
Nominal final balloon size (mm)			
Main branch	3.15 ± 0.35	3.17 ± 0.33	0.78
Side branch	2.51 ± 0.22	2.61 ± 0.24	0.02
Maximal inflation pressure (atm)			
Main branch	13.49 ± 2.46	13,71 ± 2.54	0.53
Side branch	12.33 ± 3.28	12.95 ± 2.30	0.14
Cross over (%)	19 (18.8)	3 (3.0)	<0.001
Final kissing (%)	101 (100)	101 (100)	1.0
Multi vessel PCI (%)	36 (35.6)	35 (34.7)	0.50
Contrast volume (mL)	204 ± 86	203 ± 109	0.94
Procedure time (min)	51 ± 23	56 ± 25	0.16
Fluoroscopy time (min)	13 ± 7	15 ± 9	0.20
Patient radiation exposure (Gy cm^2)	41.2 ± 23.2	47.7 ± 37.6	0.16

LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; PCI, percutaneous coronary intervention.

corresponding binary restenosis rates were 9.4 and 12.5%, respectively [relative risk (RR) 0.75; 95% CI 0.32−1.78; *P* = 0.32]. As there was no detectable late loss in the edge in either group (*Table 3*), the findings on in-stent per cent diameter stenosis were similar to those on in-segment per cent diameter stenosis (*Figure 2*).

Table 3 Quantitative coronary angiography according to bifurcation segments

	Proximal segment			Distal segment			Side branch		
	Prov.	Syst.	*P*-value	Prov.	Syst.	*P*-value	Prov.	Syst.	*P*-value
In-stent MLD (mm)									
Pre-PCI	1.53 ± 0.86	1.63 ± 0.86	0.42	1.28 ± 0.71	1.20 ± 0.67	0.43	1.13 ± 0.62	1.11 ± 0.64	0.80
Post-PCI	3.22 ± 0.45	3.17 ± 0.51	0.46	2.77 ± 0.39	2.74 ± 0.41	0.60	1.97 ± 0.46	2.30 ± 0.43	<0.001
Follow-up	3.23 ± 0.54	3.16 ± 0.58	0.37	2.77 ± 0.67	2.65 ± 0.60	0.22	1.93 ± 0.57	1.98 ± 0.76	0.65
In-stent per cent diameter stenosis									
Pre-PCI	50.3 ± 26.7	47.3 ± 26.1	0.42	53.4 ± 24.4	54.9 ± 24.3	0.64	53.1 ± 23.5	54.4 ± 22.3	0.68
Post-PCI	2.52 ± 9.34	3.03 ± 10.7	0.72	7.64 ± 8.63	9.32 ± 9.73	0.20	16.6 ± 13.9	9.56 ± 11.4	<0.001
Follow-up	2.95 ± 12.0	3.57 ± 11.4	0.71	9.90 ± 18.4	12.5 ± 14.5	0.28	18.3 ± 20.9	23.4 ± 27.3	0.15
Acute gain (mm)	1.69 ± 0.84	1.54 ± 0.83	0.21	1.48 ± 0.77	1.53 ± 0.69	0.65	0.84 ± 0.68	1.19 ± 0.60	<0.001
In-stent late loss (mm)	−0.01 ± 0.42	−0.02 ± 0.46	0.90	0.01 ± 0.62	0.08 ± 0.51	0.43	0.03 ± 0.57	0.32 ± 0.82	0.005
Edge MLD (mm)									
Post-PCI	2.92 ± 0.53	2.92 ± 0.59	0.99	2.21 ± 0.53	2.21 ± 0.46	0.97	1.90 ± 0.51	1.92 ± 0.48	0.84
Follow-up	2.94 ± 0.60	2.98 ± 0.66	0.67	2.26 ± 0.59	2.30 ± 0.48	0.62	1.94 ± 0.48	1.94 ± 0.63	0.99
Edge per cent diameter stenosis									
Post-PCI	8.37 ± 8.37	9.65 ± 9.04	0.30	14.9 ± 10.5	14.6 ± 9.36	0.83	15.1 ± 12.4	16.3 ± 10.5	0.44
Follow-up	9.70 ± 10.1	8.47 ± 10.7	0.41	13.9 ± 10.4	13.4 ± 8.19	0.70	12.5 ± 11.1	13.2 ± 11.9	0.65
Edge late loss (mm)	−0.29 ± 0.69	−0.17 ± 0.66	0.25	−0.50 ± 0.64	−0.35 ± 0.57	0.09	0.01 ± 0.29	−0.03 ± 0.33	0.62

MLD, minimal luminal diameter.

Figure 2 Cumulative frequency of per cent diameter stenosis of the side branch at 9 month angiographic follow-up in patients assigned to routine T-stenting (red) or to provisional T-stenting (green). The broken lines indicate the percentage of lesions with (above the line) and without (below the line) restenosis (per cent diameter stenois ≥50%). *P*-value by two-tailed *t*-test.

Figure 3 Comparison of maximal per cent diameter stenosis involving the bifurcation irrespective of the site of restenosis (side branch, proximal, or distal main vessel) between the two study groups, before intervention and at 9 month follow-up for the entire cohort and for strata defined by side branch or main branch involvement at 9 month follow-up. The corresponding Medina classifications are given below the graph. Columns represent mean and error bars represent standard deviation.

Consistent with the data on per cent diameter stenosis, minimal luminal diameters in the side branch at angiographic follow-up did not differ significantly between the two groups (*Table 3*). Both acute gain and late loss in the side branch were significantly larger after routine T-stenting than after provisional T-stenting (*Table 3*).

In the proximal and distal segments of the main branch, average in-stent per cent diameter stenoses at follow-up ranged between 3 and 12%, and did not show any significant differences between the two study groups (*P* = 0.28). Binary restenosis rate of the main branch was 7.3% after provisional T-stenting and 3.1% after routine T-stenting (RR 2.3; 95% CI 0.6–9.0; *P* = 0.19). Similar to the findings in the side branch, there was no detectable late loss in any of the edges of the main branch.

The maximal per cent diameter stenosis involving the bifurcation irrespective of the site of restenosis (side branch, proximal, or distal main vessel) was 29.7 ± 18.7% after provisional T-stenting and 32.2 ± 23.5% after routine T-stenting (mean difference −2.4%; 95% CI −8.5 to 3.6%; *P* = 0.43; *Figure 3*), translating into an overall binary angiographic restenosis rate of 12.5 and 13.5%, respectively (RR 0.91; 95% CI 0.39–2.12; *P* = 0.83). We did not find any significant differences in the maximal per cent diameter stenosis between the two groups, irrespective of whether only the side branch or only the main branch or both branches were involved (*Figure 3*).

Clinical outcome

Between the two study groups, there were no significant differences in clinical outcome. During 1 year follow-up (*Table 4*), target lesion intervention was performed in 10.9% of the patients
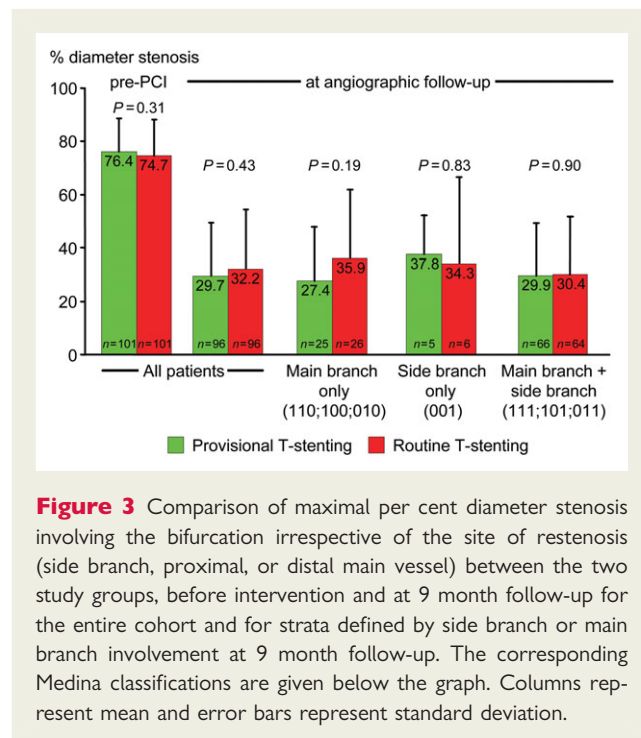
Table 4 One year clinical outcome

	Provisional T-stenting (n = 101)	Routine T-stenting (n = 101)	P-value
Death (%)	2 (2.0)	1 (1.0)	1.0
Non-fatal myocardial infarction (%)	1 (1.0)	2 (2.0)	1.0
Death or non-fatal myocardial infarction (%)	3 (3.0)	3 (3.0)	1.0
Target lesion revascularization (%)	11 (10.9)	9 (8.9)	0.64
Main branch	7 (6.9)	3 (3.0)	0.19
Side branch	5 (5.0)	8 (7.9)	0.39
Any MACE (%)	13 (12.9)	12 (11.9)	0.83
Stent thrombosis by ARC definition (%)			
Definite	1 (1.0)	2 (2.0)	1.0
Probable	1 (1.0)	0 (0)	1.0
Possible	1 (1.0)	1 (1.0)	1.0

ARC, Academic Research Consortium; MACE, major adverse cardiac event.

assigned to provisional T-stenting and 8.9% of the patients assigned to routine T-stenting (RR 1.2; 95% CI 0.5–2.9; *P* = 0.64). Likewise, we did not find a significant difference in the rate of target lesion re-intervention after routine T-stenting as compared with that after provisional T-stenting, either for the side branch (7.9 vs.
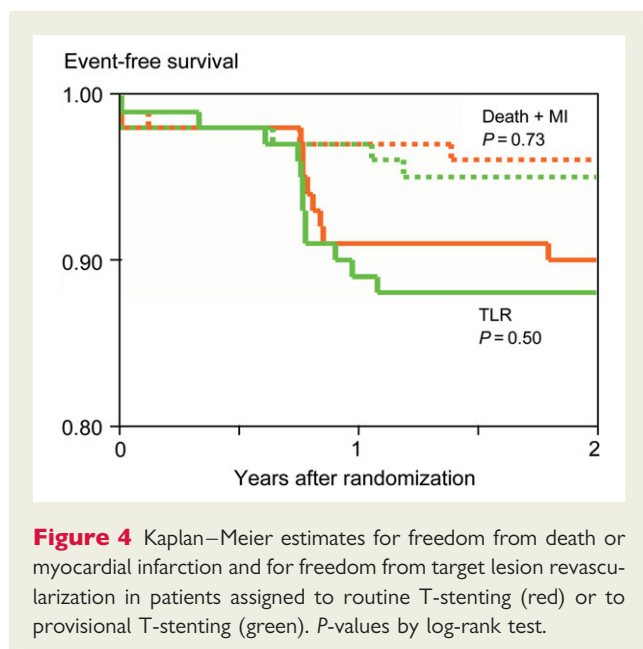
Figure 4 Kaplan–Meier estimates for freedom from death or myocardial infarction and for freedom from target lesion revascularization in patients assigned to routine T-stenting (red) or to provisional T-stenting (green). *P*-values by log-rank test.

5.0%; RR 1.6; 95% CI 0.5–4.9; $P = 0.39$) or for the main branch (3.0 vs. 6.9%; RR 0.4; 95% CI 0.1–1.7; $P = 0.19$).

During 1 year follow-up, one patient assigned to routine T-stenting and two patients assigned to provisional T-stenting died. Causes of death were sudden death at Day 48 in the patient with side-branch stent and in the patients without side-branch stents, pump failure at Day 5, and septic shock at Day 39. In addition, there were two non-fatal myocardial infarctions in the routine T-stenting group at Days 4 and 15 and one in the provisional T-stenting group at Day 3, all in the area supplied by the bifurcation treated. In both groups, three patients met the ARC criteria for definite, probable, or possible stent thrombosis during 1 year follow-up. The composite incidence of death and myocardial infarction as well as the composite incidence of death and myocardial infarction and TLR did not differ significantly between the two study groups (*Table 4*). Extending follow-up to 2 years (*Figure 4*), we observed one additional death in the routine T-stenting group (witnessed sudden death with documented open stents) and two in the provisional T-stenting group (carcinoma of pancreas, cerebrovascular accident). There were no further non-fatal myocardial infarctions, but one additional TLR in each group.

Discussion

Our randomized study on treatment of coronary bifurcation lesions with SES compared the angiographic outcome of routine T-stenting with that of provisional T-stenting. As our key result we did not find that routine T-stenting reduced the risk of the side-branch restenosis. At 9 month angiographic follow-up, none of the angiographic variables for restenosis of the side branch, including in-segment per cent diameter stenosis, our primary endpoint, showed a significant difference between the two treatment arms. We even found a trend towards a higher risk of restenosis with routine T-stenting. Consistent with the angiographic findings, the need for re-intervention at the side branch was similar in both

treatment arms and ranged <8%. Contrary to the first randomized trial on SES for coronary bifurcation lesions,[5] our findings do not raise any specific safety concerns. Irrespective of the treatment assigned, the 1 year incidences of death and myocardial infarction and of stent thrombosis by any of the ARC criteria were in the range of 3%, with very few additional cardiac events between 1 and 2 years. The clinical outcome, thus, was quite comparable with that encountered with on-label use of drug-eluting stents. Consistent with all previous studies, we found a lower angiographic and clinical restenosis in the main branch as compared with the side branch with no significant effect of side-branch treatment on main-branch outcome.

The outcome in the side branch was the result of two opposing effects: compared with the respective alternative treatment strategy, acute gain was significantly better with routine T-stenting, but late loss was significantly lower with provisional T-stenting. Previous studies showed that the mechanisms of restenosis differ substantially between plain balloon angioplasty and stent placement. After stent placement, neointima formation accounts for >90% of the lumen loss, whereas after plain balloon angioplasty the contribution of neointima formation to restenosis is <30%.[11–13] With plain balloon angioplasty, remodelling due to elastic recoil and late vessel shrinkage is the predominant mechanism of post-procedural lumen loss.[11,12] It may be speculated that the stent in the main branch, which is partially pushed into the orifice of the side branch by the kissing balloon manoeuvre, limited remodelling of the side branch. This may explain the extraordinarily low late loss in the side branch after plain balloon angioplasty, which was smaller than anything reported before for plain balloon angioplasty. Hence, the final kissing balloon manoeuvre that was performed even in all patients assigned to provisional T-stenting appears to be an important feature of our study.

While our study was under way, the results of NORDIC Bifurcation Study, another randomized study on coronary bifurcation lesions, became available.[14] NORDIC included 413 patients randomly assigned to stenting both the main vessel and the side branch or stenting the main vessel only, with optional stenting of the side branch.[14] NORDIC used the same stent type as our study, but applied a variety of procedural techniques. Consistent with our findings and those of an earlier smaller trial,[15] NORDIC did not detect any significant difference between the two study arms in its primary endpoint, major adverse cardiac events (MACE). The authors cautioned, however, that the study was considerably underpowered given the low MACE rate found.[15] Overall, MACE rates in NORDIC were lower than those in our study. This may be explained by differences in risk profile of the study cohorts.

NORDIC also reported angiographic follow-up data for 307 patients.[14] Per cent diameter stenosis of the side branch at follow-up was significantly lower in the group assigned to routine stenting of the side branch as compared with the group assigned to optional side-branch stenting only. Thus, considering the primary endpoint of our study, NORDIC was positive in favour of routine side-branch stenting.[14] When comparing the angiographic results of NORDIC to our study, it is conspicuous that the strategy with routine stenting of the side branch yielded a similar outcome at follow-up with respect to in-stent per cent

diameter stenosis (24 ± 21% in NORDIC vs. 23 ± 27% in BBK) and binary restenosis rate (11.5% in NORDIC vs. 12.5% in BBK) of the side branch. Another observation that the two studies have in common is the substantial late-loss in the side branch with routine side-branch stenting (0.20 ± 0.57 mm in NORDIC vs. 0.32 ± 0.82 mm in BBK) and the negligible late-loss with provisional side-branch stenting (−0.04 ± 0.52 mm in NORDIC vs. 0.03 ± 0.57 mm in BBK). Nevertheless, the 9 month outcome in the side branch of the group with provisional side-branch stenting in BBK was considerably better than the corresponding group in NORDIC as evidenced by in-stent per cent diameter stenosis (18.3 ± 20.9 vs. 31 ± 22%) and binary restenosis rate (9.4 vs. 19.2%) of the side branch. Given the similar side-branch late loss, the favourable outcome of the side branch in the group with provisional T-stenting in BBK must have been caused by a better acute gain as compared with NORDIC. We attribute this difference to the final kissing-balloon dilatation that was performed in all patients of the provisional T-stenting group in BBK, but only in 32% of the optional side-branch stent group in NORDIC. Hence, the intention to avoid the side-branch stent should not prevent meticulous optimization of the side-branch results by kissing-balloon inflations with adequately sized balloons.

The issue of nomenclature needs to be addressed. Dealing with two variations of the T-stenting technique with stenting of the main branch first, we addressed the question whether with this general approach a stent should be placed in every side branch or only in side branches with an inadequate primary result. This counterpart is best described by the antonyms 'systematic' vs. 'provisional'. A recent review manuscript,[7] however, which categorized more than 20 subclasses bifurcation stenting, named a T-stenting technique that places the side-branch stent first 'systematic T-stenting' whereas the technique that places the side branch after the main branch stent was named 'elective T-stenting'. We felt that the term 'elective' is misleading in the context of our study as it is generally understood as the antonym to 'emergent'. To avoid confusion, we, therefore, used the terms 'routine T-stenting' and 'provisional T-stenting'.

Limitations

We designed our trial as a mechanistic angiographic study that addressed the issue of side-branch stenting as potential means of reducing side-branch restenosis after treatment of coronary bifurcation lesions with SES. Hence, our study was not powered to address clinical endpoints. A recent survey of the published literature identified per cent diameter stenosis, our primary outcome measure, as a valid surrogate for TLR.[16] Given that the point estimate for per cent diameter stenosis at 9 months even favoured provisional stenting, our observation that routine T-stenting did not reduce the incidence of clinically relevant recurrences after treatment of coronary bifurcation lesions appears to be robust.

We need to consider the potential bias because our study could not be blinded. To avoid such bias in the assessment of our primary endpoint and other angiographic variables, we used a computerized quantitative analysis system with only minimal operator interference.

The per cent diameter stenosis in the side branch after provisional T-stenting was lower than projected, which reduces the power to detect the projected 33% reduction in per cent diameter stenosis by routine T-stenting. On the other hand, angiographic follow-up was substantially higher than anticipated, 96 instead of 80 patients in each group. Thus, with the observed mean per cent diameter stenosis of 25.4% in the entire cohort and a common standard deviation of 22.5%, we maintain an 84% power to detect a 33% relative difference in per cent diameter stenosis in the side branch between the two groups at a level of significance of 5%.

Clinical implications

Irrespective of the proportion of patients receiving a side-branch stent, our T-stenting approach to the treatment of coronary bifurcation lesions with SES resulted in a favourable 2 year clinical outcome with a need for re-intervention in 11% of our patients. Our findings do not suggest placing a stent in a side branch that achieved an acceptable primary angiographic result after final kissing-balloon dilatation. On the other hand, placement of a side-branch stent for inadequate results such as relevant residual stenosis or extensive dissection does not appear to deteriorate late outcome. Thus, the intention to avoid a side-branch stent should not prevent meticulous optimization of the side-branch result, including a final kissing balloon manoeuvre.

The observed 2 year incidence of definite and probable stent thrombosis of 2% does not raise any specific concerns with respect to the treatment of coronary bifurcation lesions with SES, but clearly needs to be improved. Recent advances in the concomitant antiplatelet therapy, such as the development of more potent $P2Y_{12}$-receptor antagonists,[17,18] hold promise in this respect.

After placement of an SES, late loss in the side branch is still substantially higher than that in the main branch. Hence, there is room for further optimization of stent design with regard to the need of side branches.

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