Randomized Study on Simple Versus Complex Stenting of Coronary Artery Bifurcation Lesions
The Nordic Bifurcation Study

Terje K. Steigen, MD; Michael Maeng, MD; Rune Wiseth, MD; Andrejs Erglis, MD;
Indulis Kumsars, MD; Inga Narbute, MD; Pål Gunnes, MD; Jan Mannsverk, MD;
Oliver Meyerdierks, MD; Svein Rotevatn, MD; Matti Niemelä, MD; Kari Kervinen, MD;
Jan S. Jensen, MD; Anders Galløe, MD; Kjell Nikus, MD; Saila Vikman, MD; Jan Ravkilde, MD;
Stefan James, MD; Jens Aarøe, MD; Antti Ylitalo, MD; Steffen Helqvist, MD; Iwar Sjögren, MD;
Per Thayssen, MD; Kari Virtanen, MD; Mikko Puhakka, MD; Juhani Airaksinen, MD;
Jens F. Lassen, MD; Leif Thuesen, MD; for the Nordic PCI Study Group

Background—The optimal stenting strategy in coronary artery bifurcation lesions is unknown. In the present study, a strategy of stenting both the main vessel and the side branch (MV+SB) was compared with a strategy of stenting the main vessel only, with optional stenting of the side branch (MV), with sirolimus-eluting stents.

Methods and Results—A total of 413 patients with a bifurcation lesion were randomized. The primary end point was a major adverse cardiac event: cardiac death, myocardial infarction, target-vessel revascularization, or stent thrombosis after 6 months. At 6 months, there were no significant differences in rates of major adverse cardiac events between the groups (MV+SB 3.4%, MV 2.9%; P=NS). In the MV+SB group, there were significantly longer procedure and fluoroscopy times, higher contrast volumes, and higher rates of procedure-related increases in biomarkers of myocardial injury. A total of 307 patients had a quantitative coronary assessment at the index procedure and after 8 months. The combined angiographic end point of diameter stenosis >50% of main vessel and occlusion of the side branch after 8 months was found in 5.3% in the MV group and 5.1% in the MV+SB group (P=NS).

Conclusions—Independent of stenting strategy, excellent clinical and angiographic results were obtained with percutaneous treatment of de novo coronary artery bifurcation lesions with sirolimus-eluting stents. The simple stenting strategy used in the MV group was associated with reduced procedure and fluoroscopy times and lower rates of procedure-related biomarker elevation. Therefore, this strategy can be recommended as the routine bifurcation stenting technique. (***Circulation.*** 2006;114:1955-1961.)

Key Words: stents ■ angioplasty ■ angiography ■ restenosis ■ bifurcation ■ follow-up studies ■ stenosis

Bifurcation lesions are frequent and occur in ≈15% of percutaneous coronary interventions (PCIs).[1] Initial results with balloon angioplasty were poor, with a high risk of acute closure of the main vessel or side branch and a high restenosis rate.[2] Therefore, stenting with bare-metal coronary stents became the routine treatment of these lesions. Implantation of coronary stents minimized the problem of acute vessel closure, but bifurcation stenting was still associated

with a high rate of restenosis.[3] The restenosis problem appeared especially pronounced when multiple stents were used.[4] The use of sirolimus-eluting stents (SES) has been reported to reduce restenosis in simple and more complicated coronary lesions.[5–12] Therefore, the use of SES in both the main vessel and the side branch might further reduce the risk of vessel restenosis.[3] Two previous randomized studies addressed the issue of bifurcation treatment with SES.[5,10] Together with data from the Stenting Coronary Arteries in Non-stress/benestent Disease (SCANDSTENT)[6] trial, these studies suggested that the use of SES reduced problems with restenosis in bifurcation lesions and that the technically correct use of these stents resulted in low restenosis rates, both for the main vessel and for the side branch.[5,10] The present randomized study compared the clinical and angiographic outcome of a simple bifurcation treatment strategy (stenting the main vessel and optional stenting of the side branch; MV) with a complex strategy (stenting of both the main vessel and the side branch; MV+SB).

Methods

Patients and Study Design

This nonblinded, randomized, multicenter trial was conducted at 28 cardiology centers in Denmark, Sweden, Finland, Norway, and Latvia. From September 2004 to May 2005, a total of 413 patients were enrolled. A flow diagram of the study is shown in Figure 1. The protocol was approved by ethics committees in all participating countries, and all participating patients gave written informed consent.

Men and women, aged 18 years or older, with stable or unstable angina pectoris or silent ischemia and a de novo coronary bifurcation lesion were considered eligible for enrollment. A bifurcation lesion was defined according to Lefevre et al[13] and could be located in the anterior descending artery and a diagonal, the circumflex artery and an obtuse marginal, the right coronary artery and posterior descending artery/posterolateral artery, or the left main stem/circumflex artery/left anterior descending artery in a right-dominant system. The diameter of the main vessel and of the side branch should be ≥2.5 mm and ≥2.0 mm, respectively, by visual estimate. Exclusion criteria were ST-segment elevation acute myocardial infarction within 24 hours, life expectancy <1 year, S-creatinine ≥200 μmol/L, allergy to any of the drugs used (aspirin, clopidogrel, ticlopidine, sirolimus, and paclitaxel), or left main bifurcation in a left dominant system.

Randomization

Randomization was performed in blocks for each participating hospital, 1:1 by computerized assignment with stratification according to sex, diabetes, age >70 years, use of glycoprotein receptor antagonists, and consent to angiographic follow-up. An automatic telephone randomization/voice response system was used. Patients were randomized before any balloon dilatation was performed.

Stent Implantation

Patients were pretreated with aspirin (75 mg) and clopidogrel (300 mg). Heparin was administered according to local hospital routine, and activated clotting time control was not mandatory. Glycoprotein receptor antagonists were used at the discretion of the operator. Aspirin was continued indefinitely, and clopidogrel was continued for 6 to 12 months according to local practice. Ticlopidine could be used if the patient did not tolerate clopidogrel.

The operator was requested to avoid pretreatment (conventional balloon or cutting balloon) of segments not covered by stent, ie, the main vessel segment in the MV group and the main vessel plus the side branch segments in the MV+SB group. The radial or femoral approach and 6F guiding catheters were used routinely. Either a 7F or 8F catheter was used in "crush technique" procedures.[14] The SES "Cypher Select" (Cordis/Johnson & Johnson, Miami Lakes, Fla) was used in the study.

The study lesion was predilated and/or postdilated at the discretion of the operator. In the MV group, the main treatment principles were (1) stenting of main vessel; (2) side branch dilation if there was Thrombolysis In Myocardial Infarction (TIMI) flow <3 in the side branch; and (3) side branch stenting if TIMI flow=0 in the side branch after dilation. In the MV+SB group, the main treatment principles were stenting of both the main vessel and the side branch by application of the crush technique,[14] culotte technique,[15] or other techniques at the discretion of the operator. In all cases of side branch stenting, the operator was required to attempt a "kissing balloon" dilation at the end of the procedure. Implantation of additional stents to cover the whole lesion or to cover a dissection was allowed. If the study stent could not be delivered, another drug-eluting stent or a bare-metal stent was allowed. Different types of drug-eluting stents in the same vessel were not allowed. Both operator and patient were aware of the assigned treatment.

Cardiac Biomarkers and ECG

Creatine kinase (CK)-MB mass, troponin-T, or troponin-I was measured at the time of the procedure and after 12 to 18 hours. CK-MB mass was used as the primary marker and troponin-T or troponin I only if CK-MB mass was not available. To avoid confounding non–procedure-related marker elevation, patients with unstable angina pectoris were included in the biomarker analysis only if preprocedure and postprocedure markers were normal. Marker elevation of ≥3 times the upper limit of normal was considered significant. A 12-lead ECG was obtained before and 12 to 18 hours after the procedure.

Follow-Up

For safety reasons, total deaths and major adverse cardiac events (MACE) were recorded by telephone call after 1 month. There was a clinical follow-up visit after 6 months for primary end-point registration. An 8-month control coronary angiography was scheduled at randomization in patients who consented herein. No patients were lost to follow-up.

Quantitative Coronary Angiography at 8 Months

Coronary angiograms obtained at baseline, at completion of the stenting procedure, and at 240 days of follow-up were submitted to 1 of 2 angiographic core laboratories (Skejby Hospital, Aarhus, Denmark, or Paul Stradins Clinical Hospital, Riga, Latvia) and were analyzed with the use of a computer-based system dedicated to bifurcation analysis (Qangio XA version 7.0, Medis, Leiden, Neth-
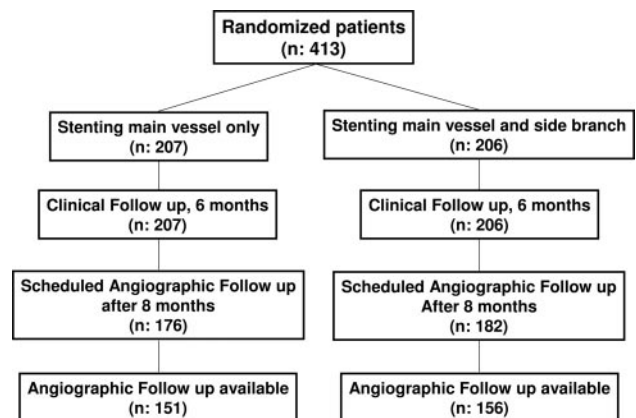

Figure 1. Flow diagram of the Nordic Bifurcation Study.

erlands). A standard operating procedure was developed in collaboration with Medis; the experienced operators were trained by staff from Medis; and the operators from the 2 centers worked out the standard operating procedure before starting the analyses.

Quantitative angiographic measurements of the bifurcation lesion were obtained in 3 segments: the proximal main vessel segment, the distal main vessel segment, and the side branch. In the main vessel segments, measurements were obtained in the stent and in the margins 5 mm proximal and distal to the main vessel stent (edge). In the side branch, the stented or balloon-treated segments and the 5 mm distal to those (edge) were assessed. If the side branch was not treated with stent or balloon, the first 5 mm of the side branch was defined as both the lesion and edge area. The analyses were not blinded.

Study End Points
The primary end point of the study was the clinical combined end point (MACE) of cardiac death, myocardial infarction, and stent thrombosis or target-vessel revascularization by PCI or coronary artery bypass surgery after 6 months. Secondary end points were (1) the individual end points of death from any cause, cardiac death, myocardial infarction, target-lesion revascularization, and target-vessel revascularization; (2) procedure-related biomarker increase (≥3 times the upper limit of normal of CK-MB mass, troponin-T, or troponin-I); and (3) the combined angiographic end point of significant restenosis (>50% diameter stenosis) of the main vessel and/or occlusion of the side branch. The clinical study end points were adjudicated blindly by an independent end-points committee.

Definitions
Non–Q-wave myocardial infarction was defined as a CK-MB mass or troponin-T/troponin-I increase to ≥3 times the upper limit of normal combined with clinical signs of myocardial infarction, in the absence of pathological Q waves and not related to an interventional procedure. Q-wave myocardial infarction was defined as development of new pathological Q waves in 2 or more contiguous leads together with clinical signs of myocardial infarction (chest pain or increase in myocardial injury markers). Target lesion revascularization was repeat revascularization by PCI or surgery of the target lesion. Target-vessel revascularization was defined as repeat revascularization by PCI or surgery of the target vessel. Stent thrombosis was angiographically documented contrast filling defect of the target lesion in the presence of an acute coronary syndrome. Acute, subacute, or late thrombosis was defined as occurring within 24 hours, within 1 month, or during the succeeding 5 months after stent implantation, respectively. Percent diameter stenosis was calculated as (reference diameter−minimal luminal diameter)/reference diameter×100. Significant stenosis was defined as >50% diameter stenosis. Late lumen loss was defined as postprocedure minimal luminal diameter minus minimal luminal diameter (in mm) at 8-month follow-up.

Statistical Analysis
Power calculations were based on an expected primary end-point event rate of 30% in the MV+SB group (α=5%, power=80%, with a 2-sided χ^2 test). To detect a reduction in the primary end-point rate to 15%, 134 patients would be needed in each group. Because of considerable uncertainty in expected end-point rates in bifurcation lesions treated with drug-eluting stents, it was decided to include 200 patients in each group.[5] Differences in categorical variables between the 2 groups were analyzed with the χ^2 test or Fisher exact test. Continuous variables were analyzed with Mann-Whitney test and time-to-event data with the Kaplan-Meier method and the log-rank test. All probability values were 2-sided. The level of significance was 5%. The analysis was performed on an intention-to-treat basis. All analyses were performed with SPSS 13.0 (SPSS Inc, Chicago, Ill).

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

TABLE 1. Baseline Clinical Characteristics

	MV (n=207)	MV+SB (n=206)	P
Age, y	63±10	62±10	0.51
Male	159 (77)	162 (79)	0.72
Current smoker	57 (28)	48 (23)	0.37
CCS angina class 2-4	186 (93)	192 (96.5)	0.17
Stable angina pectoris	139 (67)	136 (66)	0.84
Unstable angina pectoris	65 (31)	68 (33)	0.75
Silent ischemia	4 (2)	3 (2)	1.00
Hypercholesterolemia	161 (78)	149 (73)	0.21
Hypertension	110 (53)	119 (58)	0.37
Diabetes mellitus	27 (13)	24 (12)	0.76
Family history	119 (58)	111 (54)	0.55
Prior PCI	52 (25)	53 (26)	0.91
Prior CABG	8 (4)	6 (3)	0.78
Aspirin	206 (99.5)	203 (98.5)	0.37
Clopidogrel	207 (100)	205 (99.5)	0.50
GP IIb/IIIa inhibitors	106 (51)	105 (51)	1.00

CCS indicates Canadian Cardiovascular Society; CABG, coronary artery bypass grafting; and GP, glycoprotein.

Values are n (%), except for age.

Results

Baseline Characteristics and Procedural Data
The 2 groups were well balanced with regard to baseline clinical characteristics and risk factors (Table 1). In two thirds of the cases, the indication for treatment was stable angina pectoris, and in one third, it was unstable angina pectoris; in 2% of the cases, the indication was silent ischemia. The use of aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitors was similar in the 2 groups (Table 1). Procedural data are shown in Table 2. The index-lesion location was the left anterior descending artery in 73%, the circumflex artery in 18%, the right coronary artery in 7%, and the left main stem in 2%, with no difference between the groups. There was also no significant difference between the 2 groups with respect to type of bifurcation,[13] vessel size, or severity of stenosis as assessed by the operator. Angulation of side branch <70° was seen in 64.4%, calcification in 26.9%, and proximal tortuosity in 5.8% of the lesions, with no difference between the groups. There was a significantly longer procedure time and fluoroscopy time and a larger volume of contrast used in the MV+SB group. The number of stents implanted in the index lesion was 2.2±0.6 in the MV+SB group and 1.3±0.6 in the MV group. The side branch was stented in 4.3% of the MV group and 95.1% of the SB+MV group. In the MV group, the side branch was dilated through the main vessel stent in 32% of the procedures. In the MV+SB group, the bifurcation technique used was the crush technique in 50%, the culotte technique in 21%, and other techniques (primarily the T-stent technique) in 29%. A final kissing balloon dilation was performed in the majority of cases in the MV+SB group. Cypher Select was the study stent, and few other stents were used (6 Taxus Express stents [Boston Scientific, Natick,

TABLE 2. Procedural Characteristics

	MV (n=207)	MV+SB (n=206)	*P*
LVEF, (%)	58±11	58±10	0.76
Mean lesion length, mm*			
Main branch	18.0±8.3	17.5±7.5	0.47
Side branch	6.0±4.8	6.4±4.7	0.40
Mean stent length			
Main branch	23.4±8.6	23.2±8.6	0.85
Side branch	2.8±6.1	10.3±5.0	<0.0001
Reference diameter (proximal)*			
Main branch	3.3±0.4	3.3±0.4	0.90
Side branch	2.6±0.4	2.6±0.3	0.99
MV stented	206 (99.5)	203 (98.5)	0.31
SB stented	9 (4.3)	196 (95.1)	<0.0001
No. of stents	1.3±0.6	2.2±0.6	<0.0001
Final kissing balloon	65 (32)	152 (74)	<0.0001
Procedural success	200 (97)	194 (94)	0.35
Procedure time, min	62±51	76±40	<0.0001
Fluoroscopy time, min	15±9	21±10	<0.0001
Contrast volume, mL	233±93	283±117	<0.0001

LVEF indicates left ventricular ejection fraction.
Values are mean±SD or n (%).
*By visual estimate.

Mass] and 1 bare-metal stent in the MV group; 11 Taxus Express stents and 2 bare-metal stents in the MV+SB group).

Clinical Outcome

The cumulative event rate for the primary end point of MACE (cardiac death, myocardial infarction, target-vessel revascularization, or stent thrombosis) after 6 months of follow-up is shown in Figure 2. There was no significant difference in the MACE rate between the 2 groups (2.9% in the MV group and 3.4% in the MV+SB group). The individual end points after 6 months are shown in Table 3. The rates of individual end points were low in both groups, with no significant difference between groups. The Canadian Cardiovascular Society angina class was similar in the 2
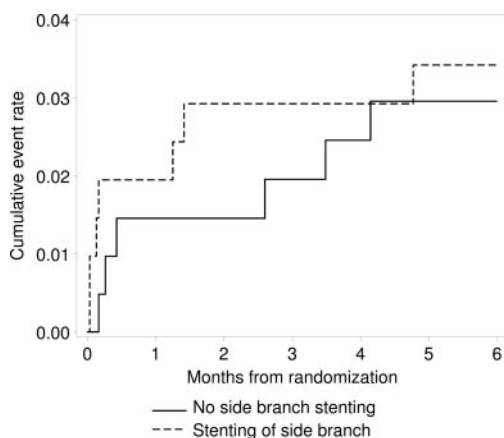

Figure 2. Cumulative MACE rate (cardiac death, myocardial infarction, target-vessel revascularization, stent thrombosis) during 6-month follow-up.

TABLE 3. Individual End Points After 6 Months

	MV (n=207)	MV+SB (n=206)	*P*
Cardiac death	2 (1.0)	2 (1.0)	1.00
Total death	2 (1.0)	3 (1.5)	0.61
Myocardial infarction	0 (0.0)	1 (0.5)	0.31
Target vessel revascularization	4 (1.9)	4 (1.9)	0.99
Stent thrombosis	1 (0.5)	0 (0.0)	0.31
Target lesion revascularization	4 (1.9)	2 (1.0)	0.36

Values are n (%).

groups before treatment and after 6 months. Canadian Cardiovascular Society class 2 to 4 was registered in 93.0% of the patients in the MV group and 96.5% in the MV+SB group before treatment and decreased to 9.2% and 8.6% after 6 months in the 2 groups, respectively.

Procedure-Related Elevation of Biomarkers

Procedure-related biomarker release could be evaluated in 279 patients (126 patients in the MV+SB group and 153 in the MV group). Marker elevation of >3 times the upper limit of normal was seen in 18% of MV+SB-stented patients and in 8% of MV-stented patients (*P*=0.011).

Quantitative Coronary Angiography Analysis

At randomization, 358 patients were scheduled for 8-month follow-up angiography. Complete angiographic evaluation was available in 307 patients (86%); of these, 151 patients were randomized to the MV group and 156 to the MV+SB group. The major reason for not having the 8-month angiographic follow-up was the long distances to the interventional centers in the northern part of Scandinavia. The combined angiographic end point of diameter stenosis >50% of main vessel and occlusion of the side branch after 8 months was found in 8 patients (5.3%) in the MV group and 8 patients (5.1%) in the MV+SB group (*P*=0.96; Table 4). The vessel diameters of the main vessel segments tended to be larger in the MV+SB group before and after treatment, but these differences were lost at follow-up. Reflecting study design, there were significant differences between the 2 treatment strategies in the side branch, with smaller minimal luminal diameters and increased diameter stenoses after the index procedure and at follow-up in the MV group. The late lumen loss was generally small in all 3 analyzed segments but was significantly larger in the side branch of the MV+SB group. Edge minimal luminal diameters after intervention and at follow-up were similar in the main vessel segments but smaller in the side branch in the MV group, the latter again reflecting study design and definition of this parameter.

The rates of stenosis (diameter stenosis >50%) in the different segments of the bifurcation lesion are given in Table 5. In the entire lesion (main vessel and side branch), the rate of stenosis was 22.5% in the MV and in 16.0% in the MV+SB group (*P*=0.15). The rate of stenosis was 4.6% and 5.1% in the main vessel (*P*=0.84) and 19.2% and 11.5% in the side branch (*P*=0.062) in the MV and MV+SB groups, respectively. Only 1 patient (MV group) had a side branch occlusion at follow-up.

TABLE 4.   Results of Quantitative Angiography in the 3 Bifurcation Segments

Variable	Proximal MV Segment			Distal MV Segment			Side Branch		
	MV	MV+SB	P	MV	MV+SB	P	MV	MV+SB	P
In-stent minimal luminal diameter, mm*									
Before	1.43±0.78	1.62±0.87	0.045	1.18±0.65	1.32±0.74	0.083	1.21±0.61	1.22±0.62	0.90
After	2.86±0.55	3.04±0.51	0.004	2.34±0.44	2.50±0.46	0.003	1.50±0.64	2.05±0.54	<0.001
Follow-up	2.86±0.54	2.94±0.66	0.25	2.29±0.49	2.38±0.58	0.13	1.52±0.58	1.86±0.60	<0.001
In-stent reference diameter, mm*									
Before	2.93±0.66	3.00±0.70	0.39	2.41±0.59	2.63±0.59	0.001	2.24±0.46	2.28±0.51	0.40
After	3.21±0.52	3.30±0.51	0.13	2.69±0.45	2.83±0.46	0.008	2.28±0.44	2.47±0.46	<0.001
Follow-up	3.19±0.55	3.24±0.57	0.52	2.69±0.42	2.79±0.53	0.11	2.24±0.52	2.43±0.45	<0.001
In-stent diameter stenosis, %*									
Before	40±27	46±27	0.25	52±24	50±25	0.49	46±26	47±26	0.70
After	11±10	7±10	0.004	13±13	11±10	0.36	34±23	16±18	<0.001
Follow-up	11±10	10±11	0.57	15±14	15±13	0.86	31±22	24±21	0.002
In-stent late lumen loss, mm*	0.00±0.55	0.10±0.6	0.15	0.04±0.47	0.10±0.50	0.30	-0.04±0.52	0.20±0.57	<0.001
Edge minimal luminal diameter, mm									
After	2.90±0.57	2.99±0.63	0.18	2.15±0.44	2.22±0.46	0.18	1.73±0.58	1.91±0.49	0.006
Follow-up	2.87±0.65	2.86±0.67	0.89	2.17±0.42	2.25±0.53	0.15	1.76±0.52	1.90±0.49	0.018

*In-stent segments included the stented areas of the main vessel and the stent/balloon-treated areas of the side branch; if the side branch was not treated, the parameters included the first 5 mm of the side branch.

Discussion

In the present randomized clinical interventional trial, we found no significant difference in cardiac death, myocardial infarction, stent thrombosis, target-vessel revascularization, or combinations thereof after 6 months between a simple and a complex coronary bifurcation stenting strategy with SES. However, the complex stenting procedures were associated with increased procedure and fluoroscopy times, more use of contrast, and a significantly higher incidence of procedure-related biomarker release. Independent of treatment strategy, the event rates were much lower than anticipated. Furthermore, quantitative coronary angiography follow-up after 8 months, deliberately separated from the clinical end point to avoid the influence of stenosis visualization on target-lesion revascularization, showed no significant difference in restenosis of the main vessel and side branch in the 2 treatment groups. Bifurcation lesions represent one of the remaining challenges in interventional cardiology, and it is an unsolved problem whether the optimal treatment strategy should be routine or provisional stenting of the side branch, the latter being the simplest and most frequently used strategy.[5,10,16]

Comparison With Other Studies

There are no randomized trials from the bare-metal stent era assessing different stent strategies in bifurcation lesions. In the drug-eluting stent era, 2 randomized studies have addressed the same issue.[5,10] The Sirius bifurcation study[5] had a design very similar to that of the present study; however, in the Sirius study, the crossover rate was high, and the results were not analyzed according to the intention-to-treat principle.[5] A 3.5% risk of stent thrombosis in patients who had been stented in both branches raised concern about this strategy.[5] In the study by Pan et al,[10] patients were randomized to a simple versus a complex strategy of bifurcation treatment with a rapamycin-eluting stent.[10] In that study, the main branch was stented and the side branch dilated with a balloon. According to randomization, the side branch was subsequently stented or not stented. MACE rates were low in both groups, and the overall conclusion from that study was that both strategies were effective in reducing restenosis rate, with no differences in terms of clinical outcome.

The present study differed from the above-mentioned studies in several aspects. The present study was considerably larger; in the majority of patients randomized to MV+SB, a

TABLE 5.   Rate of Significant Stenosis at 8-Month Follow-Up in Bifurcation Segments

Variable	Proximal MV Segment			Distal MV Segment			Side Branch		
	MV	MV+SB	P	MV	MV+SB	P	MV	MV+SB	P
In-stent stenosis, n (%)*	0 (0.0)	1 (0.6)	1.00	4 (2.6)	3 (1.9)	0.72	29 (19.2)	17 (10.9)	0.041
Edge stenosis, n (%)	3 (2.0)	4 (2.6)	1.00	0 (0.0)	2 (1.3)	0.50	11 (7.3)	6 (3.8)	0.20
SB stenosis/occlusion, n (%)	...	...		...	...		29 (19.2)	18 (11.5)	0.062

*In-stent segments included the stented areas of the main vessel and the stent/balloon-treated areas of the side branch; if the side branch was not treated, the parameters included the first 5 mm of the side branch.

Significant stenosis was defined as >50% diameter stenosis. Some of the patients had stenosis in more than 1 location.

dedicated SES bifurcation technique (crush or culotte) was used; and the angiographic end point was separated from the clinical result of bifurcation treatment. Therefore, the clinical end points were not influenced by a prescheduled angiographic follow-up. Also, we succeeded in maintaining a low crossover rate owing to the use of strict criteria for side branch stenting in the MV group. Accordingly, the present results allow an evaluation of clinical benefits and drawbacks associated with the 2 investigated bifurcation strategies.

Complexity of Procedure

A strategy of stenting both branches of a bifurcation lesion represents a complex procedure. In the present study, this was documented by a 23%, 40%, and 21% increase in procedure time, fluoroscopy time, and contrast volume, respectively. Furthermore, the rate of procedure-related increase in biomarkers of myocardial injury was significantly higher in the MV+SB group, thus establishing an association between the complexity of an interventional procedure and the risk of myocardial injury. However, the clinical and prognostic significance of biomarker elevation after PCI is questioned.[17–20] In the present study, the increased incidence of procedure-related increases in biomarkers was not associated with adverse clinical events after 6 months. It is of interest that our restrictive protocol, which only allowed side branch stenting in case of side branch occlusion in the MV group, did not result in an increased incidence of procedure-related biomarker elevation in this group.

Clinical Outcomes

Except for the increased incidence of procedure-related biomarker elevation in the MV+SB group, other adverse events were few and at a similar level in both groups. Mortality was low and comparable to that reported in 2 previously published studies.[5,10] In addition, the incidence of clinical myocardial infarction in the follow-up period was low and did not differ between the groups. In complex bifurcation stenting, the increased risk of stent thrombosis has been a concern.[5] In the present study, there was no stent thrombosis at 6 months in the MV+SB group. In this group, a final kissing balloon dilation was recommended and performed in 74% of cases. The high rate of final kissing balloon dilation might be responsible for the low rate of stent thrombosis in the present study; however, the 2 cases of sudden cardiac death may represent stent thromboses.

Patients included in the present study were severely symptomatic before treatment. After 6 months, symptomatic relief was substantial and similar in both groups. Furthermore, the need for target-lesion revascularization was low and similar to the results from the study by Pan et al.[10]

Quantitative Coronary Angiography Analysis

The 8-month quantitative angiography analysis of the 2 stenting strategies contributed new information. The use of SES in bifurcation lesions was associated with a low risk of restenosis in the main vessel, and we found no differences between a simple and a complex bifurcation stenting strategy with regard to the primary angiographic end point of restenosis in the main vessel or occlusion of the side branch. A complex bifurcation stenting strategy with double or triple

layers of stent struts in the proximal main vessel segment has been a concern but was not found to be associated with a higher risk of restenosis. In fact, in the MV+SB group, only 1 patient developed in-stent restenosis in the proximal main vessel segment, whereas 7 patients had in-stent restenosis in the distal segment. On the other hand, 7 of 9 edge stenoses in the main vessel were observed in the proximal segment. This might be associated with the fact that the kissing balloon technique was used to finalize a majority of the procedures. In the side branch of the MV group, the minimal luminal diameters were smaller and the stenosis severity greater, and there was an insignificant trend toward a higher number of >50% diameter stenoses at follow-up. However, patients in the MV group did not experience an increased risk of side branch occlusion, and they did not have more severe angina pectoris at 6-month follow-up. This indicates that a conservative strategy with regard to treatment of side branch stenoses can be advocated if normal blood flow can be maintained in the side branch.

Clinical Implications

According to the present results and those of others,[5,6,10] percutaneous intervention with the use of SES is the treatment of choice in bifurcation lesions. The use of SES in these lesions has reduced complication rates and clinical and angiographic restenosis rates to the same level as in less complex coronary artery lesion subsets.[3,4]

Several authors have advocated the simple strategy in percutaneous bifurcation treatment with stenting of the main branch and provisional side branch stenting.[5,10,16,21] The present results support this view, because there are no data in the present trial that favor the complex strategy. Instead, our finding of increased procedure and radiation times and the increased incidence of procedure-related biomarker elevation favor the use of the simpler technique. With fewer stents, less contrast, and shorter procedure time, the health economic aspect also favors this technique. On the other hand, given the complexity of bifurcation lesions, the present study does not contradict the use of a complex bifurcation stenting strategy in special situations, ie, bifurcation lesions with a very large side branch. A larger study than the present one might have shown significantly less side branch (re)stenosis in side branch–stented patients.

Study Limitations

The present study had an open design, and operators and patients were aware of the technique used. This might introduce bias in the interpretation of symptoms at follow-up. Ischemia testing was not performed, and there were no objective data to compare relief of ischemia with the 2 strategies. MACE, however, was adjudicated by a blinded events committee and should not have been influenced by the open design of the study. The study was considerably underpowered given the low MACE rate found. A properly powered study would include close to 20 000 patients. An inclusion of this order of magnitude would not be feasible in the complex lesion subset of the present study. Patients studied had a variety of lesion types and lesion locations; therefore, the overall recommendation from the study may not be valid for specific subsets of lesions. Furthermore,

although MACE rates and significant angiographic stenosis were low after 6-month clinical and 8-month angiographic follow-up, the durability of these results on a long-term basis is not known.

Conclusions

In conclusion, excellent 6-month clinical and 8-month angiographic results can be obtained with percutaneous treatment of de novo coronary artery bifurcation lesions with SES. Independent of stenting strategy, the procedural success rates were high, the MACE rate low, and the angiographic restenosis rate low in both treatment groups. The simple stenting strategy with stenting of the main vessel and optional stenting of side branch was associated with reduced procedure and fluoroscopy times and significantly reduced risk of procedure-related biomarker elevation and can be recommended as the routine bifurcation stenting technique.

Disclosures

None.

References

1. Meier B, Gruentzig AR, King SB III, Douglas JS Jr, Hollman J, Ischinger T, Aueron F, Galan K. Risk of side branch occlusion during coronary angioplasty. *Am J Cardiol*. 1984;53:10–14.
2. Pinkerton CA, Slack JD, van Tassel JW, Orr CM. Angioplasty for dilatation of complex coronary artery bifurcation stenoses. *Am J Cardiol*. 1985;55:1626–1628.
3. Al Suwaidi J, Yeh W, Cohen HA, Detre KM, Williams DO, Holmes DR Jr. Immediate and one-year outcome in patients with coronary bifurcation lesions in the modern era (NHLBI dynamic registry). *Am J Cardiol*. 2001;87:1139–1144.
4. Yamashita T, Nishida T, Adamian MG, Briguori C, Vaghetti M, Corvaja N, Albiero R, Finci L, Di Mario C, Tobis JM, Colombo A. Bifurcation lesions: two stents versus one stent: immediate and follow-up results. *J Am Coll Cardiol*. 2000;35:1145–1151.
5. Colombo A, Moses JW, Morice MC, Ludwig J, Holmes DR Jr, Spanos V, Louvard Y, Desmedt B, Di Mario C, Leon MB. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation*. 2004;109:1244–1249.
6. Kelbaek H, Thuesen L, Helqvist S, Klovgaard L, Jorgensen E, Aljabbari S, Saunamaki K, Krusell LR, Jensen GV, Botker HE, Lassen JF, Andersen HR, Thayssen P, Galloe A, van Weert A. The Stenting Coronary Arteries in Non-stress/benestent Disease (SCANDSTENT) trial. *J Am Coll Cardiol*. 2006;47:449–455.
7. Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, Breithardt G. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet*. 2003;362:1093–1099.
8. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315–1323.
9. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban HE, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346:1773–1780.
10. Pan M, de Lezo JS, Medina A, Romero M, Segura J, Pavlovic D, Delgado A, Ojeda S, Melian F, Herrador J, Urena I, Burgos L. Rapamycin-eluting stents for the treatment of bifurcated coronary lesions: a randomized comparison of a simple versus complex strategy. *Am Heart J*. 2004;148:857–864.
11. Degertekin M, Regar E, Tanabe K, Smits PC, van der Giessen WJ, Carlier SG, de Feyter P, Vos J, Foley DP, Ligthart JM, Popma JJ, Serruys PW. Sirolimus-eluting stent for treatment of complex in-stent restenosis: the first clinical experience. *J Am Coll Cardiol*. 2003;41:184–189.
12. Sousa JE, Costa MA, Abizaid A, Abizaid AS, Feres F, Pinto IM, Seixas AC, Staico R, Mattos LA, Sousa AG, Falotico R, Jaeger J, Popma JJ, Serruys PW. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation*. 2001;103:192–195.
13. Lefevre T, Louvard Y, Morice MC, Dumas P, Loubeyre C, Benslimane A, Premchand RK, Guillard N, Piechaud JF. Stenting of bifurcation lesions: classification, treatments, and results. *Catheter Cardiovasc Interv*. 2000;49:274–283.
14. Colombo A, Stankovic G, Orlic D, Corvaja N, Liistro F, Airoldi F, Chieffo A, Spanos V, Montorfano M, Di Mario C. Modified T-stenting technique with crushing for bifurcation lesions: immediate results and 30-day outcome. *Catheter Cardiovasc Interv*. 2003;60:145–151.
15. Chevalier B, Glatt B, Royer T, Guyon P. Placement of coronary stents in bifurcation lesions by the "culotte" technique. *Am J Cardiol*. 1998;82:943–949.
16. Iakovou I, Ge L, Colombo A. Contemporary stent treatment of coronary bifurcations. *J Am Coll Cardiol*. 2005;46:1446–1455.
17. Natarajan MK, Kreatsoulas C, Velianou JL, Mehta SR, Pericak D, Goodhart DM. Incidence, predictors, and clinical significance of troponin-I elevation without creatine kinase elevation following percutaneous coronary interventions. *Am J Cardiol*. 2004;93:750–753.
18. Iakovou I, Mintz GS, Dangas G, Abizaid A, Mehran R, Kobayashi Y, Lansky AJ, Aymong ED, Nikolsky E, Stone GW, Moses JW, Leon MB. Increased CK-MB release is a "trade-off" for optimal stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol*. 2003;42:1900–1905.
19. Cantor WJ, Newby LK, Christenson RH, Tuttle RH, Hasselblad V, Armstrong PW, Moliterno DJ, Califf RM, Topol EJ, Ohman EM. Prognostic significance of elevated troponin I after percutaneous coronary intervention. *J Am Coll Cardiol*. 2002;39:1738–1744.
20. Simoons ML, Van den BM, Lincoff M, Harrington R, van der WR, Vahanian A, Rutsch W, Kootstra J, Boersma E, Califf RM, Topol E. Minimal myocardial damage during coronary intervention is associated with impaired outcome. *Eur Heart J*. 1999;20:1112–1119.
21. Louvard Y, Lefevre T, Morice MC. Percutaneous coronary intervention for bifurcation coronary disease. *Heart*. 2004;90:713–722.

CLINICAL PERSPECTIVE

In the present study on optimal treatment of coronary bifurcation lesions, we compared a simple stenting strategy (stenting of main vessel and optional treatment of side branch) with a complex strategy (stenting both main vessel and side branch) in 413 patients using sirolimus-eluting stents. Independent of the stenting strategy, the procedural success rates were high, the rate of major adverse cardiovascular events was low, and the angiographic restenosis rate was low in both treatment groups. The simple stenting strategy was associated with reduced procedure and fluoroscopy time and a significantly reduced risk of procedure-related biomarker elevation. For this reason, the simple bifurcation stenting strategy can be recommended as the routine bifurcation stenting technique.