Interventional Therapy of Bifurcation Lesions
A TIMI Flow-Guided Concept to Treat Side Branches in Bifurcation Lesions—A Prospective Randomized Clinical Study (Thueringer Bifurcation Study, THUEBIS Study as Pilot Trial)

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Background—Treatment of bifurcations is a complex problem. The clinical value of treating side branches is an unsolved problem in the field of interventional cardiology.

Methods and Results—We initiated a prospective randomized controlled trial. One hundred and ten patients with bifurcations were randomly assigned to 2 arms: Stenting of the main branch (MB, Taxus-stent, paclitaxel-eluting stents) and mandatory side branch (SB) percutaneous coronary intervention (PCI; kissing balloons) with provisional SB stenting (therapy A), or stenting of the MB (paclitaxel-eluting stents) with provisional SB-PCI only when the SB had a thrombolysis in myocardial infarction flow <2 (therapy B). The primary end point was target lesion revascularization. The mean ages were 66.8 years (A) versus 65.1 years (B, \( P = 0.4 \)), 71.4% (A) versus 77.8% were men (\( P = 0.4 \)), patients with diabetes were present in 25.0% versus 25.9% (\( P = 0.9 \)). The MB was left anterior descending artery in 80.4% versus 81.5% (A versus B, \( P = 0.9 \)). The SB-PCI and kissing balloon-PCI were performed according to the study protocol in 82.1%/73.2% versus 16.7%/13.0% (\( P = 0.05 \) for both), while changing of the intended therapy was necessary in 17.9% versus 16.7% (A versus B, \( P = 0.9 \)). A final thrombolysis in myocardial infarction flow 3 (MB) was reached in all patients (groups A and B), final thrombolysis in myocardial infarction flow 3 (SB) was observed in 96.4% versus 88.9% (A versus B, \( P = 0.3 \)). Radiation time (min) and contrast medium (mL) were 14.2/210 (group A) versus 7.8/151.6 (group B; \( P \) for both <0.05). Six month follow up: major adverse cardiac events was 23.2% (A) versus 24.1% (B, \( P = 0.9 \)), target lesion revascularization was 17.9% (A) versus 14.8% (B, \( P = 0.7 \)), and late lumen loss (MB) was 0.2 mm (A) versus 0.3 mm (B, \( P = 0.5 \)). In group B, no PCI of the SB was done during follow up.

Conclusion—A simple strategy using paclitaxel-eluting stents with only provisional SB-PCI may be of equal value to a more complex strategy with mandatory SB-PCI.


Key Words: angioplasty □ catheterization □ stents □ percutaneous coronary intervention □ paclitaxel-eluting stents □ Bifurcation lesions

The practice of invasively treating for bifurcation lesions has grown significantly over recent years, where a number of practical approaches have been suggested including the “crush” technique,1 Y- and T-stenting,2 the “culotte” technique,3,4 and the “kissing stent” technique.5

Clinical Perspective on p ●●●
The “final kissing” balloon percutaneous coronary intervention (PCI) represents an important treatment of bifurcation lesions, although it is not possible to implement it with every patient.1,6 Ornstein et al7 showed that after side-branch dilatation, a distortion of the stent distal to the side branch (SB) was seen in a Plexiglas phantom, whereas side-branch dilatation can abolish this phenomenon, and thus underscoring the importance of SB-PCI.

Stenting versus balloon dilatation of the SB seems to confer no advantage among patients with bifurcation lesions, whereas a restenosis tends to occur more frequently at the ostium of the SB after drug-eluting stenting or bare metal stenting without its having any appreciable effect on target

Received July 1, 2008; accepted August 17, 2009.
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Circ Cardiovasc Intervent is available at http://circinterventions.ahajournals.org
DOI: 10.1161/CIRCINTERVENTIONS.108.833046
lesion revascularization (TLR). This reflects the low clinical relevance of these lesions.2–8–11

Stenting of the main branch (MB) with the protection of the SB using an inserted second wire keeps the SB open in a high percentage of cases.12 Occlusion of a SB after coverage with a drug-eluting stent results in a high spontaneous recanalization rate during follow-up.13

We hypothesize here that after coverage of the SB, a Thrombolysis In Myocardial Infarction (TIMI) flow-guided concept for treating the MB only when TIMI flow was 0 or 1 and/or the patient had angina was not inferior to a final-kissing balloon-PCI with provisional stenting of the SB.

Methods

Patient Selection

This single-blinded, randomized, prospective monocenter trial was conducted between September 2004 and December 2006 and involved the enrollment of 110 patients.

The intention-to-treat cohort was defined at the beginning of the study in September 2004.

The study included male or female patients older than 18 years of age with a diagnosis of stable angina or silent ischemia. Additional eligibility criteria included the presence of a de novo, true coronary bifurcation lesion, defined as stenosis >50% determined by visual estimation in both the MB and the ostium of the SB. Both branches were required to have at least a TIMI flow of 2 or 3 and a reference vessel size >2.25 mm on visual estimation or a relevant SB which the operator would not have wanted to lose during the procedure. If 2 commensurate vessels were present, the MB was defined as the largest of the 2 involved vessels. Diffuse disease of the SB represented an exclusion criterion.

The bifurcation lesions were defined according to the Medina classification.14 Angiographically apparent disease involving the proximal and distal MB as well as the ostium of the bifurcation was considered as Medina 1,1,1. Stenosis of only the proximal part of the MB was given a 1,0,0 grading, stenosis of the distal part alone a 0,1,0 grading, and stenosis of both the proximal and distal part of the MB was given a 1,1,0 grading. An isolated ostial stenosis of the SB (Medina classification 0,0,1) was not included for methodological reasons.

Patients were excluded if one of the following was present: a myocardial infarction in the 24 hours preceding treatment (ST segment elevation myocardial infarction [STEMI] and non-STEMI [NSTEMI]), myocardial infarction in the 24 hours preceding treatment (ST segment classification 0,0,1) was not included for methodological reasons.

In group B, the main treatment principles were (1) stenting of the main vessel covering the SB with Taxus Express or Taxus Liberte stents and (2) SB dilatation only if there was a TIMI flow of 0 or 1 in the SB and/or the patient had angina after removing the balloon from the interior of the lesion. Provisional stenting using paclitaxel-eluting stents was performed at the discretion of the operator.

In both treatment groups, a safety wire introduced inside the SB was mandatory and not left to the operator’s discretion.

Indications for the placement of a SB stent in both treatment modalities included (1) residual stenosis after balloon angioplasty >50%, (2) flow limiting dissection, (3) presence of thrombus, and/or (4) occlusion of the SB after balloon angioplasty.

If the planned therapy A could not be performed, a switch to therapy B (only treatment of the MB) was done (defined here as “procedural failure”). Procedural success of therapy A was defined as either simultaneous final kissing PCI or if this strategy was not achievable (see above) sequential balloon angioplasty in the SB and in the MB.

Wherever there was TIMI-flow reduction (TIMI flow 0 or 1) of the SB when therapy B was used, the SB was then treated according to the protocol defined for group B (defined here as “protocol-mandated angioplasty”).

The choice of the balloons was made to achieve a balloon-vessel ratio of ~1 after measuring the preprocedure reference vessel diameter. In our study, semicompliant balloons were used with nominal inflation pressures.

Implantation of additional paclitaxel-eluting stents to cover the whole lesion or to cover a dissection was permitted. No combination of drug-eluting stents with bare metal stents was permitted except in cases where it was not possible to insert the assigned study stent. The operator, but not the patient, was aware of the assigned treatment. Crossovers to the alternative treatment strategy were allowed. Lesion predilatation was left to the discretion of the operator.

Patients were preloaded with 300 mg clopidogrel and received life-long aspirin together with 75 mg clopidogrel per day for at least 6 months. Use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. During the procedure, intravenous heparin was given to maintain an activated clotting time of >250 seconds.

Angiographic Evaluation

Patients received intracoronary isosorbide dinitrate (0.1 to 0.3 mg) before the initial and final angiograms to achieve maximal vasodilatation. Coronary angiograms were obtained in multiple views.

Quantitative coronary angiographic (QCA) analysis was performed using Quantron QCA (version V2.0 by Pie Medical Imaging, Maasstricht, The Netherlands). QCA measurements were performed by an independent operator unaware of the details of the therapy with a dye-filled catheter as reference.

The reference vessel diameter, minimal lumen diameter, and percentage diameter stenosis were measured preprocedure, postprocedure, and at follow-up. The reference vessel diameter of the SB was set up where the diseased segment seems to be unobstructive. In-stent late luminal loss was calculated as the difference between the postprocedure and follow-up minimal lumen diameter at 6 months. In the main vessel segments, measurements were obtained within the stent and in the margins 5 mm proximal and distal to the edges of the main vessel stent. Binary restenosis was defined as the presence of >50% diameter stenosis within the target lesion including the 5-mm margins proximal and distal to the stent edge at follow-up.

Clinical Definitions and Follow-Up

Six months after the index procedure, all patients were invited back for an angiographic follow-up.

Clinical assessment was performed before follow-up angiography. Follow-up was obtained either at an office visit, at a scheduled angiography after 6 months (unless clinically indicated earlier) or by telephone call where the rate of MACE (major adverse cardiac events) was determined after 6 months, previously defined as either death, myocardial infarction (STEMI and NSTEMI), stent thrombosis, coronary artery bypass grafting (CABG), or TLR. All deaths were considered cardiac unless otherwise documented.
The diagnosis of acute myocardial infarction (STEMI or NSTEMI) both periprocedurally and at follow-up, required an elevation of creatine kinase to levels twice those of the upper normal limit together with a rise in the creatine kinase-MB fraction, an elevation of troponin I and/or new ST-segment elevations or new Q-waves (ECG). The threshold used to define a positive troponin I test was 0.1 ng/mL. For CK, the manufacturer reported a lower limit of 50% luminal diameter narrowing either within the stent or within the 5 mm proximal or distal to the MB or SB stent edge, (2) stent thrombosis, or (3) TLR-related CABG. This was undertaken in the presence of either anginal symptoms or objective evidence of an ischemia including stent thrombosis. The operator performing the follow-up angiography was unaware of the treatment group.

Target vessel revascularization was defined as revascularization by PCI or surgery within the target vessel encompassing the target lesion including TLR plus PCI target vessel-nontarget lesion plus CABG including target vessel, not related to the target lesion.

MACE was defined as target vessel revascularization plus cardiac death.

Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of a vessel occlusion or thrombus within or adjacent to a previously successfully stented vessel or, in the absence of angiographic confirmation, either acute myocardial infarction in the distribution zone of the treated vessel or death not clearly attributable to other causes. Stent thromboses were categorized according to the timing of the event into intraprocedural, subacute thrombosis (from the end of the procedure to 30 days), and late stent thrombosis (>30 days).

Creatine kinase, the MB isoenzyme, and troponin I were measured 24 hours after the index procedure whereas ECGs were obtained before the procedure, at discharge, and at the follow-up visit.

### Results

#### Baseline and Lesion Characteristics

During the screening phase n = 1187, the patients had undergone a PCI at our center. Of these, n = 114 (9.6%) patients were screened for study participation, and 2 patients refused study participation.

There were no statistically significant differences in patient characteristics between the 2 treatment groups: the mean ages of the patients were 66.8 years (therapy A) and 65.1 years (therapy B), with 71.4% (A) and 77.8% (B) being men. Cardiovascular risk factors were homogenously distributed between the 2 treatment modalities, as was the medical history (Table 1).

The distributions of the locations in the 3-target vessels were not significantly different as were the types of bifurcation according to the Medina classification system (Table 2).

Consistent with our inclusion criteria, patients were included with true coronary bifurcation lesions with a stenosis >50% in the SB and in the MB as estimated visually by the operator. Most of our patients had a true bifurcation lesion following the Medina classification, but the QCA results revealed that not all patients had a relevant stenosis of the SB, a fact which can be explained by the reduced accuracy of visual assessment.

#### Procedural Characteristics

Direct stenting was carried out in significantly more patients in group B, but stent diameter or stent length were not different regarding the MB (Table 3). The distributions of the 2 different stents used in the study due to logistic reasons (Taxus Liberte versus Taxus Express, differentially applied for logistical rea-
sons) were homogenous in groups A (Taxus Express, n=25, 44.6%) and B (Taxus Express, n=23, 42.6%, P=ns).

According to the prespecified study protocol, PCI of the SB was performed in group A in 82.1% versus 16.7% in group B (P<0.05), and a “simultaneous final kissing balloon” PCI was performed in 73.2% versus 13.0% (P<0.05). The remainder of this group underwent a sequential balloon angioplasty. Most of the patients only had a dilatation without stenting of the SB. Stenting of the SB (in group B as per protocol side branch-PCI) was only slight, although significantly more frequent in group A (Table 3). We used the Taxus Liberte stent in all cases of SB stenting.

According to our definition, procedural failures from therapy A to therapy B occurred in 10 patients (17.9%). The reasons underlying this were the failed wire passage in 3 patients (5.4%) or the failed balloon passage in 7 patients (12.5%). The reasons underlying protocol-mandated angioplasty PCI in group B were TIMI flow 0/I in 6 patients (11.1%, group A: one patient, 1.8% with TIMI flow 0/I in the SB and angina in 3 patients (5.6%). One patient from group A (1.8%) and 2 patients from group B (3.7%) had a periprocedural SB occlusion (P=ns). Attempts to reopen the SB were unsuccessful. These patients with TIMI-flow reduction were treated with GP IIb/IIIa antagonists.

A final TIMI flow III inside the MB was reached in all patients from both groups, whereas a final TIMI flow III in the SB was seen in 94.6% (group A) versus 88.9% (group B, P=0.3). Comparing the duration of radioscopy or the amount of contrast medium applied, benefits were also revealed for the less complicated strategy (Table 3).

### Follow-Up Data

During the hospital stay, increases in creatine kinase and troponin 24 hours after the indexing procedure were not significantly different (Table 4). Medication at discharge and after 6 months (ie, aspirin, clopidogrel, CSE-inhibitors, ACE-inhibitors/AT-1 receptor antagonists, and β-blockers) was homogenously distributed (data not shown). The mean duration of follow-up was between 5.7 and 6.1 months and was not significantly different between the groups (Table 4). A combination of aspirin plus clopidogrel during the follow-up period was given in 75% in group A and 75.9% in group B (P=0.9). At follow-up, the rest of our patients were on aspirin or clopidogrel alone or a combination of aspirin or clopi-

### Table 2. Lesion Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Therapy A, n=56</th>
<th>Therapy B, n=54</th>
<th>95% CI; B – A; P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bifurcation localization: LAD/SB, n (%)</td>
<td>45 (80.4)</td>
<td>44 (81.5)</td>
<td>(−13.9%; 16.0%) 0.88</td>
</tr>
<tr>
<td>Bifurcation localization: LCX/SB, n (%)</td>
<td>10 (17.9)</td>
<td>10 (18.5)</td>
<td>(−14.0%; 15.5%) 0.93</td>
</tr>
<tr>
<td>Bifurcation localization: RCA/SB, n (%)</td>
<td>1 (1.8)</td>
<td>0 (0.0)</td>
<td>(−9.4%; 4.9%) 0.32</td>
</tr>
<tr>
<td>Bifurcation type 1,1,1,* n (%)</td>
<td>35 (62.5)</td>
<td>30 (55.5)</td>
<td>(−19.3%; 16.1%) 0.66</td>
</tr>
<tr>
<td>Bifurcation type 1,0,0,* n (%)</td>
<td>8 (14.3)</td>
<td>11 (20.4)</td>
<td>(−8.3%; 20.7%) 0.40</td>
</tr>
<tr>
<td>Bifurcation type 0,1,1,* n (%)</td>
<td>3 (5.4)</td>
<td>1 (1.9)</td>
<td>(−13.0%; 5.0%) 0.33</td>
</tr>
<tr>
<td>Bifurcation type 0,1,0,* n (%)</td>
<td>10 (17.9)</td>
<td>12 (22.2)</td>
<td>(−10.8%; 19.6%) 0.57</td>
</tr>
</tbody>
</table>

*We used the Medina bifurcation classification system (13).

### Table 3. Procedural Characteristics (MB and SB)

<table>
<thead>
<tr>
<th></th>
<th>Therapy A, n=56</th>
<th>Therapy B, n=54</th>
<th>95% CI; B – A; P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct stenting MB*, n (%)</td>
<td>30 (53.6)</td>
<td>41 (75.9)</td>
<td>(4.3%; 38.9%) 0.01</td>
</tr>
<tr>
<td>Stent diameter MB, mm (mean, range, SD)</td>
<td>2.9 (2.5 to 3.5; 0.2)</td>
<td>2.9 (2.3 to 3.5; 0.3)</td>
<td>(−0.1; 0.1) 0.70</td>
</tr>
<tr>
<td>Stent length MB, mm (mean, range, SD)</td>
<td>17.8 (8.0 to 28.0; 5.4)</td>
<td>16.7 (12.0 to 28.0; 4.8)</td>
<td>(−3.0; 0.9) 0.29</td>
</tr>
<tr>
<td>Stenting MB: maximal inflation pressure, atm (mean, range, SD)</td>
<td>13.5 (10.0 to 18.0; 1.5)</td>
<td>13.9 (12.0 to 20.0; 1.9)</td>
<td>(−0.3; 1.0) 0.32</td>
</tr>
<tr>
<td>Side branch PCI, n (%)</td>
<td>46 (82.1)</td>
<td>9 (16.7)</td>
<td>(−77.3%; −49.2%) &lt;0.0001</td>
</tr>
<tr>
<td>Simultaneous balloon angioplasty as “final kissing”-PCI, n (%)</td>
<td>41 (73.2)</td>
<td>7 (13.0)</td>
<td>(−69.1%; −41.3%) &lt;0.0001</td>
</tr>
<tr>
<td>Sequential balloon angioplasty as “final kissing”-PCI, n (%)</td>
<td>5 (8.9)</td>
<td>2 (3.7)</td>
<td>(−14.9%; 5.8%) 0.43</td>
</tr>
<tr>
<td>Stenting SB, n (%)</td>
<td>10 (17.9)</td>
<td>3 (5.6)</td>
<td>(−25.2%; −0.3%) 0.05</td>
</tr>
<tr>
<td>Procedural failure/protocol mandated angioplasty A ↔ B, n (%)</td>
<td>10 (17.9)</td>
<td>9 (16.7)</td>
<td>(−15.6%; 13.4%) 0.87</td>
</tr>
<tr>
<td>Final TIMI flow III SB, n (%)</td>
<td>53 (94.6)</td>
<td>48 (88.9)</td>
<td>(−17.6%; 5.1%) 0.27</td>
</tr>
<tr>
<td>Deterioration of TIMI flow &gt;1 SB at the end of procedure, n (%)</td>
<td>2 (3.6)</td>
<td>6 (11.1)</td>
<td>(−2.6%; 19.2%) 0.13</td>
</tr>
<tr>
<td>Duration of x-ray, min (mean, range, SD)</td>
<td>14.2 (5.0 to 35.0; 6.9)</td>
<td>7.8 (3.0 to 23.0; 4.6)</td>
<td>(−8.6; −4.2) &lt;0.0001</td>
</tr>
<tr>
<td>Amount of contrast medium, mL (mean, range, SD)</td>
<td>209 (70.0 to 600; 102)</td>
<td>152 (50.0 to 430; 75.5)</td>
<td>(−92; −24) 0.0011</td>
</tr>
</tbody>
</table>

*Direct stenting: defined here as stenting without predilatation.
dogrel plus vitamin K antagonists without there being any significant differences between the 2 treatment groups (data not shown).

Clinical end points for determining anginal status or exertion-related ischemia also revealed no significant differences (Table 4).

Analysis of patients with stent thrombosis produced the following results: in group A, 1 patient had an early stent thrombosis (angiographically documented) on day 1 after intervention under double-platelet inhibition and was considered for an urgent CABG. This patient had 2 stents inside the MB, final kissing was not performed, and the location of the thrombosis was inside the MB. Another patient had a late stent thrombosis under double platelet inhibition on day 138 that resulted in a STEMI and a re-PCI. This patient had 1 stent inside the MB and had a final kissing-PCI. The thrombosis was located inside the MB stent located.

In group B, 1 patient had a late stent thrombosis after canceling the anticoagulation regime on day 39, which resulted in a STEMI plus a re-PCI. This patient had 2 stents located inside the MB and the SB with final kissing-PCI. The thrombosis was observed within the MB. Another patient had a sudden cardiac death under double platelet inhibition the day after being discharged from hospital. This event was classified as an early stent thrombosis. This patient had 2 stents inside the MB. No further evaluation was possible.

In group B, 1 patient (1.9%) relocated away and could no longer be followed-up before the conclusion of the study. In group A, all patients could be followed up (P=ns).

Noncardiac death occurred in 1 patient (1.8%) in group A that was due to a meningitis and septic shock unrelated to the intervention.

Clinically driven indications for angiography (angina pectoris CCS III/IV, exertion ischemia, and suspected stent thrombosis) were given in n=20 patients of group A (35.7%) and n=17 patients of group B (31.5%, P=ns). All other patients underwent a mandatory follow-up angiography. No patient had more than 1 angiography during follow-up (Figure).

Table 4. Follow-Up Data

<table>
<thead>
<tr>
<th></th>
<th>Therapy A, n=56</th>
<th>Therapy B, n=54</th>
<th>95% CI; B−A; P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine kinase 24 hours after index procedure, μmol/L (mean, range, SD)</td>
<td>4.6 (0.0 to 126; 17.6)</td>
<td>2.9 (0.5 to 26.9; 4.8)</td>
<td>(−6.9; 3.5) 0.52</td>
</tr>
<tr>
<td>Troponin 24 hours after index procedure, ng/mL (mean, range, SD)</td>
<td>4.0 (0.0 to 139; 20.2)</td>
<td>2.4 (0.0 to 37.0; 7.3)</td>
<td>(−7.7; 4.5) 0.60</td>
</tr>
<tr>
<td>Hospital stay, days (mean, range, SD)</td>
<td>3.0 (1.0 to 65.0; 8.6)</td>
<td>1.9 (1.0 to 12.0; 2.0)</td>
<td>(−3.5; 1.3) 0.35</td>
</tr>
<tr>
<td>Follow-up duration, months (mean, range, SD)</td>
<td>5.7 (0.5 to 8.0; 1.2)</td>
<td>6.1 (0.1 to 9.0; 1.1)</td>
<td>(−0.1; 0.8) 0.11</td>
</tr>
<tr>
<td>Angina pectoris CCS I/II, n (%)</td>
<td>48 (85.7)</td>
<td>50 (92.6)</td>
<td>(−5.3%; 19.5%) 0.25</td>
</tr>
<tr>
<td>Angina pectoris CCS III/IV, n (%)</td>
<td>8 (14.3)</td>
<td>4 (7.4)</td>
<td>(−19.5%; 5.3%) 0.25</td>
</tr>
<tr>
<td>NYHA III/IV, n (%)</td>
<td>4 (7.1)</td>
<td>2 (3.7)</td>
<td>(−13.8%; 6.3%) 0.43</td>
</tr>
<tr>
<td>Exertion ischemia, n (%)</td>
<td>10 (17.9)</td>
<td>12 (22.2)</td>
<td>(−10.8%; 19.6%) 0.57</td>
</tr>
<tr>
<td>Angiographically determined ejection fraction, % (mean, range, SD)</td>
<td>61.4 (37.0 to 78.0; 9.7)</td>
<td>59.7 (34.0 to 70.0; 9.3)</td>
<td>(−5.7; 2.3) 0.39</td>
</tr>
</tbody>
</table>

Figure. Patient flow (intention-to-treat basis).
Follow-Up Data: End Points

TLR occurred in 17.9% in group A and 14.8% in group B \((P=0.67)\).

The target vessel revascularization was 23.2% in group A versus 20.4% in group B and revealed no significant difference.

Cardiac death occurred in 2 patients from group B: 1 patient had a sudden cardiac death 1 day after discharge from hospital without any further evaluation. This event was considered as an early stent thrombosis. Another patient had a re-PCI of the MB and died after CABG because of progressive heart failure.

Looking at all MACE, almost identical results were revealed in the 2 groups: 23.2% in group A and 24.1% in group B \((P=0.9, \text{Table 5})\).

Troponin release at 24 hours after the index procedure was seen in 31 patients in group A (55.4%) and in 20 patients in group B (37.0%, \(P=0.06\), see also Table 4). CK release was observed in 7 patients in group A (12.5%) and 9 patients in group B (16.7%, \(P=0.7\). No patient in either group developed a Q-wave myocardial infarction during follow-up. Two patients (3.6%) of group A had a diagnosis of acute myocardial infarction during follow-up with an elevation of creatine kinase to levels of twice upper the upper normal limit, whereas this was the case in 1 patient of group B (1.9%, \(P=\text{ns}\)).

Nearly all patients underwent an angiographic follow-up. All patients in group A had an angiographic evaluation, but 1 patient in group B who had sudden cardiac death without further evaluation underwent no follow-up catheterization \((P=\text{ns})\).

QCA Analysis

Analysis of minimal luminal diameter, percent diameter stenosis and reference diameter of the MB before and after PCI revealed no significant differences, whereas the length of the lesion was longer in group A.

During follow-up, a binary in-segment–restenosis (>50%) of the MB was present in 10.7% (group A) versus 5.6% (group B). Binary restenosis for the target lesion (restenosis >50% inside the MB and the SB) was \(n=13\) (group A, 23.2%) and \(n=12\) (group B, 22.2%, \(P=\text{ns}\)), meaning that no significant difference was found. Late lumen loss of the MB revealed no significant differences (Table 6).

A binary (re)-stenosis of the SB was observed in 12.5% (A) versus 16.6% \((P=0.6)\) of cases.

Discussion

The invasive treatment of bifurcation lesions represents a complex problem in interventional cardiology where several techniques have been used and systematic studies are sparse.

The approach of stenting the SB using bare metal or drug-eluting stents was found to convey no advantage during follow-up. Other studies have shown that after covering the SB with protection of an inserted second wire, the SB remains open in a high percentage of cases. The clinical relevance of restenosis occurring in a SB also seems to be low, especially in vessels with a diameter of \(\approx 2\) mm as it was in our study.

These observations led to the question put forward in this study: does a simple concept involving the coverage of the ostium of the SB by a paclitaxel-eluting stents (where a SB-PCI was used only if TIMI-flow reduction or angina symptoms were observed) represent an attractive approach to treat these complex lesions?

We confirmed this idea by conducting a prospective randomized study involving 2 treatment modalities, where the control group consisted of patients treated with a final kissing-PCI and provisional stenting of the SB, ie, the strategy which until now has produced the best evaluated results until now.

We included 110 consecutive patients with true bifurcation lesions diagnosed according to the Medina classification, where baseline parameters were all homogeneously distributed. According to the study protocol, stenting of the SB was only required in a few patients, while kissing balloon-PCI was carried out in the complex strategy in 73% of the patients, a figure compliant with other studies addressing this issue. Application of the complex strategy resulted in a high rate of procedural failure. We observed a relatively high rate of compromised SB flow in 11.1% (for the simple strategy) and an incidence of a binary SB restenosis in 16.6% (group
study by Steigen et al, a complex approach using 2 stents for treatment strategies, as was also reported by other authors.8 was not observed to differ significantly between these 2 concepts. The authors concluded that this concept was preferable to the complex strategy, a result which complied well with our analysis. Given the complexity of bifurcation lesions, however, this study does not contradict the use of a complex bifurcation stenting strategy in special situations, for example with bifurcation lesions involving a very large SB.

**Study Limitations**

This study is a monocenter study and was of an open design. The operators (but not the patients or the operator performing follow-up angiography) were aware of the technique being used. This might have introduced some bias into the interpretation of symptoms at follow-up.

Other limitations of this study are the 20% crossover rate and the low power for a post hoc noninferiority end point. It should be kept in mind that our study was not adequately powered to test the primary end point of TLR.

The study is also hampered by the fact that the studied cohort included a high percentage of lesions without significant SB disease by QCA, and that the diameter of the arteries treated was low.

### Table 6. QCA Analysis

<table>
<thead>
<tr>
<th></th>
<th>Therapy A; n=56</th>
<th>Therapy B; n=54</th>
<th>95% CI; B−A; P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal luminal diameter, before/after PCI, mm (mean, range, SD)</td>
<td>0.9 (0.4 to 2.0; 0.3)</td>
<td>1.0 (0.3 to 1.8; 0.3)</td>
<td>(−0.1; 0.1) 0.53</td>
</tr>
<tr>
<td>% diameter stenosis before/after PCI (mean, range, SD)</td>
<td>2.3 (1.4 to 3.2; 0.4)</td>
<td>2.3 (1.4 to 3.1; 0.4)</td>
<td>(−0.1; 0.2) 0.74</td>
</tr>
<tr>
<td>Reference diameter, mm (mean, range, SD)</td>
<td>65.2 (48.0 to 85.0; 8.2)</td>
<td>63.5 (47.0 to 88.0; 7.9)</td>
<td>(−4.7; 1.3) 0.27</td>
</tr>
<tr>
<td>Lesion length, mm (mean, range, SD)</td>
<td>21.7 (3.0 to 43.0; 8.8)</td>
<td>21.7 (9.0 to 44.0; 8.3)</td>
<td>(−3.2; 3.3) 0.97</td>
</tr>
<tr>
<td>SB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal luminal diameter, before/after PCI, mm (mean, range, SD)</td>
<td>6.1 (2.4 to 13.6; 2.8)</td>
<td>5.1 (1.6 to 11.2; 2.1)</td>
<td>(−1.9; −0.0) 0.04</td>
</tr>
<tr>
<td>% diameter stenosis before/after PCI (mean, range, SD)</td>
<td>6.0 (0.0 to 8.0; 0.2)</td>
<td>6.0 (0.0 to 8.0; 0.2)</td>
<td>(−0.2; 0.2) 0.81</td>
</tr>
</tbody>
</table>

These facts had to be borne in mind when the results during follow-up were assessed.

The consequence of this simple approach was to significantly reduce contrast media usage and radiation exposure time while maintaining comparable crossover rates. We observed a final TIMI flow III in the SB in a high percentage of cases without any significant differences between these 2 treatment strategies.

We determined a tendency for a shorter hospital stay using our simple strategy, where other authors using a comparable approach succeeded in finding a significant difference. In a study by Steigen et al, a complex approach using 2 stents for both branches was compared with a TIMI-flow-guided concept for treating the SB. The authors concluded that this concept was preferable to the complex strategy, a result which complied well with our analysis.

During follow-up, the rate of TLR or MACE in our study was not observed to differ significantly between these 2 treatment strategies, as was also reported by other authors. No SB of group B was revascularized during follow-up. The incidence of a binary restenosis of the MB was lower in the simple strategy group, but the rate of re-PCI was nearly identical in both groups.

Consistent with our results, Brueck et al confirmed that a permanent or transient compromising of the SB cannot improve any immediate or long-term outcome. Consistent with our results, they were also able to show that simultaneous kissing balloon angioplasty reduces the rate of transient side-branch occlusion compared with sequential PTCA (sequential kissing balloon angioplasty) without improving long-term outcome compared with sequential PTCA for bifurcation lesions.17

We conclude that the simpler strategy is not inferior to the complex strategy involving a routine PCI of the SB either with regard to the short- or the long-term results.

With fewer stents, less contrast media, and shorter procedure times, the technique is also much more cost-effective.
Analysis of the reason why the initially estimated 35% TLR occurrence was so far off its mark at 17.9 revealed that the initial data generating these assumptions were data involving the treatment of coronary bifurcations with bare metal stents (BMS), whereas drug-eluting stents (DES) used in our study were introduced in 2002. During the planning phase of our study, no other data were available concerning the use of drug-eluting stents for the treatment of these. The results of treating these lesions with drug-eluting stents were better than expected, which might explain the difference between the expected and the actual TLR.

Conclusions

We conclude that a TIMI-flow-guided therapy or an angina-associated strategy for treating the SB stenoses in patients with bifurcations can be advocated if a moderately reduced blood flow can be maintained in the SB. Furthermore, a high rate of procedural failure occurs in patients where the complex strategy is used. Finally, the high rate of compromised SB flow and SB restenosis must also be taken into consideration.

Acknowledgments

We thank the 110 women and men who participated in this trial.

Disclosure

None.

References


CLINICAL PERSPECTIVE

The treatment of coronary bifurcations is a complex problem, and the clinical value of treating side branches remains an unsolved problem in the field of interventional cardiology. We studied the effect of stenting of the main branch with drug-eluting stents + mandatory side branch-PCI (kissing balloons) with provisional side branch stenting versus stenting of the main branch with provisional side branch-percutaneous coronary intervention only when the side branch had a thrombolysis in myocardial infarction flow <2. As we showed, no significant difference regarding target lesion revascularization or clinical end points was found. The duration of x-ray and the amount of contrast media were significantly less, in favor of the simpler strategy. We conclude that more complex strategies for the treatment of coronary bifurcations may show better short-term angiographic outcome without a clinical benefit for the patients.
Interventional Therapy of Bifurcation Lesions: A TIMI Flow-Guided Concept to Treat Side Branches in Bifurcation Lesions—A Prospective Randomized Clinical Study (Thueringer Bifurcation Study, THUEBIS Study as Pilot Trial)
Hubertus v. Korn, Jiangtao Yu, Marc A. Ohlow, Burkhard Huegl, Walter Schulte, Andreas Wagner, Gernot Wassmer, Stefan Gruene, Oliver Petek and Bernward Lauer

Circ Cardiovasc Interv. published online November 10, 2009;
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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