Ultrasound-Guided Strategy for Provisional Stenting With Focal Balloon Combination Catheter

Results From the Randomized Strategy for Intracoronary Ultrasound-Guided PTCA and Stenting (SIPS) Trial

Axel W. Frey, MD, PhD; John M. Hodgson, MD; Christian Müller, MD; Hans-Peter Bestehorn, MD; Helmut Roskamm, MD

**Background**—Intracoronary ultrasound (ICUS) has provided insights into vascular pathology and interventional therapy. The Strategy for ICUS-Guided PTCA and Stenting (SIPS) trial tested the hypothesis that routine ICUS guidance of coronary interventions improves outcome.

**Methods and Results**—A single-center consecutive-patient randomized design (with 6-month angiographic and 2-year clinical follow-up) was used. Consecutive patients (no chronic total occlusions or emergency procedures) were randomized to ICUS-guided provisional stenting or standard angiographic guidance. Quantitative angiographic minimal lumen diameter (MLD), angiographic restenosis, clinically driven target lesion revascularization, and major adverse cardiac events (MACEs) were evaluated. A total of 291 procedures (356 lesions) were included. Procedure success was higher in the ICUS-guided group than the group randomized to standard guidance (94.7% versus 87.4%, respectively; \( P = 0.033 \)), whereas time (65.2 \pm 31.0 versus 60.5 \pm 34.0 minutes, \( P = 0.18 \)) and contrast use (209.3 \pm 94.1 versus 197.5 \pm 89.5 mL, \( P = 0.23 \)) were not significantly different. Stenting rates were similar (49.7% versus 49.5%, \( P = 0.89 \)). Acute gain was greater in the ICUS-guided group than in the standard guidance group (1.85 \pm 0.72 versus 1.67 \pm 0.76 mm, respectively; \( P = 0.02 \)). Angiographic 6-month analysis revealed no difference in MLD (1.71 \pm 0.94 versus 1.57 \pm 0.90, \( P = 0.19 \)) or binary restenosis rate (>50% diameter stenosis) (29% versus 35%, \( P = 0.42 \)). Clinical follow-up (602 \pm 307 days) showed a significant decrease in clinically driven target lesion revascularization in the ICUS group compared with the standard guidance group (17% versus 29%, respectively; \( P = 0.02 \)).

**Conclusions**—Although angiographic MLD did not differ significantly after 6 months, ICUS-guided provisional stenting improved 2-year clinical results after intervention. *(Circulation. 2000;102:2497-2502.)*

**Key Words:** coronary disease ■ imaging ■ angioplasty ■ restenosis ■ stents
same-setting PTCA occurred only for emergency procedures. Vessel-size criteria were based on the available device sizes. Exclusions included emergency intervention, planned atherectomy, chronic total occlusion of the target vessel, and failure to give informed consent. A total of 491 consecutive patients underwent 595 interventions during the study period. Approximately one third of these patients had intervention for chronic total occlusion (n=203) and were excluded. Exclusion for other reasons was rare (n=19) and was primarily for lesions in saphenous vein grafts >4.6 mm.

**Randomization**
A total of 291 procedures in 269 patients were included. Patients were scheduled several days in advance. The patients were randomized on a day-to-day block schedule; randomization was performed in the morning of each day. Add-on patients were rare. After randomization, 166 lesions were treated by ICUS guidance, and 190 were treated by Angio.

**Catheterization Laboratory Protocol**
A strategy of provisional stenting was used. Stenting was discouraged unless a significant dissection was present (type C or greater by National Heart, Lung, and Blood Institute [NHLBI] criteria) or unless angiographic results were unacceptable. Selection of planned therapy was at the discretion of the operator. Initial and final angiography was performed after intracoronary administration of nitroglycerin (50 to 100 μg) and, whenever possible, in 2 views. Periprocedural medication included oral aspirin (100 mg daily) and heparin (10 000 to 20 000 IU given intravenously during the procedure). Patients receiving stents were treated with 250 to 500 mg aspirin intravenously and begun on 250 mg ticlopidine twice daily. No other medications were given routinely. Patients received glycoprotein IIb/IIa receptor inhibitors only under emergency situations (n=5).

**ICUS-Guided Group**
A balloon size with a diameter 50% between the ICUS-defined lumen and external elastic lumina diameters of the smallest reference was calculated (Clinical Outcomes With Ultrasound Trial [CLOUT] criteria). This balloon size was obtained by high-pressure inflation of the combination ICUS/variable diameter balloon (Oracle Focus, Endosonics). This balloon incorporates both compliant (central 10-mm segment) and noncompliant (5-mm end segment) material, resulting in expansion up to 0.7 mm above nominal of the central compliant balloon segment, In cases in which the diameter determined by ICUS could not be achieved simply by high-pressure dilatation, a larger conventional balloon was chosen. If, after use of a balloon with diameter based on ICUS measurements, the lesion lumen area did not meet the ICUS criteria, stenting was considered. ICUS measures of the lumen and total vessel diameters and areas were made proximal and distal to the lesion in the angiographically uninvolved reference segments. Repeat interventions were performed in an iterative fashion with ICUS imaging until the minimal lumen area within the lesion was >65% of the mean reference area. This target value was predefined on the basis of data from the CLOUT Trial. When the lesion was ostial, the nearest appropriate size reference was used. Stents were delivered by use of the manufacturer’s delivery system (if applicable) or hand-crimped on the combination ICUS/balloon device. Quantitative measures for successful stent implementation were based on the criteria of the Multicenter Ultrasound Stenting in Coronaries Study (MUSIC) investigators.

If multiple lesions were present, they were all treated with the same device whenever possible.

**Angio-Guided Group**
As in the ICUS group, a general strategy of provisional stenting was used. Procedural guidance in this group was performed by use of fluoroscopy and cine angiography. Primary dilation was performed by use of a standard unidiameter balloon of the operator’s choice, which was based on visual angiographic estimation of size. The operator was encouraged to achieve an optimal result predefined as <35% residual angiographic diameter stenosis by visual estimation. When a stent was deployed, the angiographic target criterion for success was <10% diameter stenosis with no evidence of uncovered dissection.

If patients underwent multiple procedures during the study period, they retained their originally assigned randomization for the subsequent procedures.

**Follow-Up**

**Angiographic Follow-Up**
All patients were requested to return at 6 months. Angiographic follow-up was complete in 77% of the ICUS lesions and 79% of the Angio group lesions. Angiography performed for clinical indications occurring before 6 months was included in the analysis. Restudy was performed in the same projections. Vessel segments for sequential comparison were selected by use of side-by-side viewing of the cine angiograms to ensure exact matching.

**Clinical Follow-Up**
Patients were contacted at 6 months and 2 years after their index procedure. Referral physician records, hospital records, and patient questionnaires were collected to assess rates of clinically driven TLR. Myocardial infarction, and death. Follow-up was 100% complete. Patients were censored at the time of their first major adverse clinical event. For patients with no events, data were assessed 720 days after their procedures.

**Analysis**
For quantitative coronary angiography (QCA), angiograms were analyzed by use of validated commercial software (CAAS II) in a core laboratory. The reproducibility and accuracy of measurements performed in this core laboratory have been reported previously. Specifically, the long-term variability for repeated measures (2.3 years) of sequential angiograms was 0.34 mm (stenosis diameter), 0.66 mm (reference diameter), and 6.52% (percent diameter stenosis).

Frames for analysis were chosen by a physician not involved in the performance of the procedure; however, the characteristic appearance of the ICUS/balloon catheter precluded blind selection. Values were calculated for the single worst view on the basis of the initial MLD. The reference segment was user-defined as the closest normal-appearing segment proximal to the lesion (except for ostial locations, for which a distal reference was chosen). Lesions were classified according to the modified American Heart Association/ American College of Cardiology classification. Residual dissections were classified according to the NHLBI type.

**Definitions**

**Clinically Driven TLR**
All patients with anginal pain before and at the time of admission to the hospital (either before or at the time specified by the study protocol) and who had angiographic restenosis in the target segment treated with either repeat PTCA or CABG were considered to have clinically driven TLR. Their clinical status was assessed in a blinded fashion independent from the operator by a quality of life questionnaire and exercise tolerance testing.

**Myocardial Infarction**
Myocardial infarction was defined as a rise in creatinine phosphokinase >2 times the upper limit of normal with a myocardial band fraction of >10%.

**Procedure Success**
Procedure success was defined as discharge from the hospital without repeat revascularization, myocardial infarction, or death, with a core laboratory QCA-determined percentage diameter stenosis for all lesions treated of <50%.
Acute Gain, Late Loss, and Net Gain

Acute gain was defined as the difference between the initial MLD and final MLD. Late loss was the difference between follow-up MLD and final MLD. Net gain was the difference between follow-up MLD and initial MLD.

Statistical Analysis

Data were analyzed by use of Statistica (StatSoft). Comparisons were made by either ANOVA (continuous variables) or χ² analysis (categorical variables). Kaplan-Meier survival analysis with a Gehans-Wilcoxon test for significance was used for the follow-up comparisons. Power calculations for sample size assumed a 35% stent implantation rate, a 0.19-mm acute group difference in MLD, a 0.104-mm chronic difference in MLD, and an SD of 0.48 mm for QCA analysis (α=0.05, β=0.20). With these assumptions, 140 lesions per group were needed to detect the chronic MLD difference. Significance was assumed at P<0.05. Data are displayed as mean±1 SD unless otherwise noted.
a balloon/artery ratio of 1.17, close to the 1.25 ratio for the nominal combination balloon size.

Clinical Results
In-hospital acute and 2-year MACEs are shown in Table 5. In general, the total event rates for the ICUS-guided group were less than those for the Angio-guided group, but this difference achieved statistical significance only for the 2-year TLR rate (Figure).

All revascularization rates and all MACE rates, including all revascularization procedures, myocardial infarction, and deaths expressed per patient, were not significantly different (Table 5). Some patients underwent catheterization outside our hospital. Several of the visually assessed “restenotic” lesions resulted in a reintervention that was not clinically driven, by our definition of TLR.

To control for bias, we also compared the clinical status by evaluating anginal score and maximum exercise tolerance. For the patients with TLR (clinically driven procedures), the anginal score was 2.5 (ICUS) versus 2.5 (Angio), and the maximum exercise tolerance was 50 versus 75 W. Patients with “nonclinically” driven procedures had an anginal score of 0 (ICUS) versus 0 (Angio) and an exercise tolerance of 125 versus 112 W, respectively (Table 6). Thus, independent blinded assessment of clinical status was not different for patients receiving TLR in the 2 groups.

Discussion
The present study demonstrates that a strategy of ICUS-guided intervention results in a significantly improved acute angiographic outcome and is associated with a trend toward lower acute cardiac event rates than a strategy guided by angiography alone. Importantly, the 2-year clinically driven TLR rate was significantly reduced for the ICUS-guided group. However, the primary end point (6-month angiographic MLD) was not different between groups. Although the achieved chronic MLD difference of 0.15 mm exceeded our estimates, the SD of the QCA analysis was twice projected. This is probably due to the broad range of vessel sizes treated in the present study.

TABLE 3. Quantitative Angiography

<table>
<thead>
<tr>
<th></th>
<th>ICUS-Guided</th>
<th>Angio-Guided</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>3.01±0.59</td>
<td>3.00±0.70</td>
<td>0.94</td>
</tr>
<tr>
<td>Lesion MLD, mm</td>
<td>0.64±0.46</td>
<td>0.70±0.55</td>
<td>0.24</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>79.1±13.8</td>
<td>76.8±17.6</td>
<td>0.17</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>9.74±6.41</td>
<td>9.71±5.51</td>
<td>0.96</td>
</tr>
<tr>
<td>After intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion MLD, mm</td>
<td>2.49±0.66</td>
<td>2.38±0.67</td>
<td>0.12</td>
</tr>
<tr>
<td>Acute gain MLD, mm</td>
<td>1.85±0.72</td>
<td>1.67±0.76</td>
<td>0.02</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>18.8±17.3</td>
<td>22.5±19.7</td>
<td>0.07</td>
</tr>
<tr>
<td>Balloon artery ratio (measured)</td>
<td>1.03±0.15</td>
<td>1.02±0.15</td>
<td>0.32</td>
</tr>
<tr>
<td>Follow-up (6 mo)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Reference diameter, mm</td>
<td>3.03±0.78</td>
<td>2.89±0.65</td>
<td>0.09</td>
</tr>
<tr>
<td>Lesion MLD, mm</td>
<td>1.71±0.9</td>
<td>1.56±0.9</td>
<td>0.19</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>44.5±26.8</td>
<td>46.2±28.2</td>
<td>0.61</td>
</tr>
<tr>
<td>Late loss, mm</td>
<td>0.83±0.91</td>
<td>0.82±0.93</td>
<td>0.87</td>
</tr>
<tr>
<td>Net gain, mm</td>
<td>1.06±0.91</td>
<td>0.87±1.01</td>
<td>0.12</td>
</tr>
<tr>
<td>Late loss index</td>
<td>0.42±0.47</td>
<td>0.53±0.86</td>
<td>0.20</td>
</tr>
<tr>
<td>Restenosis (&gt;50% diameter stenosis), %</td>
<td>29</td>
<td>35</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Values are mean±1 SD.

TABLE 4. ICUS Measurements

<table>
<thead>
<tr>
<th></th>
<th>ICUS</th>
<th>Angio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal reference lumen diameter, mm</td>
<td>3.19±0.60</td>
<td>3.00±0.60</td>
</tr>
<tr>
<td>Proximal reference vessel diameter, mm</td>
<td>4.43±0.71</td>
<td>3.50±0.71</td>
</tr>
<tr>
<td>Distal reference lumen diameter, mm</td>
<td>3.00±0.58</td>
<td>3.00±0.58</td>
</tr>
<tr>
<td>Distal reference vessel diameter, mm</td>
<td>3.94±0.73</td>
<td>3.94±0.73</td>
</tr>
<tr>
<td>Calculated CLOUT balloon size, mm</td>
<td>3.66±0.57</td>
<td>3.66±0.57</td>
</tr>
<tr>
<td>Nominal Focus balloon size, mm</td>
<td>3.89±0.43</td>
<td>3.89±0.43</td>
</tr>
<tr>
<td>CLOUT balloon/proximal lumen diameter (ICUS)</td>
<td>1.17±0.12</td>
<td>1.17±0.12</td>
</tr>
<tr>
<td>Nominal balloon/proximal lumen diameter (ICUS)</td>
<td>1.25±0.18</td>
<td>1.25±0.18</td>
</tr>
<tr>
<td>Final area stenosis (all lesions), %</td>
<td>17.06±19.6</td>
<td>17.06±19.6</td>
</tr>
</tbody>
</table>

Values are mean±1 SD.
The present study was performed in a realistic clinical setting. Chronic total occlusions were excluded for 3 reasons. First, we do not believe that the combined catheter would be an effective first-line device for these lesions. Second, the high restenosis rates suggest that primary stenting is the best treatment option. Finally, the clinical success rate is much lower.

**Study Limitations**

The present study used a variable-diameter balloon catheter. If the variable-diameter balloon is sized at 0.5 mm above nominal (expected growth ex vivo at 12 atm), the balloon/artery ratio in the ICUS-guided group is significantly larger than that in the Angio-guided group (1.23±0.21 versus 1.03±0.22, respectively; \( P<0.0001 \)). There could be a non–ICUS-related impact of the special balloon design used in the ICUS group.

The present study was not designed to assess ICUS-guided direct stenting. In a strategy of provisional stenting, the primary goal is to achieve an “optimal” PTCA result without stenting. We did not randomize a group to primary stenting.

Some of the revascularization procedures were clinically driven, and some were performed after scheduled angiographic follow-up, driven by the decision of the interventionist. Even though the independently assessed clinical status was nearly the same in the ICUS and Angio groups, this could be a limitation of the present study. The operator may also have been biased because of recognition of the specific catheter design used in the ICUS group when viewing the former cine run.

Although prospectively randomized and controlled, these results should be confirmed in larger multicenter trials.

**Conclusions**

A strategy of ICUS-guided intervention can be applied to a wide range of patients in routine clinical practice. Although there was no significant difference in MLD at 6 months, we conclude that this strategy provides an angiographically superior acute result and reduces the 2-year clinically driven TLR rate.

**Appendix**

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