Intravascular Ultrasound–Guided Balloon Angioplasty Compared With Stent
Immediate and 6-Month Results of the Multicenter, Randomized Balloon Equivalent to Stent Study (BEST)

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Background—Balloon angioplasty guided by intravascular ultrasound (IVUS) makes it possible to choose the balloon size according to the true vessel diameter and to detect suboptimal results requiring subsequent stent implantation. The Balloon Equivalent to STent (BEST) study aimed to assess whether this strategy would give the same results as systematic stenting.

Methods and Results—A total of 132 of 254 patients were randomized to IVUS-guided percutaneous transluminal coronary angioplasty (aggressive PTCA), and 122 were randomized to stenting (stent group). We hypothesized that a difference of <8% in the 6-month angiographic restenosis rate (primary end point) could be considered noninferior. The aggressive PTCA procedure was longer and had a greater use of contrast medium than stenting. In the aggressive PTCA group, crossover to stent was needed in 58 patients (44%). At 6 months, 20 of 119 patients (16.8%) in the aggressive PTCA group and 21 of 116 patients (18.1%) in the stent group had restenosis. The difference was −1.3%, with an upper limit of 95% confidence interval of 7.1% (ie, less than the noninferiority boundary). The in-stent restenosis rate was higher in the stent group (15.5% versus 5%; *P*=0.02). The differences in minimum lumen diameter, lumen cross-section area, and 1-year event rate were not significant.

Conclusions—A strategy of IVUS-guided angioplasty with provisional stenting is feasible and safe. At the cost of a more complex procedure, it reduces the stent rate by half, with similar 6-month angiographic IVUS and clinical outcome compared with stent implantation. (Circulation. 2003;107:545-551.)

Key Words: angioplasty ■ ultrasonics ■ stent ■ restenosis

Elective intracoronary stent implantation is the predominant strategy in angioplasty; this is justified by the favorable long-term results and cost-effectiveness ratio compared with percutaneous transluminal coronary angioplasty (PTCA).1-4 Nevertheless, a strategy of provisional stenting has been advocated5 in an effort to reduce the problems associated with in-stent restenosis and its treatment.6 Patients with a “stent-like” result after balloon angioplasty alone have a favorable clinical outcome and a target lesion revascularization rate of 14% to 25%.7 The key element in the provisional stenting strategy is the selection of patients who do not require stent implantation.8 Indeed, previous randomized studies comparing systematic with angiography-guided provisional stenting have provided conflicting results.9-13 Intravascular ultrasound (IVUS)–guided PTCA is based on sizing balloons according to the vessel diameter, and it leads to favorable clinical outcomes.14-18 Furthermore, after intervention, IVUS imaging can be used to help decide on provisional stenting.17,19 In this context, combining IVUS-guided PTCA with IVUS-guided provisional stenting could be a valuable angioplasty strategy, which, thus far, has not been compared with stenting. The Balloon Equivalent to Stent (BEST) study was designed to assess whether a strategy of IVUS-guided aggressive PTCA would provide similar late angiographic results as systemic stent implantation.

Methods

Study Design, End Points, and Sample Size Calculation
The BEST study was a noninferiority, randomized, multicenter study. The primary end point was the 6-month angiographic restenosis rate, as assessed by quantitative coronary angiography. Sec-
ondary end points were angiographic minimum lumen diameter (MLD), minimum lumen cross-sectional area (L-CSA) at lesion site, and 1-year event rate (survival without myocardial infarction, unstable angina, major bleeding, or target vessel revascularization). Noninferiority was assessed for the primary end point. Secondary end points were compared using the relevant statistical difference tests.

We hypothesized that both strategies would result in a similar restenosis rate of 20%. The noninferiority boundary was determined from the results of the Belgium Netherlands Stent Study Group II (Benestent II study),1 in which the difference in angiographic restenosis rates (stent versus balloon) was 15%, with a 95% confidence interval (CI) of 8.3% to 21.7%. The noninferiority boundary for our study was set at 8%. We conjectured that a difference in restenosis rate with a 95% CI <8% would be grounds to consider that IVUS-guided PTCA was superior to a hypothetical control (conventional PTCA) arm.

The sample size, which was calculated assuming a 20% restenosis rate in both groups (difference, 0%; upper limit of the 95% CI <8%) was 130 patients per group, with an α risk of 5% and a β risk of 20%. This sample size would also make it possible to detect, with 80% power, a difference of 0.20 mm in MLD and 0.65 mm² in L-CSA (hypothesis of a 2.00±0.6 mm MLD and a 6.0±2.5 mm² L-CSA at 6-month follow-up in the stent group).20

**Patient Selection**

All patients aged 18 to 80 years submitted to angioplasty were eligible. Inclusion criteria were (1) stable or unstable angina or demonstrated ischemia, (2) a significant stenosis no longer than 20 mm that was suitable for stent implantation and without excessive calcification or angulation, (3) lesion not located on the left main artery, ostium, or bifurcation, and (4) written, informed consent. Exclusion criteria included (1) recent (<3 days) or evolving acute coronary syndrome, (2) left ventricular ejection fraction <30%, and (3) contraindication to aspirin, ticlopidine, or clopidogrel treatment.

The study complied with the Declaration of Helsinki and was approved by the local Ethics Committee. Patients received detailed information and gave written consent.

**Intervention**

**Participating Centers**

Nine investigators in 3 French centers participated in this study. Randomization was stratified by center using customized computer software. The physicians were not blinded to the randomization.

**Angioplasty**

All procedures were performed according to standard practice. Glycoprotein IIb/IIIa inhibitors were used only in cases of unstable angina or suspected intracoronary thrombus.

**IVUS Preintervention Imaging**

All IVUS images were performed using the same system (CVIS/Boston Scientific Corp) at a pullback speed of 0.5 mm/s.

**Stent Group**

In the stent group, decisions were based on angiography. Premounted NIR (Boston Scientific Corp) stents were used, and balloon angiography before or after dilatation was performed at the discretion of the operator. No decisions were made on the basis of IVUS images in this group.

**Aggressive PTCA Group**

Vessel diameter at lesion site (defined as mean diameter of external elastic membrane) was assessed from preintervention IVUS images. The nominal balloon size chosen was the closest size to the vessel diameter, and inflation pressure was determined based on the compliance curve to attain the exact vessel diameter. After balloon angioplasty, angiographic and IVUS imaging was performed to determine the need for adjunctive balloon inflation or stent implantation. The criteria for stent implantation were: (1) flow-limiting dissection, (2) >30% angiographic residual stenosis (assessed by online quantitative coronary angiography), and (3) >30% IVUS area stenosis associated with a <6 mm² minimum lumen area. These criteria for IVUS-guided PTCA have been described previously.17 By protocol, the presence of a non–flow-limiting dissection was not a criterion for stenting.

**End Point Assessment**

All angiographies, IVUS videotapes, and case report forms were centralized and analyzed in the coordinating center. Primary and secondary end points were assessed by technicians trained for these measurements who were not involved in the procedure performance and who were blind to randomization.

**Quantitative Coronary Angiography**

All angiograms were analyzed using an automated edge detection algorithm (MEDIS). The measurements were performed for each pair of orthogonal views and averaged. Angiographic restenosis was defined as >50% diameter stenosis at the target site.

**IVUS Offline Analysis**

After longitudinal reconstruction, the segment of interest was selected using natural landmarks or the metallic stent struts when present. The L-CSA was assessed by manual planimetry at reference and at lesion levels. IVUS analysis was repeated in 2 separate sessions using a computer-assisted manual tracing system (Echo Plaque, Indec Systems), and the average of the measurements were recorded. The reliability of IVUS measurements has previously been assessed and published.20

**Clinical End Point**

Patients were monitored at 12 months for major adverse clinical events. The decision to perform revascularization of the target lesion was left to the investigator’s discretion.

**Statistical Analysis**

Continuous data are presented as mean±SD and qualitative data as percentages. The 95% CI of the difference in restenosis rate was calculated to test the noninferiority hypothesis. Data were compared in a 2-sided situation using Fisher’s exact probabilities or likelihood ratio χ² test for qualitative data and Student’s t or the Mann-Whitney U test for quantitative data, when appropriate.

**Results**

**Population**

Between January 1998 and July 2001, 254 patients were included in the study, 132 in the aggressive PTCA group and 122 in the stent group (Figure 1). The study population represented 4.2% of the patients submitted to coronary angioplasty during this time. The main reasons for nonparticipation in the study were (1) operator’s decision to implant a stent systematically (or not), (2) the presence of exclusion criteria, and (3) patient refusal. There was no difference in baseline characteristics between the 2 groups, despite a trend for more diabetic patients and more patients with unstable angina in the aggressive PTCA group (Table 1).

**Procedure and Immediate Outcome**

In the aggressive PTCA group, IVUS-guided intervention was feasible and safe in all cases but 10 (7.5%). The IVUS-guided balloon angioplasty procedure was more complex and was associated with longer procedure time (51±18 versus 39±14 min; P=0.001), longer fluoroscopic time (10.6±4 versus 8.6±2.4 min; P=0.01), and greater use of contrast medium (192±82 versus 158±83 mL; P=0.001) than the stenting procedure. A typical example of IVUS-guided PTCA is presented in Figure 2. No patient died during
angioplasty. Glycoprotein IIb/IIIa inhibitors were used in 15 patients (versus 8 in the stent group; \( P=0.18 \)), transient occlusion occurred in 12 patients (versus 2; \( P=0.02 \)) and side branch occlusion occurred in 3 patients (versus 3; \( P=0.92 \)). Angiographic dissections were observed in 42 patients, including 15 that were smaller than type C.

All patients from the stent group received a stent, as per protocol. In the aggressive PTCA group, 58 patients (44%) received a stent; this was decided on the basis of angiography alone in 37 patients (29%) and was based on additional IVUS information in 21 patients (16%). The reasons for crossover to stent were dissection in 24 patients (18%) and unsatisfactory result in 34 patients (26%). The final lumen size at target site, as assessed by angiography or IVUS, was larger in the stent group, but patients from the aggressive PTCA group who crossed over to stent had similar immediate results as those in the stent group.

Early emergency revascularization for acute closure at the lesion site was needed in 2 patients from the aggressive PTCA group and in 1 patient from the stent group. Procedural details are presented in Table 2.

**Follow-Up**

A total of 235 of 254 patients (93%) had 6-month angiographic data and 215 of 254 patients (85%) had IVUS data suitable for secondary end point assessment (Figure 1). The 6-month results are presented in Table 3.

**Primary End Point**

Of the 235 patients with angiographic follow-up, 41 (17.4%) had restenosis, 20 of 119 (16.8\%±6.7\%) in the aggressive PTCA group and 21 of 116 (18.1\%±7.0\%) in the stent group. The difference in restenosis rates (aggressive PTCA group minus stent group) was −1.3\%, and the upper limit of 95\% CI of this difference was 7.1\%, which is less than the selected noninferiority boundary of 8\%. Thus, according to the study design, the noninferiority hypothesis was accepted.

**Secondary End Points**

At the 6-month follow-up, a trend for higher late loss was observed in the stent group (0.71\%±0.54 versus 0.55\%±0.60 mm; \( P=0.06 \)). Angiographic MLD and minimum L-CSA were comparable in both groups; the differences in MLD (−0.07\%±0.14 mm) and in L-CSA (−0.12\%±0.70 mm²) were not significant (Figure 3). Clinical follow-up was complete for all but one patient: 2 patients died (stent group), 3 had myocardial infarctions, 6 suffered unstable angina, and 43 had coronary revascularization. A combined clinical event occurred in 45 of 254 patients (18\%): 21 (16\%) from the aggressive PTCA group and 24 (20\%) from the stent group (\( P=0.52 \)). In addition, in-stent restenosis was observed more
frequently in the stent group than in the aggressive PTCA group (18 of 116 [15.5%] versus 6 of 119 [5.0%], respectively; \( P = 0.02 \)).

Discussion

Summary of Findings

This study shows that IVUS-guided balloon angioplasty with provisional stenting, based on angiography and on IVUS, is feasible and safe and results in a 44% stent implantation rate.

Study Design

Herefore, only angiography-guided provisional stenting has been compared with systematic stenting through randomized studies. The strategy of IVUS-guided PTCA, which was initially described in the Clinical Outcomes with Ultrasound Trial, has shown favorable long-term clinical outcomes. This strategy has matured into IVUS-guided provisional stenting by using IVUS criteria for stenting in addition to IVUS balloon sizing, thus leading to better results than with angiography-guided provisional stenting. In this context, the time was right for a randomized comparison of this IVUS-guided strategy with systematic stenting.

We hypothesized that a provisional stenting strategy would provide similar (but not better) results to stenting at a significantly lower stenting rate. Therefore, a noninferiority design was mandatory. The definition of what qualifies as an “acceptable” noninferiority boundary is debatable, because it must fit both medical and statistical considerations. In our study, the statistical consideration for the noninferiority
boundary selection was based on the results of a randomized trial,\(^3\) as advocated and previously used,\(^{23,24}\) even if a boundary as high as 8% more restenosis may seem considerable clinically.

**Comparison With Other Studies**

**Procedure**

The IVUS-guided PTCA procedure used in our study was similar to that previously described.\(^{14,15,17-19,21}\) IVUS criteria for crossover to stent (<30% residual stenosis or <6 mm\(^2\) minimum L-CSA) were adapted from previous IVUS-guided PTCA studies,\(^{17,19}\) except regarding non-flow-limiting dissection, because several trials have shown favorable clinical outcomes in these cases.\(^{15,21,25}\) Crossover to stent was needed in 44% of patients; this rate is comparable to that observed in previous IVUS-guided PTCA studies,\(^{17,19}\) but it is higher than the usual 30% reported in studies with angiographic guidance alone.\(^{9-13}\) In our study, aggressive PTCA was more complex than systematic stenting.

**Immediate Results**

In the stent arm, the immediate results were similar to those observed in the Benestent II trial, whereas in the PTCA arm, larger MLDs and lower residual stenosis were observed compared with angiographically guided provisional stenting studies.\(^{10,11,13,19}\) Our immediate and late results were consistent with reports of IVUS-guided PTCA, with a similar rate of crossover to stent.\(^{17-19}\)

**Long-Term Results**

The restenosis rate observed in the stent arm was close to that expected given the lumen area after angioplasty (7.28 ± 2.22 mm\(^2\)).\(^{26}\) The low restenosis rate observed in the aggressive PTCA group was confirmed by the results in angiographic MLD, diameter stenosis, L-CSA, and clinical event rate. These results are consistent with the favorable outcome observed with IVUS-guided angioplasty in a large single-center registry\(^{17}\) and in a matched comparison with traditional stenting in long lesions.\(^{21}\) Moreover, because less in-stent restenosis was observed in the aggressive PTCA arm, it is likely that more favorable clinical outcomes could be observed in the subset of patients submitted for lesion revascularization.

**Potential Impact**

The main concern associated with routine application of this IVUS-guided angioplasty technique is the increase in the duration and difficulty of the procedure because longer angioplasty procedures, although effective, are not widely accepted.\(^{11,22}\) Nevertheless, such a strategy could become helpful if, for any reason, restrictions on stent implantation were introduced.

**Study Limitations**

First, although this was a randomized study, we cannot rule out the possibility of a bias linked to the lack of double blinding. Second, a true equivalence trial would have needed

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**TABLE 2. Procedural Details and Angiographic and IVUS Immediate Results**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Aggressive PTCA (A; n = 132)</th>
<th>Stent (B; n = 122)</th>
<th>Balloon Alone (C; n = 74)</th>
<th>Crossover to Stent (D; n = 58)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nominal balloon size, mm</td>
<td>3.60 ± 0.52</td>
<td>3.37 ± 0.47</td>
<td>3.66 ± 0.51</td>
<td>3.59 ± 0.56</td>
<td>0.001</td>
</tr>
<tr>
<td>Balloon inflation pressure, atm</td>
<td>13.32 ± 3.41</td>
<td>14.53 ± 2.97</td>
<td>13.2 ± 3.1</td>
<td>13.5 ± 3.8</td>
<td>0.015</td>
</tr>
<tr>
<td>Actual balloon size, mm</td>
<td>3.85 ± 0.48</td>
<td>3.75 ± 0.41</td>
<td>3.92 ± 0.51</td>
<td>3.81 ± 0.43</td>
<td>0.03</td>
</tr>
<tr>
<td>Balloon/artery ratio, nominal</td>
<td>1.25 ± 0.29</td>
<td>1.19 ± 0.27</td>
<td>1.29 ± 0.31</td>
<td>1.19 ± 0.25</td>
<td>0.08</td>
</tr>
<tr>
<td>Stent implantation, n (%)</td>
<td>58 (44)</td>
<td>121 (100)</td>
<td>0</td>
<td>58 (100)</td>
<td>0.001</td>
</tr>
<tr>
<td>No. of balloons</td>
<td>192</td>
<td>188</td>
<td>84</td>
<td>108</td>
<td>0.001</td>
</tr>
<tr>
<td>No. of stents</td>
<td>81</td>
<td>127</td>
<td>0</td>
<td>69</td>
<td>0.001</td>
</tr>
<tr>
<td>Procedural time, min</td>
<td>51 ± 18</td>
<td>39 ± 14</td>
<td>47 ± 15</td>
<td>60 ± 19</td>
<td>0.001</td>
</tr>
<tr>
<td>Fluoroscopic time, min</td>
<td>10.6 ± 4.4</td>
<td>8.6 ± 4.2</td>
<td>10 ± 4</td>
<td>12 ± 5</td>
<td>0.03</td>
</tr>
<tr>
<td>Contrast media, mL</td>
<td>192 ± 82</td>
<td>158 ± 83</td>
<td>273 ± 80</td>
<td>226 ± 77</td>
<td>0.001</td>
</tr>
<tr>
<td>CK release, U</td>
<td>120 ± 135</td>
<td>110 ± 149</td>
<td>129 ± 143</td>
<td>104 ± 118</td>
<td>0.61</td>
</tr>
<tr>
<td>CK release &gt;3 ULN, n (%)</td>
<td>5 (4)</td>
<td>4 (3)</td>
<td>3/74 (4)</td>
<td>2/58 (3)</td>
<td>0.75</td>
</tr>
<tr>
<td>Reference before PCI, mm</td>
<td>2.96 ± 0.63</td>
<td>2.89 ± 0.54</td>
<td>2.99 ± 0.63</td>
<td>2.93 ± 0.51</td>
<td>0.69</td>
</tr>
<tr>
<td>MLD before PCI, mm</td>
<td>1.06 ± 0.31</td>
<td>1.08 ± 0.36</td>
<td>1.08 ± 0.32</td>
<td>1.06 ± 0.31</td>
<td>0.80</td>
</tr>
<tr>
<td>Diameter stenosis before PCI, %</td>
<td>64 ± 9</td>
<td>63 ± 10</td>
<td>63 ± 9</td>
<td>64 ± 9</td>
<td>0.36</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>10.22 ± 4.43</td>
<td>9.46 ± 3.98</td>
<td>10.5 ± 4.21</td>
<td>9.97 ± 4.51</td>
<td>0.26</td>
</tr>
<tr>
<td>Reference after PCI, mm</td>
<td>3.08 ± 0.54</td>
<td>3.18 ± 0.35</td>
<td>2.99 ± 0.56</td>
<td>3.17 ± 0.52</td>
<td>0.14</td>
</tr>
<tr>
<td>MLD after PCI, mm</td>
<td>2.55 ± 0.49</td>
<td>2.75 ± 0.49</td>
<td>2.43 ± 0.45</td>
<td>2.69 ± 0.49</td>
<td>0.013</td>
</tr>
<tr>
<td>Diameter stenosis after PCI, %</td>
<td>16 ± 7</td>
<td>13 ± 6</td>
<td>18 ± 7</td>
<td>15 ± 6</td>
<td>0.001</td>
</tr>
<tr>
<td>L-CSA before PCI, mm</td>
<td>1.79 ± 0.72</td>
<td>2.03 ± 0.62</td>
<td>1.79 ± 0.81</td>
<td>1.80 ± 0.78</td>
<td>0.07</td>
</tr>
<tr>
<td>L-CSA after PCI, mm</td>
<td>6.60 ± 2.05</td>
<td>7.28 ± 2.22</td>
<td>6.06 ± 1.87</td>
<td>7.29 ± 2.09</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are mean ± SD or number of patients (percentage). CK indicates creatine kinase; PCI, percutaneous coronary intervention.

*ANOVA with Bonferroni-Dunn correction; significant if \(P < 0.016\)
a third arm for this study, ie, a group with angiography-guided provisional stenting. Third, only patients with lesions suitable for stent implantation were included in this study, and the results cannot be extrapolated to other types of lesions. Finally, a comparison of the cost-effectiveness of the 2 strategies was not part of the study design.

Conclusions
A strategy of IVUS-guided angioplasty with provisional stenting is feasible and safe. At the cost of a longer and more complex procedure, it makes reduces the stent rate by half, with a similar 6-month angiographic restenosis rate and similar clinical outcome compared with stent implantation.

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References


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