Heparin-Coated Stent Placement for the Treatment of Stenoses in Small Coronary Arteries of Symptomatic Patients

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Background—The role of stents, especially of heparin-coated stents for the treatment of stenoses in small coronary arteries, is still unclear. Therefore, we performed this prospective, randomized trial to evaluate the angiographic and clinical outcome after treatment of stenoses in small coronary arteries (2.0 to 2.6 mm) of symptomatic patients.

Methods and Results—We randomly assigned 588 patients to angioplasty (n=195), bare stenting (n=196), or heparin-coated stenting (n=197). The primary end point was minimal lumen diameter (MLD) at 6 months. With comparable baseline parameters, the two stent arms showed a larger postinterventional MLD, larger acute gain, and smaller residual percent diameter stenosis, although a residual stenosis of 12±16% was achieved in the angioplasty arm, including a 27% crossover rate to stenting. Eighty percent of patients had follow-up angiography, which documented a borderline significantly larger MLD and smaller percent diameter stenosis for the two stent groups (1.34±0.48 mm and 42±20% after angioplasty, 1.47±0.48 mm and 36±20% after bare stenting, and 1.45±0.54 mm and 38±23% after heparin-coated stenting; P=0.049 and P=0.038, respectively), but restenosis rates were not different (32%, 25%, and 30%). Thrombotic events occurred in 1.0% after angioplasty and 0.5% after bare or heparin-coated stenting. Survival without myocardial infarction or target vessel revascularization at 250 days was 84.6% (angioplasty), 88.3% (bare stenting), and 88.3% (heparin-coated stenting; log-rank P=0.39).

Conclusion—Compared with angioplasty with provisional stenting, bare and heparin-coated stenting confer superior angiographic results and a nonsignificant 24% reduction in clinical events, with no difference between bare and heparin-coated stenting in the treatment of stenoses in small coronary arteries. (Circulation. 2003;107:1265-1270.)

Key Words: stents ■ angioplasty ■ heparin ■ restenosis

The efficacy of stenting in preventing restenosis has been proved by randomized studies in different situations in vessels that usually have diameters of >3.0 mm.1–6 A subgroup analysis of the STEnt REStenosis Study (STRESS) trials also showed a reduced restenosis rate after stenting in vessels <3.0 mm in diameter,7 whereas a meta-analysis of the BENESTENT and STRESS trials only showed a benefit for stenting in vessels ranging from 2.6 to 3.6 mm in diameter. In current practice, however, 35% to 67% of lesions are located in small (<3.0 mm) coronary arteries, a setting associated with poor short-term and long-term results after standard balloon angioplasty (PTCA).8 The role of stenting in small coronary arteries is unclear. Several retrospective or nonrandomized studies in small vessels have suggested better clinical results and lower restenosis rates with stenting than with PTCA.9–11 Recently, four randomized trials documented safety and early efficacy of stenting in small coronary arteries, but the long-term outcome, including the antirestenotic potential, remained unclear.12–15

Heparin-coated stents should overcome the problem of subacute stent thrombosis, in addition to offering more pronounced antiaggregation when combined with aspirin plus ticlopidine or clopidogrel in patients at high risk for thrombotic complications.15–18 Nevertheless, conclusive data to determine the role of heparin-coated stents are lacking.

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*The COAST Trial Investigators are listed in the Appendix.

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Therefore, we designed a prospective, randomized trial to evaluate the potential angiographic and clinical benefit of stenting, especially heparin-coated stenting, in comparison to PTCA for the treatment of stenoses in small native coronary arteries.

**Methods**

**Patients**

Patients with stable or unstable angina presenting stenoses in native coronary arteries ranging from 2.0 to 2.6 mm in diameter were randomly assigned to one of the three treatment arms after giving informed consent: (1) PTCA; (2) implantation of a bare JOSTENT Flex stent (JOMED); or (3) implantation of a heparin-coated JOSTENT Flex stent. Lesion length was limited to 26 mm. Patients were excluded if they had acute or evolving myocardial infarction; severe heart failure (left ventricular ejection fraction <30%); or contraindication to aspirin, ticlopidine, or clopidogrel. Additional angioplasties of lesions in different arteries >3.0 mm in diameter in the same patient were allowed, although not recommended. The treatment of several lesions in two or more small coronary artery segments in the same patient was not allowed.

**Procedural Protocol**

Preinterventional online quantitative coronary angiography (QCA) was used to confirm the intended reference vessel size, ranging from 2.0 to 2.6 mm. Angioplasty or stent implantation was performed in the conventional manner by femoral or radial approach. In the stent groups, predilatation was strongly recommended. The intended balloon-to-artery ratio was 1.1, and the recommended stent implantation pressure was 14 atm. Aspirin was prescribed, and 10 000 IU of heparin was given before the procedure. The use of glycoprotein IIb/IIIa blockers was discouraged. In the PTCA group, crossover to stent implantation was allowed in case of abrupt or threatened closure, defined as dissection types C through F (National Heart, Lung and Blood Institute classification), TIMI flow <3, or ≥50% residual stenosis with myocardial ischemia. Crossover stents had to exclude JOSTENT Flex stents. After the procedure, all patients received aspirin (100 mg per day). Patients in the stent arms additionally received 500 mg ticlopidine per day or a loading dose of 300 mg clopidogrel followed by 75 mg per day for 4 weeks.

**Stents**

The JOSTENT Flex stent was used in the bare stent arm. It was available in 9-, 16-, and 26-mm lengths with a strut thickness of 0.115 mm, and it was manually crimped to the stent delivery balloon. In the heparin-coated stent arm, the same JOSTENT Flex stent was used with the Corline heparin coating, which attaches a proteoglycan-like conjugate of covalently bound unfractionated heparin to the stent. The heparin surface concentration is 0.5 to 1 μg/cm², providing 2 to 4 pmol/cm² antithrombin III binding sites. This conjugate is stable and compliant with stent expansion and does not release heparin.

**Quantitative Coronary Angiography**

Angiography was performed before intervention, after intervention, and at 6-month follow-up or earlier if needed. Intracoronary nitroglycerin was given before each angiography. Core laboratory QCA was performed with the use of the validated CMS 5.0 edge-detection system (Medis). Offline QCA measurements were performed in a single projection showing the most severe stenosis, which was repeated after intervention and at follow-up, with the contrast-filled guiding catheter used for calibration. Minimal lumen diameter (MLD) was measured, and percentage diameter stenosis was calculated according to the interpolated reference diameter approach. Acute gain, late loss, net gain, and loss index were calculated.

**End Points**

The primary end point was MLD at follow-up angiography. Secondary end points included procedural success rates and the incidence of death, myocardial infarction, thrombotic events, angiographic restenosis (defined as ≥50% diameter stenosis), target vessel revascularization, and event-free survival estimated at the end of hospitalization and at 30 and 250 days.

Procedural success was defined as successful completion of the intended intervention without complication or crossover.

All deaths were considered cardiac unless an unequivocal noncardiac cause could be established.

Q-wave myocardial infarction was defined by new Q waves >0.04 seconds in duration and postinterventional elevation of serum creatinine kinase to >3 times the upper limit of normal with an elevated MB fraction (>8%). Non-Q-wave myocardial infarction was based only on enzyme elevation without new Q waves.

Target vessel revascularization required recurrent angina and/or signs of ischemia.

**Statistical Analysis**

A minimum difference of 0.15 mm in MLD in one of the treatment arms was expected to be significant. Assuming a standard deviation of the residuals of 0.4 mm, a power of 80%, an α-error of 5% (2-sided test), a maximum of 10% crossover cases in any group, and an 80% reangiography rate, 600 patients had to be enrolled.

The primary analysis of angiographic and procedural outcomes was based on intention to treat. A secondary analysis assessed MLD and restenosis rates according to treatment received. Results are presented as mean±SD. For comparisons of continuous variables, ANOVA was used according to the type of data and their distribution. For comparison between groups, χ² test or Fisher’s exact test was used. Statistical significance was considered to be indicated by a 2-tailed probability value of <0.05. Kaplan-Meier curves for event-free survival were analyzed by log-rank test.

**Results**

From December 1997 to November 2000, 605 patients were randomized. Seventeen patients were excluded after randomization and before treatment: Five patients had withdrawn their informed consent, and in 12 patients online QCA immediately before the intervention revealed a reference diameter >3.0 mm, which was an exclusion criteria. Therefore, 588 patients were treated at 22 centers according to their assigned intervention. Baseline clinical and procedural data are summarized in Tables 1 and 2. Groups were quite comparable, with approximately 20% of patients being diabetic, approximately 80% presenting multivessel disease, and approximately 25% having complex American Heart Association/American College of Cardiology type B2 or C lesions. Multivessel and multilesion interventions were performed in about 3% of patients.

**Procedural Data**

Procedural success was achieved in 142 of 195 patients (72.8%) after PTCA compared with 192 of 196 (97.9%) after bare stenting and 193 of 197 (97.9%) after heparin-coated stenting (P<0.0001). In the PTCA arm, 53 patients (27.2%) required crossover to stenting. During bare stenting, two stent embolizations happened with subsequent successful retrieval. In two other patients, the stent or the guidewire could not cross the target lesion. During heparin-coated stenting, one stent embolization occurred proximal to the target lesion without successful retrieval. This stent was implanted at that spot after recrossing with a balloon. Three additional patients had unsuccessful crossing of the heparin-coated stent with...
successful retrieval. The number of implanted stents per lesion was similar between the two stent groups and the subgroup of the PTCA arm that required bail-out stents (Table 2). Maximum balloon diameter and inflation times in the PTCA arm were significantly higher and longer, whereas maximum pressure was lower.

### Angiographic Results
Reference diameter, baseline stenosis severity, and length were comparable among the three groups (Table 3). Postinterventional MLD and acute gain were significantly smaller in the PTCA arm, whereas residual stenosis was larger, although a residual stenosis of 12.2%±16% was achieved. Follow-up angiography was performed in 467 of 584 eligible patients (80%) after 6±2 months. The remaining patients refused repeat angiography. MLD at follow-up was marginally but significantly smaller in the PTCA arm (Figure 1), whereas percent diameter stenosis was significantly larger (Table 3). There was no difference in MLD at follow-up between the two stent arms. Late loss was not different among the three groups, and net gain was significantly smaller in the PTCA arm. On the basis of intention-to-treat, the restenosis rate was 32.2% after PTCA with provisional stenting, 24.8% after bare stenting, and 29.6% after heparin-coated stenting, with no significant difference (P=0.34). To assess results on the basis of the actual treatment received, 53 patients of the PTCA arm crossed over to the bare stent arm, whereas three patients of the bare stent arm and four patients of the heparin-coated stent arm crossed over to the PTCA arm. In these new patient cohorts, MLD and restenosis rates at follow-up were not significantly different (1.34±0.44 mm, 1.44±0.50 mm, and 1.45±0.66 mm, P=0.162; and 32.1%, 27.1%, and 29.8%, P=0.627).

### Clinical Events
During hospitalization and at 30 days, no clinical events were detected in the PTCA arm. In the bare stent arm, one patient with 3-vessel disease and poor left ventricular function required emergency bypass operation for abrupt vessel closure during the index procedure, with fatal outcome. Another patient developed non-Q-wave myocardial infarction the day after the procedure and was treated medically. In the heparin-coated stent group one patient with 3-vessel disease and poor left ventricular function required emergency bypass operation for abrupt vessel closure during the index procedure, with fatal outcome. Another patient developed Q-wave myocardial infarction the day after implantation because of suspected stent thrombosis. This patient was treated medically. Until day 30 no additional events occurred in any group. At 250 days, one additional

### TABLE 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Cardiovascular risk factors</th>
<th>PTCA (n=195)</th>
<th>Bare Stent (n=196)</th>
<th>Heparin-Coated Stent (n=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±10</td>
<td>61±11</td>
<td>62±10</td>
</tr>
<tr>
<td>Male/female</td>
<td>141/54</td>
<td>148/48</td>
<td>147/50</td>
</tr>
<tr>
<td>Smoking</td>
<td>93 (48)</td>
<td>107 (55)</td>
<td>101 (51)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>141 (70)</td>
<td>140 (71)</td>
<td>147 (75)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>33 (17)</td>
<td>36 (18)</td>
<td>41 (21)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>136 (70)</td>
<td>11 (61)</td>
<td>137 (70)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>33 (17)</td>
<td>36 (18)</td>
<td>41 (21)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>136 (70)</td>
<td>11 (61)</td>
<td>137 (70)</td>
</tr>
</tbody>
</table>

### TABLE 2. Procedural Characteristics

<table>
<thead>
<tr>
<th>Procedure details</th>
<th>PTCA (n=195)</th>
<th>Bare Stent (n=196)</th>
<th>Heparin-Coated Stent (n=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum balloon diameter, mm</td>
<td>2.58±0.27</td>
<td>2.53±0.38</td>
<td>2.51±0.27</td>
</tr>
<tr>
<td>Balloon-to-artery ratio</td>
<td>1.11±0.16</td>
<td>1.09±0.14</td>
<td>1.09±0.15</td>
</tr>
<tr>
<td>Stent length, mm</td>
<td>16.36±4.86</td>
<td>15.09±5.14</td>
<td>15.49±6.03</td>
</tr>
<tr>
<td>No. of stents implanted</td>
<td>1.1±0.3*</td>
<td>1.1±0.4</td>
<td>1.1±0.4</td>
</tr>
<tr>
<td>Maximum pressure, atm</td>
<td>12±3</td>
<td>14±3</td>
<td>14±3</td>
</tr>
<tr>
<td>Maximum inflation time, s</td>
<td>74±66</td>
<td>34±23</td>
<td>30±14</td>
</tr>
<tr>
<td>Multivessel intervention</td>
<td>5 (2.6)</td>
<td>6 (3.1)</td>
<td>7 (3.6)</td>
</tr>
<tr>
<td>Glycoprotein Ibb/Illa blocker administration</td>
<td>3 (1.6)</td>
<td>2 (1.0)</td>
<td>3 (1.5)</td>
</tr>
</tbody>
</table>

*Values are given as mean±SD or n (%).

*Crossover stents (no study stents) in the PTCA group.
sudden cardiac death occurred in the bare stent arm at day 166 and one non–cardiac-related death in the heparin-coated stent arm at day 183. Ischemia-driven target vessel revascularization was performed in 14.4%, 10.2%, and 11.2%, respectively (P/H11005 = 0.418). Survival without myocardial infarction or target vessel revascularization was not different among the three treatment arms over a period of 250 days (Figure 2).

Discussion

The present study is the first to compare heparin-coated stents with bare stents of the same design and strut thickness, and to compare PTCA with provisional stenting for the treatment of lesions in small coronary arteries. The results documented that all three treatment strategies can be safely performed with low short-term and long-term event rates. Bare and heparin-coated stenting showed superior angiographic results and a nonsignificant 24% reduction in clinical events compared with PTCA with provisional bare stenting. Although the study was underpowered for this clinical end point, this 24% reduction was in line with other randomized stent study results.

The major reason for this outcome was the best final PTCA result ever reported in small coronary arteries, with a residual stenosis of 12±16%, utilizing a balloon-to-artery ratio of 1.11. In recently published randomized trials comparing PTCA and stenting in small coronary arteries, Kastrati et al12 documented a residual diameter stenosis of 19% after PTCA, Koning et al13 of 29%, Doucet et al14 of 26%, and Moer et al15 of 25%. Only the study with the largest residual stenosis after PTCA showed a significant restenosis reduction for the stent arm.

Our quite effective PTCA strategy used provisional stenting in 27% of patients. In the other trials, this crossover rate

<table>
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<th>TABLE 3. Results of Quantitative Coronary Angiography</th>
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<tr>
<td><strong>At baseline</strong></td>
</tr>
<tr>
<td>Reference diameter, mm</td>
</tr>
<tr>
<td>MLD, mm</td>
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<tr>
<td>Stenosis, %</td>
</tr>
<tr>
<td>Lesion length, mm</td>
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<tr>
<td><strong>After procedure</strong></td>
</tr>
<tr>
<td>Reference diameter, mm</td>
</tr>
<tr>
<td>MLD, mm</td>
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<tr>
<td>Stenosis, %</td>
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<tr>
<td>Acute gain, mm</td>
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<tr>
<td><strong>At 6 months</strong></td>
</tr>
<tr>
<td>Reference diameter, mm</td>
</tr>
<tr>
<td>MLD, mm</td>
</tr>
<tr>
<td>Stenosis, %</td>
</tr>
<tr>
<td>Late loss, mm</td>
</tr>
<tr>
<td>Loss index</td>
</tr>
<tr>
<td>Net gain, mm</td>
</tr>
</tbody>
</table>

Values are mean±SD or as indicated.
During hospitalization
Death
Q-wave myocardial infarction
Non-Q-wave myocardial infarction
Thrombotic event
Target vessel revascularization
Repeat PCI
CABG
Any event
At 30 days
Death
Q-wave myocardial infarction
Non-Q-wave myocardial infarction
Thrombotic event
Target vessel revascularization
Repeat PCI
CABG
Any event
At 250 days
Death
Q-wave myocardial infarction
Non-Q-wave myocardial infarction
Thrombotic event
Target vessel revascularization
Repeat PCI
CABG
Any event

Values are given as n (%).
There was no significant difference between the groups.

was slightly lower, with 16.5%,¹₂ 23%,¹³ 20%,¹⁴ and 14%,¹⁵ Surprisingly, in our study late lumen loss after PTCA was similar to that after bare or heparin-coated stenting, which was not reported in most of the other trials and was supposed to be related to the aggressive PTCA strategy.

Although MLD at follow-up and net lumen gain were significantly higher in the bare stent group, both stent arms failed to show a significant reduction in binary restenosis rate, which confirmed previous results.¹²¹⁴¹⁵ Even an analysis that excluded crossover cases did not present favorable results for the two stent arms. In addition, the study was underpowered for this end point.

Heparin coating was intended to limit stent thrombosis, which was thought to occur more frequently in small vessels. Our results document a very low 0.5% rate of thrombotic events after both elective bare and heparin-coated stenting, although glycoprotein IIb/IIIa blockers were not routinely administered and treatment with ticlopidine or clopidogrel was initiated in most cases immediately after stenting. These thrombotic event rates are comparable to those of other heparin-coated stent trials, ranging from 0.8% to 1.9%.¹⁵⁻¹⁸ Although the Corline heparin coating used in the present trial is different from other heparin coatings with regard to the conditioning layer, the heparin attachment, and the antithrombin III–binding activity,¹⁹ the low thrombotic event rate after elective bare stenting of small vessels with adjunctive administration of aspirin and ticlopidine or clopidogrel makes the additional antithrombotic benefit of any heparin coating questionable. This message cannot be extrapolated to different scenarios like stenting in acute coronary syndromes, including ST-elevation myocardial infarction.

Although experimental data suggest that heparin has some additional antiproliferative capacities to limit restenosis,¹⁹,²⁰ we did not expect the Corline heparin coating to reduce restenosis because it does not release heparin to the vessel wall.

More recently, stents with an active antiproliferative coating have become available, which showed almost no late lumen loss and no restenosis.²¹,²² The use of these stents in small vessels could have produced more favorable results in the stent arm.

Limitations of This Trial
Small coronary arteries were defined as vessels 2.0 to 2.6 mm in diameter according to online QCA interpolation of proximal and distal references. This is an arbitrary definition that can create an inhomogeneous group in terms of restenosis risk. Another limitation is related to the atherosclerosis process, which may be diffuse in nature, so that the diseased vessel may have a reduced lumen along its entire length, giving the angiographic impression of a small vessel. Only intravascular ultrasound provides an accurate measurement of the true vessel size.²³,²⁴ Therefore, we could have included in our trial larger vessels with diffuse disease that represent a completely different population compared with small vessels with discrete lesions.

Results were obtained for de-novo lesions and cannot be extrapolated to other lesion characteristics such as restenotic or long lesions or bypass graft location.

Stent design and strut thickness can influence outcomes.²⁵,²⁶ Our findings with the bare and heparin-coated JOSTENT Flex stent may not be extrapolated to other stent types.

Even if the creatinine kinase cutoff level for a more contemporary definition of myocardial infarction were changed to 2 times the upper normal limit, only one additional patient in each stent group would have developed non–Q-wave myocardial infarction.

In conclusion, bare or heparin-coated stenting compared with PTCA with provisional stenting showed superior angiographic results and a nonsignificant 24% reduction in clinical events, with no difference between bare and heparin-coated stenting.

Appendix
The following additional institutions and investigators participated in the COAST trial:
R.A. Foale, St Mary’s Hospital, London, Great Britain; M.J. Pieper, Herzzentrum Bodensee, Kreuzlingen, Switzerland; A.M. Zeiher, University Frankfurt, Frankfurt, Germany; W. Wijns, O.L.V. Ziekenhuis, Aalst, Belgium; M.T. Rothman, Chest Hospital, London,
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