Intracoronary Stenting and Angiographic Results
Strut Thickness Effect on Restenosis Outcome (ISAR-STEREO) Trial

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Background—Increased thrombogenicity and smooth muscle cell proliferative response induced by the metal struts compromise the advantages of coronary stenting. The objective of this randomized, multicenter study was to assess whether a reduced strut thickness of coronary stents is associated with improved follow-up angiographic and clinical results.

Methods and Results—A total of 651 patients with coronary lesions situated in native vessels >2.8 mm in diameter were randomly assigned to receive 1 of 2 commercially available stents of comparable design but different thickness: 326 patients to the thin-strut stent (strut thickness of 50 μm) and 325 patients to the thick-strut stent (strut thickness of 140 μm). The primary end point was the angiographic restenosis (≥50% diameter stenosis at follow-up angiography). Secondary end points were the incidence of reinterventions due to restenosis-induced ischemia and the combined rate of death and myocardial infarctions at 1 year. The incidence of angiographic restenosis was 15.0% in the thin-strut group and 25.8% in the thick-strut group (relative risk, 0.58; 95% CI, 0.39 to 0.87; \( P = 0.003 \)). Clinical restenosis was also significantly reduced, with a reintervention rate of 8.6% among thin-strut patients and 13.8% among thick-strut patients (relative risk, 0.62; 95% CI, 0.39 to 0.99; \( P = 0.03 \)). No difference was observed in the combined 1-year rate of death and myocardial infarction.

Conclusions—The use of a thinner-strut device is associated with a significant reduction of angiographic and clinical restenosis after coronary artery stenting. These findings may have relevant implications for the currently most widely used percutaneous coronary intervention. (Circulation. 2001;103:2816-2821.)

Key Words: coronary disease ■ restenosis ■ stents ■ trials

Coronary stenting is an established form of treatment for the majority of patients with symptomatic coronary artery disease.1-4 The main benefit of stenting compared with conventional percutaneous transluminal coronary angioplasty (PTCA) consists of the reduction of restenosis. In fact, the reduction of restenosis is exclusively the result of a bigger initial lumen achieved with stenting. This initial gain is more than sufficient to compensate for the greater neointima formation induced by the metal endoprosthesis.5

Recent advances in stent design have generally improved the procedural success rate and short-term lumen gain. They may have a different impact on restenosis, however, as demonstrated by a series of recent studies on the relative efficacies of various stent designs.6-9 Although it has been possible to differentiate between stents in terms of their long-term efficacy, the mechanisms underlying these differences have not yet been elucidated. Major efforts and resources are concentrated on strategies aiming at the prevention of in-stent restenosis.10 The identification of stent properties that induce less lumen renarrowing may offer a simple, cost-effective, and readily available option against restenosis.

We hypothesized that a stent with a reduced strut thickness has a favorable effect on restenosis and tested this hypothesis in a multicenter randomized trial by comparing 2 commercially available stents with different strut thicknesses but with similar design.

Methods

Patients

The inclusion criteria for this trial were symptomatic coronary artery disease and lesions situated in native coronary vessels >2.8 mm in diameter (on the basis of online digital estimation). The study was conducted according to the principles of the Declaration of Helsinki and approved by the institutional ethics committees. All patients had given their informed consent for participation in this trial.
Randomization, Stent Placement, and Poststenting Treatment

Immediately after successful passage of the guidewire through the target lesion, the patients were randomly assigned to receive 1 of the 2 premounted stents with an interconnected-ring design and different strut thicknesses: the thin-strut stent, ACS RX Multi-Link, with strut thickness of 50 μm and strut width of 100 μm, in lengths of 15, 25, and 35 mm; and the thick-strut stent, ACS Multi-Link RX Duet with strut thickness of 140 μm and strut width of 100 μm, in lengths of 8, 13, 18, 23, 28, and 38 mm. The design of the 2 models is very similar, except for a slightly decreased number of inter-ring articulations in the thick-strut stent. Both stents were manufactured by the same company (Guidant/Advanced Cardiovascular Systems). Stents were deployed by use of the manufacturer’s delivery system at the recommended pressures for each type. Low-compliance balloons were used for the final dilatation, and the decision about which final pressure to apply was left to the operator’s discretion. A final pressure of 12 to 15 atm was recommended, however, on the basis of previous experience.

During the intervention, patients received heparin and aspirin intravenously. The patients considered to be at higher risk for stent thrombosis received abciximab as a bolus followed by a 12-hour intravenous infusion and heparin dosage reduced by 50%. All patients received a combined therapy with 250 mg ticlopidine plus 100 mg aspirin twice daily for 4 weeks; aspirin was taken indefinitely.

Angiographic Evaluation

All digital angiograms were analyzed offline with the automated edge-detection system CMS (Medis Medical Imaging Systems) at the core angiographic laboratory. The operators who performed the quantitative assessment were unaware of both the patient’s participation in the study and the randomly assigned treatment. The same projections were used to obtain angiographic images before and immediately after the intervention and at follow-up. The measurements were performed on angiograms recorded after intracoronary nitroglycerin administration. The contrast-filled nontapered catheter tip was used for calibration. Late lumen loss was calculated as the difference in the minimal lumen diameter between that immediately after the procedure and that at follow-up.

Definitions and End Points of the Study

Procedural success was defined by stent placement with a residual stenosis of <30% and Thrombolysis in Myocardial Infarction flow grade ≥2. Device success was defined as achievement of procedural success with the randomly assigned stent.

The primary end point of the study was the incidence of angiographic restenosis, defined as a diameter stenosis of ≥50% at 6-month reangiography measured at any point within the stented segment or in the 5-mm proximal or distal segments adjacent to the stent. Secondary end points of the trial were the need for target vessel revascularization (balloon angioplasty or aortocoronary bypass surgery) due to restenosis-induced symptoms or signs of ischemia and the combined rate of death and myocardial infarction at 1 year after the procedure. The diagnosis of acute myocardial infarction was based on the presence of ≥2 of the following criteria: prolonged and typical chest pain (>20-minute duration), new pathological Q waves, and a value of creatine kinase (CK) or its MB isoenzyme ≥2 times the upper limit. CK was determined before and immediately after the procedure, every 8 hours for the first 24 hours after stenting, and daily afterward until discharge. The follow-up protocol included a telephone interview at 30 days, a clinical visit at 6 months, and an additional telephone interview at 1 year after the procedure. For patients reporting cardiac symptoms during the telephone interview, ≥1 clinical and ECG follow-up visit was scheduled and performed at the outpatient clinic or by the referring physician. At 1 year, all information available from hospital readmission records, the referring physician, or the outpatient clinic was entered into a computer database.

Statistical Analysis

The sample size estimation was based on the following assumptions: a 2-sided α-level of 0.05 and power of 80% and an angiographic restenosis rate of 25% in the thick-strut stent group and 15% in the thin-strut stent group, as shown in a previous trial. Accordingly, a sample size of 250 patients in each group was calculated; we enrolled a total of 651 patients to accommodate for missing angiographic follow-up studies.

The main analyses were performed on the basis of the intention-to-treat principle. The results are shown as mean ± SD or as proportions (%). The differences between the 2 groups were assessed by χ² test or Fisher’s exact test, as appropriate, for categorical data and t test for continuous data. Survival parameters were compared by the log-rank test. A multivariate logistic regression analysis was also planned to adjust for the influence on restenosis of eventual differences in baseline or procedural characteristics. Probability values of P<0.05 were considered significant.

Results

Baseline Characteristics and Procedural Results

A total of 651 patients were randomized to receive either a thin-strut stent (n=326) or a thick-strut stent (n=325). Demographic and clinical data at presentation were comparable between the 2 groups, as shown in Table 1. Notably,
TABLE 2. Baseline Angiographic and Hemodynamic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Thin-Strut Group (n=326)</th>
<th>Thick-Strut Group (n=325)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivessel disease, n (%)</td>
<td>233 (71.5)</td>
<td>229 (70.5)</td>
<td>0.78</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>56.3±13.8</td>
<td>57.5±14.1</td>
<td>0.29</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mm Hg</td>
<td>100.7±11.0</td>
<td>101.8±11.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Coronary vessel, n (%)</td>
<td>8 (2.4)</td>
<td>6 (1.9)</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>146 (44.8)</td>
<td>145 (44.6)</td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>57 (17.5)</td>
<td>58 (17.8)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>115 (35.3)</td>
<td>116 (35.7)</td>
<td></td>
</tr>
<tr>
<td>ACC/AHA lesion type, n (%)</td>
<td>6 (1.9)</td>
<td>9 (2.8)</td>
<td>0.53</td>
</tr>
<tr>
<td>A</td>
<td>51 (15.6)</td>
<td>62 (19.1)</td>
<td></td>
</tr>
<tr>
<td>Chronic occlusions, n (%)</td>
<td>10 (3.1)</td>
<td>15 (4.6)</td>
<td>0.30</td>
</tr>
<tr>
<td>Restenotic lesion, n (%)</td>
<td>8 (2.5)</td>
<td>9 (2.8)</td>
<td>0.80</td>
</tr>
<tr>
<td>Bifurcation lesions, n (%)</td>
<td>18 (5.5)</td>
<td>14 (4.3)</td>
<td>0.47</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>13.9±7.7</td>
<td>13.8±7.8</td>
<td>0.95</td>
</tr>
<tr>
<td>Vessel size, mm</td>
<td>3.10±0.47</td>
<td>3.10±0.48</td>
<td>0.91</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>73.8±18.6</td>
<td>74.7±18.6</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Data are mean±SD or number of patients (%) as LAD indicates left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; and ACC/AHA, American College of Cardiology/American Heart Association.

~15% of the patients underwent stenting in acute myocardial infarction. Renal insufficiency, which may have an important impact on the outcome after stenting,15 was present in a comparable proportion of patients, and only 1 patient in each group presented with end-stage renal disease on chronic dialysis. Angiographic characteristics were also essentially identical (Table 2). Table 3 displays the procedural characteristics in detail. The length of the stented segment was greater by 2.5 mm in the thin-strut group, and the final diameter stenosis favored the thick-strut group. The procedural success was achieved in a comparable proportion of patients, yet the device success rate was higher among thin-strut patients.

TABLE 3. Procedural Data

<table>
<thead>
<tr>
<th></th>
<th>Thin-Strut Group (n=326)</th>
<th>Thick-Strut Group (n=325)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration of abciximab, n (%)</td>
<td>161 (49.4)</td>
<td>157 (48.3)</td>
<td>0.78</td>
</tr>
<tr>
<td>Multilesion intervention, n (%)</td>
<td>97 (29.8)</td>
<td>84 (25.8)</td>
<td>0.27</td>
</tr>
<tr>
<td>Maximal balloon pressure, atm</td>
<td>13.1±2.3</td>
<td>13.3±2.4</td>
<td>0.44</td>
</tr>
<tr>
<td>Balloon-to-vessel ratio</td>
<td>1.12±0.11</td>
<td>1.13±0.13</td>
<td>0.18</td>
</tr>
<tr>
<td>No. of implanted stents</td>
<td>1.3±0.7</td>
<td>1.3±0.6</td>
<td>0.27</td>
</tr>
<tr>
<td>Length of stented segment, mm</td>
<td>22.9±12.3</td>
<td>20.5±13.5</td>
<td>0.006</td>
</tr>
<tr>
<td>Final diameter stenosis, %</td>
<td>5.7±11.0</td>
<td>4.0±9.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Procedural success, n (%)</td>
<td>321 (98.5)</td>
<td>321 (98.8)</td>
<td>0.74</td>
</tr>
<tr>
<td>Device success, n (%)</td>
<td>302 (92.6)</td>
<td>315 (96.9)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are mean±SD or number of patients (%).

FIGURE 1. Cumulative distribution curves of diameter stenosis immediately after procedure and at 6-month follow-up angiography in both study arms. Although final result in thin-strut group was less optimal than that achieved in thick-strut group (rightward displacement of curve of diameter stenosis immediately after stenting, P=0.03), diameter stenosis at follow-up was significantly reduced in thin-strut vs thick-strut group (leftward displacement of respective curve, P=0.002).

Early 30-Day Outcome
The early mortality rate was 1.5% among the thin-strut patients and 2.5% among the thick-strut patients (P=0.40). The complication of myocardial infarction was observed in 0.9% of the thin-strut patients and 1.2% of the thick-strut patients (P=0.99). During the first 30 days, urgent revascularizations were required in 1.5% of the patients of both groups. A procedure-related, isolated CK elevation (>3 times the normal limit) was found in 3.1% of the thin-strut patients and 2.8% of the thick-strut patients (P=0.82).

Late Outcome
The number of patients eligible for follow-up angiography (patients with successful procedure without major adverse event such as death, myocardial infarction, or revascularization during the first 30 days) was 311 in the thin-strut group and 307 in the thick-strut group (P=0.59). Of these, 246 thin-strut stent patients (79.1%) and 252 thick-strut stent patients (82.1%) (P=0.35) underwent follow-up angiography at 6 months. The most frequent reason for missing angiographic restudy at 6 months was patient refusal. Eight patients (4 in each group) died before scheduled follow-up angiography. During the quantitative evaluation of the follow-up angiography, manual contour editing was required in 8.5% of the thin-strut group and 10.7% of the thick-strut group (P=0.41).

Despite a better short-term result achieved with the thick-strut stent, diameter stenosis at follow-up was significantly smaller in the thin-strut group (Figure 1). Late lumen loss was also considerably lower in the thin-strut group, 0.94±0.74 versus 1.17±0.78 mm in the thick-strut group (P=0.001).
The primary end point of the trial, angiographic restenosis, was reached in 15.0% of the thin-strut stent patients and 25.8% of the thick-strut stent patients (P=0.003; Figure 2), which corresponds to a risk reduction of 42% (relative risk, 0.58; 95% CI, 0.39 to 0.87). We applied a multivariate logistic regression model to correct for the possible influence on restenosis of the stented segment length and final diameter stenosis (the 2 parameters that were significantly different between the treatment groups, as shown in Table 3). The adjusted risk for restenosis associated with the thin-strut stent was 0.42 (95% CI, 0.26 to 0.68). A greater stented segment length and final (residual) diameter stenosis were independently associated with an increased risk for restenosis (P<0.001 and P=0.03, respectively). When the analysis was confined to only patients with device success (ie, patients who actually received the randomly assigned treatment), the restenosis rate was 14.3% in the thin-strut group and 25.5% in the thick-strut group (P=0.002). In addition, among patients in whom no manual contour editing of the follow-up angiogram was required during the quantitative assessment (90.4% of the study population), the restenosis rate was 14.7% in the thin-strut group and 25.3% in the thick-strut group (P=0.005).

Complete 1-year follow-up was obtained in all but 5 patients (2 in the thin-strut and 3 in the thick-strut stent groups), ie, in 99.1% of the entire population. During the 1-year follow-up period, 8.6% of the thin-strut stent patients and 13.8% of the thick-strut stent patients required reintervention because of restenosis-induced ischemia (P=0.03, Figure 2), which means a 38% risk reduction for this secondary end point (relative risk, 0.62; 95% CI, 0.39 to 0.99). Notably, the diameter stenosis among the patients with restenosis who required reintervention was 71.0±15.1% for the thin-strut group and 71.9±15.3% for the thick-strut group (P=0.85). The 1-year mortality rate was similar, 4.9% among thin-strut patients and 5.2% among thick-strut patients (P=0.84). The other secondary end point of death or myocardial infarction 1 year after stenting was reached in 6.4% of the thin-strut patients and 6.2% of the thick-strut patients (relative risk, 1.04; 95% CI, 0.57 to 1.93; P=0.89).

**Discussion**

In this randomized trial, we assessed the impact of stent strut thickness on restenosis and restenosis-driven clinical events.

For this purpose, we implanted 2 FDA-approved stents in 651 patients. The 2 stents had identical material composition and a very similar design. The major difference between the 2 models was their strut thickness. We included a consecutive series of patients with a broad spectrum of clinical and lesion characteristics in an attempt to avoid the limitation of including only highly selected populations in stent-versus-PTCA randomized trials. The only exclusion criterion was smaller vessel size, because of the unproven superiority of stenting over PTCA. The study demonstrated that the implantation of coronary stents constructed with thin metal struts is associated with a significant reduction of angiographic (−42%) and clinical (−38%) restenosis compared with a stent with a strut thickness twice as great. The results achieved in the present trial are in compliance with those previously reported by studies that assessed the same thin- and thick-strut models separately.

Although the baseline lesion length and the number of stents placed in each group were similar, the overall length of stents implanted in the thin-strut group was significantly greater. The reason for this is that the thick-strut model was available in a finer length graduation, which permitted a better adjustment to the actual lesion length. The final angiographic result was also less optimal in the thin-strut group, as indicated by a greater residual stenosis at the end of the procedure in this group. Both a greater stented segment length and a worse final angiographic outcome are generally considered to have a negative impact on restenosis. This was also confirmed by the results of the multivariate analysis in the present study. The better long-term outcome with the thin-strut stent despite a less favorable short-term angiographic result underscores the pivotal role of stent design in the development of in-stent restenosis.

Stents provoke a higher degree of injury, thrombosis, and inflammation and consequently more extensive neointimal formation than plain PTCA. The greater magnitude of these reactions is, at least in part, the corollary effect of the presence of the endovascular implant. Although the relation between strut thickness and vascular wall reaction seems to be very intuitive, relatively little attention has been paid to this issue as yet. In an animal study focused mainly on the relation between stent and artery geometry and intimal thickening, Garasic et al also analyzed the effects of increasing stent strut thickness from 125 to 200 μm and found no significant impact on early luminal thrombus or late neointimal hyperplasia. The results of this study should not be considered at odds with ours. The study by Garasic et al was not specifically designed to assess the role of strut thickness: 2 different thickness levels (125 and 200 μm) were included, much above the 50-μm value of the thin-strut model shown to be advantageous in the present study. This fact may be relevant, considering the results of a recent study on the influence of stent thickness on the capacity of endothelialization that used confluent culture of endothelial cells. The latter study clearly showed that endothelialization capacity is well maintained up to a thickness of 75 μm and that beyond this threshold, it is almost completely eliminated. Although the findings of that study provide one possible explanation for the results of our study, considering the
beneficial role of reendothelialization after stenting, further investigations are clearly needed to elucidate the relation between strut thickness and long-term patency of the stented vessel.

Limitations of the Study
We achieved a reappearance of the angiography rate of 81%. Previous trials on restenosis have also shown the impossibility of achieving higher rates because of patient refusal in an inevitable proportion of cases. Patients who do not present for follow-up angiography, however, are believed to have a lower probability of restenosis and are unlikely to have produced a significant bias in the present trial. Moreover, the differences in outcome between the thin-strut and thick-strut groups in our study were also evident from measures of clinical restenosis such as the need for reintervention.

Another limitation of the study is related to the unblinded nature of the trial. The different appearance of the various stent types does not allow the interventionalists to remain blinded to the type of stent; this is an unavoidable problem with all of the stent trials. In the present study, however, the primary end point of the trial, angiographic restenosis, was assessed in the core laboratory by personnel who were not involved in performance of the procedures. In the core laboratory, the operators performed the measurements as part of their routine work, being unaware of the patient’s participation in the study; they may, however, have been able to distinguish between stent types with different strut thicknesses. Although we cannot rule out the possibility of a bias in the analysis of restenosis, 2 points indicate that this bias was not relevant. First, the significant difference in angiographic restenosis between the 2 study groups was also present after exclusion of the patients in whom the lumen contour was manually corrected. Second, for patients who required a reintervention because of restenosis-induced ischemia, there was no difference in angiographic restenosis severity between the thin- and the thick-strut stent groups.

There are a few subtle differences in the architecture of the 2 stent models used in this trial. The thin-strut model contains a few (20%) more cross-links than the thick-strut model. Because more restenosis would have been expected from a higher number of cross-links on the basis of experimental data, however, a positive effect of this factor is highly unlikely.

The 2 stent models used in this trial were premounted on different delivery systems. The thick-strut model had a newer and more advanced delivery system. This is reflected in the higher device success rate achieved in the thick-strut group. Studies on the influence of delivery systems on restenosis are lacking, but a relevant role of this factor in the better long-term results achieved in the thin-strut group is only a remote possibility.

Conclusions
This randomized trial demonstrates that coronary stents with thinner struts are associated with a reduced risk for angiographic and clinical restenosis. The long-term benefit with the thin-strut stent was observed despite the more unfavorable short-term procedural results. These findings may have important implications for stent technology to improve the results achieved with the currently most frequently performed percutaneous coronary intervention.

Appendix
The following centers and investigators participated in the ISAR-STEREO trial:
Data Coordinating Center: A. Kastrati, M. Hadamitzky, H. Kreuzberg.

Acknowledgments
This trial was supported by a grant from the Technische Universität München. We highly appreciate the invaluable contribution of the medical and technical staffs operating in the catheterization laboratories and wards of the participating institutions.

References


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Circulation. 2001;103:2816-2821
doi: 10.1161/01.CIR.103.23.2816

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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