Increased Risk of Restenosis After Placement of Gold-Coated Stents
Results of a Randomized Trial Comparing Gold-Coated With Uncoated Steel Stents in Patients With Coronary Artery Disease

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Background—Gold is a highly biocompatible material. Experimental evidence suggests that coating the stent with a gold layer may have a beneficial influence. In this randomized trial, we assessed whether gold-coated stents were associated with a better clinical and angiographic outcome after coronary placement.

Methods and Results—Patients with symptomatic coronary artery disease were randomly assigned to receive either a gold-coated Inflow stent (n = 367) or an uncoated Inflow stainless steel stent (n = 364) of identical design. Follow-up angiography was routinely performed at 6 months. The primary end point of the study was the occurrence of any adverse clinical event (death, myocardial infarction, or target-vessel revascularization) during the first year after stenting. At 30 days, there was no significant difference in the combined incidence of adverse events, with 7.9% in the gold-stent group versus 5.8% in the steel-stent group (P = 0.25). The incidence of angiographic restenosis ($>50\%$ diameter stenosis) was $49.7\%$ in the gold-stent group and $38.1\%$ in the steel-stent group ($P = 0.003$). One-year survival free of myocardial infarction was $88.6\%$ in the gold-stent group and $91.8\%$ in the steel-stent group ($P = 0.14$). One-year event-free survival was significantly less favorable in the gold-stent group ($62.9\%$ versus $73.9\%$ in the steel-stent group; $P = 0.001$).

Conclusions—Coating steel stents with gold had no significant influence on the thrombotic events observed during the first 30 days after the intervention. However, gold-coated stents were associated with a considerable increase in the risk of restenosis over the first year after stenting. (Circulation. 2000;101:2478-2483.)

Key Words: stents ■ thrombosis ■ restenosis ■ trials

Coronary placement of Palmaz-Schatz stents has demonstrated advantages over conventional PTCA for a wide range of lesion and patient subsets.1-4 Several studies have focused on the optimization of the results with stenting by assessing the role of placement technique5 and periprocedural therapy.4,6,7 New generations of stents have been developed to increase the feasibility and ameliorate the results achieved with this intervention. Although there is strong experimental evidence about the relevant role of stent design, material, and surface,8-11 the clinical significance of these properties has not been fully elucidated.12

Gold is a highly biocompatible material.13,14 Gold coatings are currently being used for coronary stents. In vitro, gold coating of stainless steel stents was associated with a reduction of platelet activation and thrombus mass.15 Gold-plated stents elicited less aortic wall reaction, as documented by fewer macroscopic and histopathological changes, as well as a thinner neointima formation compared with stents plated with other metals.16 The improved visibility during fluoroscopy achieved with the gold layer facilitates precise positioning of the stent into the target lesion. In addition, gold coating is being used to prepare radioactive stents because of the excellent radiochemical stability obtained with the gold layer.17 It is therefore of particular interest to know whether these properties of gold coating are translated into a meaningful clinical benefit for patients treated with coronary stent placement.

The objective of this randomized trial was to assess whether plating the stainless steel stent with a gold layer improved the 1-year outcome of patients undergoing coronary stent placement.

Methods

Patients
A consecutive series of patients with symptomatic coronary artery disease treated with stenting in the period between June 1997 and February 1998 were eligible for this study. Exclusion criteria were cardiogenic shock before the intervention, prior randomization, and unwillingness or inability to provide written informed consent for
participation in the trial. All patients were randomly assigned to a steel or gold-plated stent by means of sealed envelopes before the intervention. Patients also gave informed consent for routine control angiographic examination at 6 months. The study was conducted according to the principles of the Declaration of Helsinki and approved by the institutional ethics committee.

Stent Placement and Poststenting Treatment
During the intervention, patients received heparin (15 000 U) and aspirin (500 mg) intravenously. In addition, patients considered at higher risk for stent thrombosis (eg, large residual dissections or thrombus at the stent site) received abciximab (with half-dose heparin). Heparin infusion was continued for 12 hours after the intervention. All patients received combination therapy with 250 mg of ticlopidine plus 100 mg of aspirin twice daily for 4 weeks; aspirin was taken indefinitely.

Both stent types used in the present study were hand-crimped on balloon catheters before delivery. They were manufactured by the same company (Inflow Dynamics AG). The Inflow steel stent is a slotted-tube stent manufactured from 316L medical grade stainless steel by laser cutting. The stent is composed of tubular, interconnected sinusoidal waves with oval strut cross section, 6 waves per circumference. Strut dimensions are 0.003-in thick and 0.006-in wide. The Inflow gold stent is of identical design. After electropolishing, a special 3-layer process is used for gold coating to obtain a firm and homogenous attachment of the gold to the steel. The thickness of the gold layer is 5 \( \mu \text{m} \). Strut dimensions are the same as for the steel stent: 0.003-in thick and 0.006-in wide. The integrity of gold coating was tested by submerging the stent in 30% hydrogen peroxide for 30 minutes and by ultrasonic application (35 kHz, 160 W). Electron micrographic examination of this gold stent has revealed a uniform gold coating and the absence of cracks and fissures.

Procedural results were assessed by angiography only; no intra-vascular ultrasound studies were performed. The procedure was considered successful when stent placement was associated with a residual stenosis of <30% and Thrombolysis In Myocardial Infarction (TIMI) flow grade 2 or 3.

Angiographic Evaluation
Lesions were classified by the modified American College of Cardiology/American Heart Association grading system. Left ventricular function was assessed qualitatively on the basis of biplane angiograms by use of a 7-segment division; the diagnosis of reduced left ventricular function required the presence of hypokinesia in ≥2 segments. Digital angiograms were analyzed offline with the automated edge-detection system CMS (Medis Medical Imaging Systems). With respect to optical density, the gold stent is between the Palmaz-Schatz (less opaque) and Wiktor (more opaque) stents. For both of these stent models, quantitative coronary angiography has been shown to be sufficiently accurate, and it is associated with only a minimal risk of overestimation of the true lumen with the Wiktor stent.

Matched views were selected for angiograms recorded before and immediately after the intervention and at follow-up. The parameters obtained were minimal lumen diameter (MLD), reference diameter, diameter stenosis, and diameter of the maximally inflated balloon during stent placement. Acute elastic recoil was measured as the difference between measured balloon diameter and MLD at the end of the procedure. Acute lumen gain was the difference between MLD at the end of the intervention and MLD before balloon dilatation. Late lumen loss was calculated as the difference in MLD noted between measurements after the procedure and at follow-up.

Definitions and End Points of the Study
The primary end point of the study was event-free survival at 1 year after the procedure. Death of any cause, myocardial infarction, and target-vessel revascularization (PTCA or CABG) were considered adverse events. All deaths were considered due to cardiac causes unless an autopsy established a noncardiac cause. The diagnosis of acute myocardial infarction was based on the criteria applied in the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting) trial (new pathological Q waves or a value of creatine kinase [CK] or its MB isoenzyme at least 3 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. Target-vessel revascularization was performed in the presence of angiographic restenosis and symptoms or signs of ischemia. Cardiac events were monitored throughout the follow-up period and analyzed at 30 days and 1 year. The assessment was made on the basis of the information provided by hospital readmission records, the referring physician, or telephone interview with the patients or all patients. Provoked cardiac symptoms during the interview, at least 1 clinical and electrocardiographic check-up was performed at the outpatient clinic or by the referring physician.

The angiographic outcome after stenting was also assessed. First, the incidence of stent thrombosis was assessed during the early 30-day period. The diagnosis was made on the basis of a TIMI flow grade 0 or 1 during an angiographic control examination performed whenever recurrent ischemia was suspected or routinely before discharge in patients who underwent stenting in the setting of an acute myocardial infarction. Second, the incidence of restenosis (defined as a diameter stenosis ≥50%) was assessed with the 6-month follow-up angiography.

Statistical Analysis
The number of patients included in the study was based on the sample-size estimation for our primary end point, the occurrence of any major adverse event during the first year after the procedure. We assumed a 1-year event-rate of 20% for patients with steel stents and 12% for those with gold stents and gave the study a power of 80% for detecting a difference with an \( \alpha \) level of 0.05. The sample size estimated was 714 patients, and we enrolled a total of 731 patients to accommodate possible losses at follow-up.

The analysis was performed on an intention-to-treat basis, and the results are expressed as mean±SD or as proportions (%). The differences between groups were assessed by \( \chi^2 \) test or Fisher’s exact test for categorical data and \( t \) test for continuous data. Survival analysis was made by the Kaplan-Meier method. Differences in survival parameters were assessed for significance by means of the log-rank test. Statistical significance was accepted for all values of \( P<0.05 \).

Results
Of the 731 patients enrolled in the study, 367 were assigned to a gold and 364 to a steel stent. Table 1 shows the baseline clinical characteristics of the patients. Patients assigned to the steel stent were significantly older than their counterparts, with all other characteristics being comparable between the groups. Approximately half of the patients in both groups presented with acute myocardial infarction or unstable angina. Stent implantation was attempted in 418 lesions of the gold-stent group and 442 lesions of the steel-stent group (1.1±0.4 versus 1.2±0.5 lesions per patient, respectively; \( P=0.018 \)). Table 2 shows that baseline angiographic characteristics of the patients were also similar. Procedural data are displayed in Table 3. Compared with patients in the steel-stent group, a greater balloon-to-vessel ratio and a smaller final diameter stenosis were achieved in the gold-stent group. Abciximab was administered to 26% of patients in both groups. The criteria of procedural success were met in 99.7% of gold-stent patients and 98.4% of steel-stent patients (\( P=0.056 \)). A steel stent was placed in 3 patients assigned to the gold stent because the gold stent was unexpectedly not available during the procedure. A gold stent was implanted in 36 patients assigned to the steel stent in whom the operator considered particularly important the more precise position-
ing enabled by the better visibility of the gold stent. Thus, 0.8% of the patients in the steel stent and 9.9% of the patients in the gold-stent group \((P<0.001)\) did not receive the randomly assigned stent.

### Early 30-Day Outcome

Stent thrombosis occurred in 9 patients (2.5%) in the gold-stent group and 3 (0.8%) in the steel-stent group \((P=0.083)\).

### TABLE 2. Baseline Lesion Angiographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Gold Stent Mean ± SD</th>
<th>Steel Stent Mean ± SD</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel, %</td>
<td></td>
<td></td>
<td>0.676</td>
</tr>
<tr>
<td>Left main</td>
<td>1.0 ± 0.15</td>
<td>2.0 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>41.4 ± 8.0</td>
<td>41.4 ± 7.9</td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>21.5 ± 8.2</td>
<td>23.1 ± 9.0</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>28.5 ± 8.0</td>
<td>26.2 ± 9.0</td>
<td></td>
</tr>
<tr>
<td>Bypass graft</td>
<td>7.6 ± 1.0</td>
<td>7.3 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>ACC/AHA lesion type, %</td>
<td></td>
<td></td>
<td>0.712</td>
</tr>
<tr>
<td>A</td>
<td>5.0 ± 0.5</td>
<td>4.8 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>18.2 ± 8.2</td>
<td>15.4 ± 10.3</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>54.1 ± 9.0</td>
<td>57.0 ± 10.3</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>22.7 ± 8.0</td>
<td>22.8 ± 9.0</td>
<td></td>
</tr>
<tr>
<td>Chronic occlusions, %</td>
<td>6.9 ± 0.5</td>
<td>4.5 ± 0.4</td>
<td>0.127</td>
</tr>
<tr>
<td>Restenotic lesions, %</td>
<td>11.0 ± 0.5</td>
<td>13.6 ± 1.0</td>
<td>0.252</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>13.4 ± 7.5</td>
<td>12.9 ± 7.8</td>
<td>0.375</td>
</tr>
<tr>
<td>Vessel size, mm</td>
<td>3.03 ± 0.47</td>
<td>3.04 ± 0.53</td>
<td>0.886</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>0.43 ± 0.40</td>
<td>0.45 ± 0.38</td>
<td>0.575</td>
</tr>
<tr>
<td>DS before procedure, %</td>
<td>85.2 ± 12.5</td>
<td>84.4 ± 12.4</td>
<td>0.308</td>
</tr>
</tbody>
</table>

\(LAD\) indicates left anterior descending coronary artery; \(LCx\), left circumflex coronary artery; \(RCA\), right coronary artery; \(ACC/AHA\), American College of Cardiology/American Heart Association; and \(DS\), diameter stenosis.

Data are mean \(\pm\) SD or percentages.

Table 4 indicates the number of patients with adverse events within the first 30 days after the procedure. There was a trend to a higher incidence of nonfatal myocardial infarction and repeat PTCA in the gold-stent group. In total, 29 (7.9%) patients in the gold-stent group and 21 (5.8%) in the steel-stent group had at least 1 adverse event during this period.

### Angiographic Follow-Up

Of the 681 patients without adverse events within the first 30 days after the procedure, 550 (81%) had a 6-month angiographic control examination. The results of quantitative assessment of the follow-up angiogram for lesions of both groups are presented in Table 5 on an intention-to-treat basis. The incidence of restenosis was 49.7% in the gold-stent group and 38.1% in the steel-stent group \((P=0.003)\). Other measures of restenosis, such as diameter stenosis, late lumen loss (Figure 1), and loss index, were all significantly less favorable in the gold-stent group. Table 6 shows that the higher incidence of restenosis in the gold-stent group was also present after stratification in various subgroups. In addition, when the patients were analyzed according to actual treatment received, the restenosis rate was 50.4% among lesions treated with gold stents and 35.9% among lesions treated with steel stents \((P<0.001)\).

### One-Year Clinical Outcome

Thirteen patients, 6 in the gold and 7 in the steel-stent group, were lost to follow-up after the 30-day contact. During the 1-year period, 46 deaths (26 among gold and 20 among steel-stent patients) were observed. All but 8 cases (3 in the...
TABLE 5. Results of the 6-Month Angiographic Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Gold Stent (n=316)</th>
<th>Steel Stent (n=323)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD, mm</td>
<td>1.43±1.03</td>
<td>1.68±1.00</td>
<td>0.002</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>53.3±31.9</td>
<td>45.3±29.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Late lumen loss, mm</td>
<td>1.61±0.96</td>
<td>1.34±0.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Loss index</td>
<td>0.64±0.39</td>
<td>0.55±0.39</td>
<td>0.003</td>
</tr>
<tr>
<td>Incidence of restenosis, %</td>
<td>49.7</td>
<td>38.1</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are mean±SD or percentages.

gold-stent group and 5 in the steel-stent group) were of cardiac origin. No significant differences were observed either for overall survival (92.9% in the gold-stent group versus 94.5% in the steel-stent group; P=0.379) or for survival free of myocardial infarction after 1 year (88.6% in the gold-stent group versus 91.8% in the steel-stent group; P=0.142). On an intention-to-treat basis, our primary end point of event-free survival was 62.9% in the gold-stent group and 73.9% in the steel-stent group (P=0.001). Figure 2 depicts the clinical course of patients by means of Kaplan-Meier event-free survival curves. There was an increasing difference in outcome that became significant from the fourth month after the procedure, well before the scheduled 6-month angiography. After the first month, 149 patients (92 gold-stent patients [25.1%] and 57 steel-stent patients [15.7%]; P=0.002) required target-vessel revascularization owing to recurrent chest pain (84%) or stress-test signs of ischemia (16%) combined with angiographic restenosis. In these patients, diameter stenosis before the reintervention was 85.8±12.9% in the gold-stent group and 84.3±9.8% in the steel-stent group. When the analysis was performed according to the actual treatment received, the target-vessel revascularization rate was 26.0% among patients treated with gold stents and 13.6% among patients treated with steel stents (P<0.001).

Discussion

This is the first randomized trial for the assessment of potential advantages of gold coating of coronary stents. The randomized trials on coronary stenting have frequently been characterized by a relatively narrow range of selection criteria, which may limit the applicability of their findings to patient groups currently undergoing this intervention. In the present trial, we included patients with coronary artery disease irrespective of clinical and lesion-related characteristics, reflecting the indications of stenting in everyday practice. A high proportion of our patients presented with acute coronary syndromes, multivessel disease, and complex lesions. The advantages of a similar study design that is not confined to selected patient subsets have recently been emphasized for trials comparing different stent types.12 We achieved an excellent angiographic result with a residual stenosis of 2% to 3% in both groups. We were able to obtain a 6-month angiographic follow-up in 81% of the candidates, which enables a largely unbiased analysis of restenosis. The objective of this trial was to assess the value of gold coating of stents. Because differences in stent design may be associated with differences in outcome,12 we chose 2 stents with identical design, with the only difference being the presence or absence of gold coating. The main finding of this trial was that coating stainless steel stents with a gold surface was associated with a significantly lower 1-year event-free survival rate. The trend toward a less favorable clinical outcome with the gold-coated stent was present from the first month after the intervention, and the difference became increasingly significant afterward.

Gold Coating and Early Thrombotic Events

In a pulsed floating model, the expression of the platelet activation–dependent glycoproteins CD62p and CD63 was significantly decreased with gold-coated stents compared with uncoated stents.15 On the basis of in vitro findings, we expected a reduction in thrombus-induced events with the gold stent, but we did not find any benefit with gold stents regarding angiographic stent thrombosis, the incidence of myocardial infarction, and reinterventions. On the contrary, the group of patients treated with the gold-coated stent tended to have a higher incidence of angiographic stent thrombosis and adverse events in the first 30 days after the procedure. On the basis of serial CK measurements, we found a 2.5% incidence of non–Q-wave myocardial infarction in the entire population, which is relatively low compared with the incidence reported in the EPISTENT trial.4 Although our trial was not sufficiently powered to assess the end point of early adverse events after stenting, the trend in favor of the steel
considering the angiographic results, we should acknowledge the limitation inherent to the quantitative assessment of lesions stented with the gold-coated model. The higher fluoroscopic density of the gold stent precludes a blinded quantitative assessment so that it is difficult for operators to remain unaware of the stent model used. We believe, however, that the final result, which is in contrast with the study hypothesis, may not support a significant operator bias. In addition, the bias, if any existed, might be found in the lumen overestimation caused by a more opaque stent, which may produce a spurious decrease in restenosis rate. Finally, the clinical outcome, our primary end point, provided additional strong evidence of a major risk for restenosis in patients treated with gold-coated stents. Before definitive conclusions on the existence of an unfavorable relation between gold material and restenosis are made, we should take into account potential problems relative to the technique of gold coating. Hehrlein et al showed that the process of covering the stent with a single layer of gold by galvanization may lead to surface porosity, cracks, and fissures, which are likely to have a negative effect on thrombus and neointima formation. Systematic angiographic follow-up provided the explanation for this difference. All indexes of restenosis were markedly less favorable in the group with gold stents. On an intention-to-treat basis, the analysis showed a restenosis rate of 49.7% in patients assigned to the gold-coated stent and 38.1% in patients assigned to the steel stent. The restenosis rate for patients who actually received a steel stent was 35.9%, and 13.6% of them required reintervention because of restenosis. Recent studies have also reported restenosis rates higher than 30% after stenting in unselected patients. The incidence of restenosis observed with the steel stent is certainly a consequence of the high-risk profile of the patients enrolled in our trial, but we cannot exclude a role played by the particular stent design used.

The restenosis rate observed in the gold-stent group in this trial is very concerning. It is one of the highest restenosis rates ever reported in stent trials. Because it was much higher than in the control group with the steel stent, the clinical and angiographic profile, which was largely similar among the study groups, could not serve to explain this risk increase. The only differences seen, such as the older age in steel-stent patients and the slightly greater balloon-to-vessel ratio with a better final result in the gold-stent group, would have favored a better outcome in the gold-stent group. This higher risk for restenosis requires an explanation, because gold coating, with its better visibility and ease of precise deployment, is otherwise very attractive for the interventional cardiologist. In considering the angiographic results, we should acknowledge the potential differences in gold-coating technologies may not allow an extrapolation of the present findings to other gold-coated stents currently available on the market.

**Conclusions**

This randomized trial indicates that coronary placement of gold-coated stents was associated with good acute procedural results but with no beneficial influence on early thrombotic events. Despite the good procedural results, gold-coated stents were associated with a considerable increase in the risk of restenosis and target-vessel revascularization over the first year after coronary stenting.

**References**


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**TABLE 6. Incidence of Restenosis in Various Subgroups**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Gold Stent n</th>
<th>Gold Stent Restenosis Rate, %</th>
<th>Steel Stent n</th>
<th>Steel Stent Restenosis Rate, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No acute myocardial infarction</td>
<td>254</td>
<td>52</td>
<td>271</td>
<td>38</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetic patients</td>
<td>64</td>
<td>58</td>
<td>66</td>
<td>42</td>
<td>0.079</td>
</tr>
<tr>
<td>No therapy with abciximab</td>
<td>236</td>
<td>50</td>
<td>241</td>
<td>38</td>
<td>0.007</td>
</tr>
<tr>
<td>Single-lesion stenting</td>
<td>249</td>
<td>47</td>
<td>222</td>
<td>37</td>
<td>0.027</td>
</tr>
<tr>
<td>Vessels ≤3 mm</td>
<td>143</td>
<td>59</td>
<td>156</td>
<td>47</td>
<td>0.038</td>
</tr>
<tr>
<td>Lesions ≥15 mm in length</td>
<td>98</td>
<td>60</td>
<td>106</td>
<td>42</td>
<td>0.011</td>
</tr>
</tbody>
</table>


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