Cost Analysis From Two Randomized Trials of Sirolimus-Eluting Stents Versus Paclitaxel-Eluting Stents in High-Risk Patients With Coronary Artery Disease

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OBJECTIVES
This study sought to analyze the cost of percutaneous coronary interventions with use of sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES) in patients at high risk of restenosis.

BACKGROUND
Recent studies have shown different clinical efficacy with these drug-eluting stents. Whether this difference extends on cost estimates between the 2 stents is not known.

METHODS
We included 450 patients with diabetes mellitus and in-stent restenosis from 2 randomized studies comparing SES with PES. Assigned costs for the economic evaluation were the initial hospitalization and all subsequent cardiac-related inpatient/outpatient health resources during 9 to 12 months of clinical follow-up. The economic evaluation was performed from the health insurance system’s perspective.

RESULTS
There were no differences between the 2 study groups regarding mortality (p = 0.78) and myocardial infarction rates (p = 0.76). Target lesion revascularization was performed in 16 patients (7.1%) in the SES group and in 34 patients (15.1%) in the PES group (p = 0.01). Initial hospital costs were not significantly different between the 2 stents (p = 0.53). The follow-up costs were, however, different: 2,684 ± 2,072€ per patient treated with SES and 4,527 ± 6,466€ per patient treated with PES (p < 0.001). Total costs also differed at the end of the follow-up: 8,924 ± 3,077€ per patient treated with SES and 10,903 ± 7,205€ per patient treated with PES (p < 0.001).

CONCLUSIONS
In patients at high risk of restenosis, use of SES is associated with lower costs compared with PES. The cost savings are mainly due to the reduced need of repeat revascularization procedures with SES. (J Am Coll Cardiol 2006;48:262–7) © 2006 by the American College of Cardiology Foundation

Drug-eluting stents (DES) are the most recent major technological advance in percutaneous coronary interventions (PCIs) (1). They work by releasing controlled amounts of antiproliferative agents at the local level, leading to the suppression of neointimal proliferation, which is the chief cause of restenosis after stent implantation (2,3). Although several DES have been developed, only 2 of them, the sirolimus-eluting stents (SES) and the paclitaxel-eluting stents (PES), are currently approved for use (2,4,5). In the last few years, numerous randomized trials have studied the clinical impact of SES and PES in various subsets of patients with coronary artery disease. Accumulated evidence demonstrates that, compared to bare-metal stents (BMS), DES are highly effective in reducing angiographic restenosis and the need for repeat revascularization procedures, and their benefit also extends to patients with high-risk angiographic and clinical characteristics (6–11).

The better clinical efficacy of DES comes, however, at a substantially higher price (12). As the economic burden of new technologies plays an important role in the decision-making process of their acceptance in clinical practice, special attention has been paid to the economic impact of DES. Recently, the results of two studies suggested that, in the context of randomized studies involving patients treated for single de novo lesions, use of SES is cost-effective (13,14). Similar results have also been reported from another study, which estimated the cost-effectiveness of the SES in an unselected patient population (15). Although differences between studies may exist regarding the analyzed patient populations, methods used for the assessment of cost-effectiveness, and magnitude of benefit with DES, it is commonly accepted that use of DES will be cost-effective for most patients undergoing PCIs, in particular for those considered to have a high risk of restenosis (12).

Recently, several studies have assessed the relative efficacy of the SES and PES in patients with various risk profiles (16–19). The results of these studies as well as of their meta-analysis show that SES are associated with better outcomes than PES (16–20). It is not known, however, whether treatment with SES could also be economically more attractive than PES. This issue is of particular importance considering the high cost of these devices and their expanding utilization during PCIs (12,21).
The goal of this study was to evaluate the costs of PCIs with implantation of SES and PES in patients who are at high risk of restenosis, such as those with diabetes and in-stent restenosis, in relation to the clinical effectiveness of the 2 stent types.

**METHODS**

**Patients.** This study evaluated data collected from 450 patients who participated in the DES arms of the ISAR-DESIRE (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis) and ISAR-DIABETES (Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit from Paclitaxel-Eluting and Sirolimus-Eluting Stents?) randomized studies. Details of patients’ recruitment and design of the studies have been described elsewhere (16,18).

All patients were pre-treated with a 600-mg loading dose of clopidogrel at least 2 h before the intervention. Both trials had follow-up angiography scheduled at 6 to 8 months after randomization as part of their protocol. Patients were followed up clinically for 9 to 12 months. Specifically, the ISAR-DESIRE trial was a randomized, open-label controlled study conducted among 300 patients with angiographically significant in-stent restenosis. The primary end point of the study was recurrent angiographic restenosis at follow-up angiography. All patients were randomly assigned to 1 of the 3 treatment groups: sirolimus stent, paclitaxel stent, or balloon angioplasty (100 patients in each group). Adverse events monitored were death, myocardial infarction, and target lesion revascularization. Reintervention was performed according to the decision of investigators based on symptoms and/or signs of ischemia. The ISAR-DIABETES study enrolled 250 diabetic patients with coronary artery disease. Of these, 125 were assigned to treatment with PES and 125 to treatment with SES. The primary end point was in-segment late lumen loss. Adverse events monitored were death, myocardial infarction, and target lesion revascularization.

Exclusion criteria for both studies included acute ST-segment elevation myocardial infarction; a target lesion located in left main trunk or bypass grafts; and contraindications to aspirin, heparin, and clopidogrel. For the ISAR-DIABETES trial, in-stent restenosis was also an exclusion criterion.

Clinical outcomes of interest for the present study were death, myocardial infarction, and target lesion revascularization. The diagnosis of myocardial infarction during follow-up was made in the presence of new Q waves in the electrocardiogram and/or an elevation of creatine kinase or its MB isoenzyme to at least 3 times the upper limit of normal. Target lesion revascularization was defined as any repeat PCI or aortocoronary bypass surgery involving the target lesion. The angiographic outcome of interest was binary angiographic restenosis, which was defined as a diameter stenosis of at least 50% in the segment including the stented segment as well as its 5-mm proximal and distal margins at follow-up angiography.

**Costs.** We investigated the costs that health insurance companies have to reimburse hospitals and not the actual cost incurred by hospitals. According to the German health care system, during the time period in which the ISAR-DESIRE and ISAR-DIABETES studies were carried out, hospitals were reimbursed by a 2-tier system of charges. The first component consisted of a hospital-specific basic per diem covering non-medical costs and a department-specific per diem covering medical costs including nursing, pharmaceuticals, and procedures. The second component consisted of case fees (covering the costs for a patient’s entire hospital stay) and procedure fees (paid on top of slightly reduced per diems). Case fees were based on a combination of a certain diagnosis (4-digit International Classification of Diseases, Ninth Revision) and a specific intervention. These fees were set through an ordinance by the Federal Ministry of Health, while the monetary conversion factor was negotiated at local level each year separately between sickness (health insurance) funds and hospitals. For the purpose of this analysis, running costs were calculated from hospital financial departments for each patient enrolled in the study. Running costs included personnel costs, as hospital physicians are salaried employees of the hospitals. Running costs were calculated by summing case fees, procedure fees, and per diem charges, as appropriate for the specific year.

Costs incurred from the use of medical resources before inclusion of patients in the 2 randomized studies were not included in the present analysis. Assigned costs for the economic evaluation were the initial hospitalization and all subsequent cardiac-related inpatient or outpatient health resources usages during clinical follow-up, excluding medications used outside a health care facility. The costs of the protocol-specified angiogram admission were included in the follow-up costs, but as they were incurred by both groups, these costs had no material relevance to our analysis. Indirect costs such as productivity loss were not included in the analysis; thus, only direct medical costs were analyzed.
The economic evaluation was performed from the health insurance system’s perspective. Total costs per patient were measured as the sum of initial hospital costs and follow-up hospital or outpatient visit costs (9 months for the ISAR-DIABETES study and 1 year for the ISAR-DESIRE study). All costs are expressed in euros. The protocol of this study was designed to calculate incremental cost-effectiveness ratio (additional cost per additional event-free survivor) in case higher efficacy was associated with higher costs.

**Statistical analysis.** The data are presented as means ± SD; or counts or percentages. Continuous data were compared with the Student t test. Categorical data were compared with the chi-square test or the Fisher exact test when expected cell values were <5. A p < 0.05 was considered to indicate statistical significance.

**RESULTS**

A total of 450 patients were included in this study; one-half (225 patients) received SES and the other one-half PES. Table 1 shows the baseline demographic, clinical, and angiographic characteristics of the study population. There were no significant differences on demographic characteristics between the two groups. Also, vessel size and lesion length were similar among patients assigned to the SES and PES groups. There were also no differences with respect to the number of stents used and length of stented segments. Only 1 diabetic patient in the PES group suffered early stent thrombosis. There were no significant differences in the standard medications provided to the patients in the respective DES groups.

**Efficacy.** Clinical outcomes are presented in Table 2. Clinical follow-up was completed in all patients. Mean clinical follow-up interval was 311 days for the SES group and 308 days for the PES group (p = 0.61). Six patients (2.7%) in the SES group and 7 patients (3.1%) in the PES group died within this period of time (p = 0.78). Myocardial infarction occurred in 6 patients (2.7%) in the SES group and in 5 patients (2.2%) in the PES group (p = 0.76). Target lesion revascularization was performed in 16 patients (7.1%) in the SES group and in 34 patients (15.1%) in the PES group (p = 0.01). Two patients in the PES group, but none in the SES group, required coronary bypass surgery. Of the 50 patients who underwent target lesion revascularization, 34 patients (10 in the SES group and 24 in the PES group) required repeat intervention before scheduled follow-up angiography. There were 27 patients (12%) with major adverse cardiac events (MACE) in the SES group and 43 patients (19%) with MACE in the PES group (p = 0.04).

Follow-up angiography was performed in 193 patients (86%) in the SES group and in 195 patients (86%) in the PES group. Binary angiographic restenosis was found in 20 patients (10.4%) in the SES group and in 37 patients (19%) in the PES group (p = 0.02). There was no significant difference between the 2 groups regarding the total length of in-hospital stay for all hospitalizations needed during the

### Table 1. Baseline Characteristics of the Patients and the Lesions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SES (n = 225)</th>
<th>PES (n = 225)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>65.8 ± 10.5</td>
<td>66.9 ± 10.3</td>
<td>0.26</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>54 (24)</td>
<td>57 (25)</td>
<td>0.57</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>156 (69)</td>
<td>152 (68)</td>
<td>0.68</td>
</tr>
<tr>
<td>Current smoker</td>
<td>29 (13)</td>
<td>25 (11)</td>
<td>0.56</td>
</tr>
<tr>
<td>Arterial hypertension (%)</td>
<td>121 (54)</td>
<td>138 (61)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>131 (58)</td>
<td>131 (58)</td>
<td>1</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>75 (33)</td>
<td>64 (28)</td>
<td>0.26</td>
</tr>
<tr>
<td>Prior myocardial infarction (%)</td>
<td>84 (37)</td>
<td>104 (46)</td>
<td>0.06</td>
</tr>
<tr>
<td>Prior aortocoronary bypass surgery</td>
<td>29 (13)</td>
<td>28 (12)</td>
<td>0.89</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>51.9 ± 12.6</td>
<td>52.9 ± 12.4</td>
<td>0.42</td>
</tr>
<tr>
<td>Target vessel</td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
<td>104 (46)</td>
<td>106 (47)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex coronary artery</td>
<td>63 (28)</td>
<td>67 (30)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>58 (26)</td>
<td>52 (23)</td>
<td></td>
</tr>
<tr>
<td>Length of stented segment, mm</td>
<td>23.3 ± 9.6</td>
<td>22.4 ± 9.4</td>
<td>0.24</td>
</tr>
<tr>
<td>No. of stents</td>
<td>1.10 ± 0.36</td>
<td>1.10 ± 0.38</td>
<td>0.78</td>
</tr>
<tr>
<td>Vessel size, mm</td>
<td>2.66 ± 0.49</td>
<td>2.70 ± 0.52</td>
<td>0.33</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>13.9 ± 7.7</td>
<td>13.3 ± 8.3</td>
<td>0.46</td>
</tr>
<tr>
<td>Diameter stenosis before procedure, %</td>
<td>62.1 ± 14.2</td>
<td>60.3 ± 13.0</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Values are means ± SD or n (%). PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

### Table 2. Clinical Outcome at Follow-Up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SES (n = 225)</th>
<th>PES (n = 225)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>6 (2.7)</td>
<td>7 (3.1)</td>
<td>0.78</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6 (2.7)</td>
<td>5 (2.2)</td>
<td>0.76</td>
</tr>
<tr>
<td>Reintervention</td>
<td>16 (7.1)</td>
<td>34 (15.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Re-PTCA</td>
<td>16 (7.1)</td>
<td>32 (14.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Bypass</td>
<td>0 (0.0)</td>
<td>2 (0.9)</td>
<td>0.50*</td>
</tr>
<tr>
<td>Major adverse cardiac events</td>
<td>27 (12)</td>
<td>43 (19)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Fisher exact test. Values are n (%). PCTA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table 1.
was a significant difference in the average total costs between the SES and the PES (9,166 ± 3,200€ vs. 11,360 ± 7,941€; p = 0.002). Similarly, in the non-diabetic subgroup of the study population, there was a significant difference in the total costs calculated for the SES as compared with PES (8,378 ± 2,724€ vs. 9,954 ± 5,282€; p = 0.03). It is worth observing that diabetic patients had higher costs than non-diabetic patients during the initial hospitalization and during follow-up for both the SES and PES groups.

Follow-up costs in the subset of patients without target lesion revascularization were similar between the SES and PES groups (2,450 ± 1,928€ vs. 2,905 ± 4,014€; p = 0.14), implying that the difference in total costs between the 2 groups of patients was mainly due to the higher rate of target lesion revascularization incurred during follow-up among patients treated with PES.

The analysis of the efficacy and costs in this study showed that use of SES is a cost-saving (dominant) treatment strategy, being associated with a higher effectiveness and reduced costs. Therefore, there was no need for analyzing the cost-effectiveness relationship between the two study groups.

**DISCUSSION**

This is the first study to comparatively evaluate the costs of the currently approved DES, the SES and the PES, in relation to their clinical effectiveness when used in patients with coronary artery disease. Both groups of patients treated with the respective DES had an overall low rate of MACE, although a significantly smaller number of patients in the SES group experienced MACE. There were no differences between patients in the 2 stent groups with respect to mortality and myocardial infarction rates during the follow-up period. On the other hand, patients assigned to the SES group had significantly lower rates of angiographic and clinical restenosis compared with patients assigned to
the PES group. Hence, the difference in clinical effectiveness between the 2 DES in this study is attributed to the reduced need of repeat revascularization procedures with SES. We found that although the initial hospital costs were similar for both stent groups, there was a significant difference in follow-up and in total costs that favored the SES group. Higher costs associated with the use of PES almost entirely reflect the difference in the efficacy in the reduction of repeat revascularization procedures between the 2 DES.

Although use of DES is associated with a marked clinical benefit among patients with coronary artery disease, concerns remain with respect to their high costs. Therefore, for a DES platform to achieve acceptability and widespread use, an optimal balance between cost and effectiveness should be demonstrated in addition to clinical efficacy (12). In this context, head-to-head comparisons of different DES would allow a full appreciation, from different perspectives (including the societal perspective), of the economic impact of introducing or expanding the use of different types of DES. Our study shows that because of the difference in clinical effectiveness, use of DES that perform better will be a cost-saving strategy, provided initial hospital costs are similar.

Calculated costs for initial hospitalization, follow-up, and total costs for the SES in our study were similar to those reported in previously published analyses (13,14) that compared costs associated with use of DES and BMS. These studies found reasonable balance between costs and effects for SES as compared with BMS for both simple and complex coronary lesions. Basically, both previous studies analyzed all the resources used during initial interventions and at follow-up, including hospitalization days, different fees, and use of medical and other materials, and unit costs were estimated for each resource used. Our approach was to examine the costs from insurer perspectives, which are interested in the overall costs for a disease and intervention without focusing on the variations in inter-institutional use of resources and on the unit prices. It is also interesting to note that the total costs in our study compare favorably with those reported from historical studies on treatment of complex lesions, including restenotic lesions treated with balloon angioplasty or intracoronary brachytherapy (22–25); however, it is difficult to compare costs in different countries and in different time periods because of various factors, including different unit prices and inflation rates. Though the precise euro amounts may not be readily translated, the directionality of our findings probably is translatable.

Our analysis was performed from the health insurance system’s perspective as an approximation for the societal perspective. It is important to emphasize the perspective from which the economic evaluation is performed (26). The payer perspective is the only entity that reaps the overall benefits of this sort of cost-effectiveness. It is also worthy to note that other perspectives, such as the provider (physicians or hospitals) would not reap the benefit of this cost-effectiveness. Indeed, for the hospitals it is a double jeopardy of losing future revenues and bearing the higher costs of DES versus BMS.

Indirect costs were not measured, and thus the total costs estimated in this study may not provide a complete picture of the cost estimates from the societal perspective. The anginal pain and the accompanying anxiety extended beyond pain period, disability, productivity loss, and possible increase of hospitalization appear to justify the increasing use of revascularization as an end point in cost-effectiveness calculations in recent studies, especially from the payer, patient, and societal perspectives (13,23,27). Therefore, the higher rate of revascularization may well reflect increased indirect costs and decreased quality of life. A recent study found that patients undergoing PCIs assign an important value to the avoidance of restenosis (28). Thus, inclusion of these measurements probably would have increased the difference in costs between our study groups.

Our analysis is based on the ISAR-DESIRE and ISAR-DIABETES studies, which included patients with in-stent restenosis and diabetic patients. This is a high-risk population, and the results of this study do not necessarily apply to other patient subsets. Therefore, further studies must be conducted to assess not only efficacy but also costs of intervention of these 2 platforms of DES.

Mandatory, protocol-driven angiographic follow-up of the study population may have increased the frequency of repeat revascularization procedures and, consequently, total costs. However, the possible inflated cost for this increase in reinterventions is likely to be balanced between both groups as a consequence of the randomization process and the similar rate of angiographic follow-up. Therefore, the bias toward any of the study cohort groups should be minimal. The fact that the majority of patients who underwent target lesion revascularization required repeat intervention before the scheduled follow-up angiography further reduces the possible bias related to protocol-mandated angiographic follow-up.

Quality of life was not assessed in this study. There were no quality-measuring instruments designed in the protocols of the randomized trials, which provided the patients for this analysis. Quality-adjusted year of life gained as a standard cost-effectiveness measure would have allowed for comparison across different diseases as opposed to the disease-specific measure, such as cost per repeat revascularization procedure avoided.

In conclusion, the results of this study show that use of SES is economically more attractive than PES in patients with coronary artery disease presenting with high clinical and angiographic risk profiles. Implantation of the SES is a cost-saving strategy, mainly because of the significant reduction in clinical restenosis with this DES.
REFERENCES