Randomized Trial of a Nonpolymer-Based Rapamycin-Eluting Stent Versus a Polymer-Based Paclitaxel-Eluting Stent for the Reduction of Late Lumen Loss

Julinda Mehilli, MD; Adnan Kastrati, MD; Rainer Wessely, MD; Alban Dibra, MD; Jörg Hausleiter, MD; Birgit Jaschke, PhD; Josef Dirschinger, MD; Albert Schömig, MD; for the Intracoronary Stenting and Angiographic Restenosis–Test Equivalence Between 2 Drug-Eluting Stents (ISAR-TEST) Trial Investigators

Background—Although drug-eluting stents (DESs) constitute a major achievement in preventing restenosis, concerns remain regarding the increased inflammatory and thrombogenic responses associated with the polymers used. Recently, we showed that a nonpolymer on-site coating with rapamycin not only is feasible and safe but also leads to a dose-dependent reduction in restenosis.

Methods and Results—To assess whether polymer-free stents coated on-site with 2% rapamycin solution are inferior to polymer-based paclitaxel-eluting stents for the prevention of restenosis, we randomly assigned a total of 450 patients with de novo lesions in native coronary vessels, excluding the left main trunk, to either the polymer-free, rapamycin-coated Yukon DES (rapamycin stent) or the polymer-based, paclitaxel-eluting Taxus stent (paclitaxel stent). The primary end point was in-stent late lumen loss. Secondary end points were angiographic restenosis and target lesion revascularization. The study was designed to test the noninferiority of the rapamycin stent compared with the paclitaxel stent with respect to late lumen loss according to a noninferiority margin of 0.13 mm. Follow-up angiography was completed in 81% of the patients. The mean difference in in-stent late lumen loss between the rapamycin-stent group and the paclitaxel-stent group was 0.002 mm, and the upper limit of the 1-sided 95% confidence interval was 0.10 mm ($P=0.02$ from test for noninferiority). No significant differences were observed regarding angiographic restenosis rates (14.2% with the rapamycin stent and 15.5% with the paclitaxel stent) and target lesion revascularization rates due to restenosis (9.3% in both groups).

Conclusions—The polymer-free, rapamycin-coated stent has an antirestenotic effect that is not inferior to that observed with the polymer-based paclitaxel-eluting stent. (Circulation. 2006;113:273-279.)

Key Words: coronary disease • restenosis • stents • drugs

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Drug-eluting stents (DESs) represent a major advance in the treatment of restenosis. They have dramatically reduced the need for repeated revascularization procedures and because of the excellent results obtained in various patient subsets, these devices are now used in almost 90% of the stent implantation procedures performed in US hospitals. Along with the increasing number of patients receiving DESs and the availability of long-term follow-up data, concern has arisen regarding the safety of these devices. At the core of this concern is the potential for increased inflammatory and thrombogenic responses and the life-threatening consequences associated with the polymers used for the delivery of antirestenotic agents.

Growing interest in polymer-free stents with a microporous surface as an alternative to stents with polymer coatings for local drug delivery has arisen. Recently, we developed a mobile system that enables coating in the catheterization laboratory of polymer-free stents with different drug doses or combinations thereof. Using a porcine coronary model of restenosis, we found that coating with rapamycin of a polymer-free microporous stent is feasible and effectively reduces neointimal proliferation. More recently, in a clinical study in which the efficacy of several doses of rapamycin was assessed, we showed that a nonpolymer coating with rapamycin is safe and leads to a dose-dependent reduction in restenosis. Although the advantage derived from the lack of a polymer coating in on-site–coated, rapamycin-eluting stents is readily understandable, their relative efficacy compared with commercially available polymer-based, DESs has yet to be evaluated.
The current study was designed to assess whether polymer-free microporous stents coated with rapamycin are not inferior to the standard polymer-based, paclitaxel-eluting stents in their antirestenotic effects in patients with coronary artery disease.

Methods

Study Population and Protocol

Patients who were at least 18 years old, had stable or unstable angina or a positive stress test, and were to undergo percutaneous coronary interventions for de novo lesions in a native coronary artery were considered eligible for this study. Patients with myocardial infarction within 48 hours before enrollment, a target lesion located in the left main trunk, and contraindications or known allergy to aspirin, heparin, thiopopyridines, rapamycin, paclitaxel, or stainless steel were considered ineligible for the study. The study protocol was approved by the institutional ethics committee responsible for both participating centers, the Deutsches Herzzentrum and Medizinische Klinik I, Klinikum rechts der Isar, Munich, Germany. All patients gave their written, informed consent for participation in this trial.

At least 2 hours before undergoing catheterization, patients received a loading dose of 600 mg clopidogrel. Randomization was performed after wiring of the target vessel with sealed, opaque envelopes containing a computer-generated random sequence. The catheterization laboratories of both participating centers were provided with sealed envelopes. No stratification was performed. Patients were assigned to receive either the polymer-free, 2% rapamycin-eluting stent (rapamycin stent) or the polymer-based, paclitaxel-eluting stent (Taxus, Boston Scientific Corp.). The stent platform needed to prepare the rapamycin stent consists of a premounted, sand-blasted, 316L stainless steel microporous stent in a disposable coating cartridge (Yukon DES, Translumina) and the coating device. A detailed description for creating the microporous and the coating process has been reported previously, along with the rapamycin-release profile of this stent platform.11,13 The 2% rapamycin solution used for the stent coating in this study was selected on the basis of results from a dose-finding study in which the antirestenotic effectiveness of various concentrations of rapamycin solution was evaluated.12 Paclitaxel-eluting stents were available in diameters of 2.25, 2.5, 2.75, 3.0, and 3.5 mm and in lengths of 8, 12, 16, 20, 24, 28, and 32 mm. Rapamycin stents were available in diameters of 2.0, 2.5, 3.0, and 3.5 mm and in lengths of 8, 12, 16, 18, 23, and 25 mm. Stenting in multiple lesions and the use of >1 stent per lesion were allowed under the condition that the same randomly assigned stent had to be implanted in all lesions.

Aspirin and unfractionated heparin were administered per standard practice: the use of abciximab (ReoPro, Lilly) was generally restricted to patients with acute coronary syndromes (positive troponin results or ST-segment depression on the surface ECG). After the procedure, patients were maintained on aspirin 100 mg BID indefinitely, clopidogrel 75 mg BID until discharge, and 75 mg daily for at least 6 months. Other medications such as β-blockers, statins, and angiotensin-converting-enzyme inhibitors were given as appropriate. After enrollment, patients remained in the hospital for at least 48 hours. For all patients, ECGs were recorded and blood was collected at least 6 months. Other medications such as heparin, thienopyridines, rapamycin, paclitaxel, or stainless steel were considered ineligible for the study. The study protocol was approved by the institutional ethics committee responsible for both participating centers, the Deutsches Herzzentrum and Medizinische Klinik I, Klinikum rechts der Isar, Munich, Germany. All patients gave their written, informed consent for participation in this trial.

Data Management, End Points, and Definitions

Relevant data were collected and entered into a computer database by specialized personnel of the Clinical Data Management Center. All data were verified against source documentation, and all adverse events were adjudicated by an event committee blinded to treatment allocation. Baseline, postprocedural, and follow-up cineangiograms were forwarded to the Quantitative Angiographic Core Laboratory (Deutsches Herzzentrum, Munich, Germany) for assessment by experienced technicians unaware of the treatment allocation. Angiographic image acquisition of the target lesion was done after intracoronary administration of nitroglycerin, and the same single worst-view projection was measured at all time points. Qualitative morphological lesion characteristics were characterized by standard criteria.14 The off-line quantitative coronary angiographic analysis was performed with an automated edge-detection system (QCA-CMS V 6.0, Medis, Medical Imaging Systems). The contrast-filled, nontapered catheter tip was used for calibration. The reference diameter was measured by interpolation. Minimal lumen diameter was measured within the stent and within the 5-mm proximal and distal edges of the stent. Quantitative analysis was performed in the in-stent area (in-stent analysis) and in the in-segment area including the stented segment, as well as both 5-mm margins proximal and distal to the stent (in-segment analysis).

The primary end point of the study was in-stent late lumen loss. Secondary end points were angiographic restenosis (diameter steno- sis of at least 50% based on in-segment analysis) at follow-up angiography and the need for target lesion revascularization due to restenosis in the presence of symptoms or objective signs of ischemia during the 9-month follow-up. The incidence of angiographic stent thrombosis, myocardial infarction, and all-cause death was also assessed during the 9-month follow-up. The diagnosis of myocardial infarction required the presence of new Q waves on the ECG and/or elevation of creatine kinase or its MB isoenzyme to at least 3 times the upper limit of normal in no fewer than 2 blood samples.

Statistical Methods

The objective of the study was to assess the noninferiority of the rapamycin stent compared with the paclitaxel stent. Sample size calculation was based on a margin of noninferiority for in-stent late lumen loss set at 0.13 mm. This value is equal to one third of the mean late lumen loss of 0.39 mm observed in patients who received the Taxus stent in the TAXUS-IV trial.1 A total of 360 patients, 180 in each treatment arm, were needed to demonstrate that rapamycin stents have a mean late lumen loss within 0.13 mm of that of paclitaxel-eluting stents, or better, with 80% power, with use of a 1-sided statistical test with an α level of 0.05. Expecting that as much as 20% of patients would not present for follow-up coronary angiography, we included 450 patients in the study. Sample size calculation was performed with nQuery Advisor, version 4.0 (Statistical Solutions) according to the method described by O’Brien and Muller.10 The analyses were performed on an intention-to-treat basis. In patients with multilesion interventions, only the first treated lesion was included in the analysis. Categorical variables are summarized as counts or percentages and were compared by the χ² or Fisher’s exact test. Continuous variables are expressed as mean±SD or median with 25th and 75th percentiles and were compared by Student’s t test or the Wilcoxon rank-sum test. The noninferiority hypothesis was tested with EquivTest (Statistical Solutions) according to the method described by Chow and Liu.11 Survival parameters were compared with the log-rank test. A 2-sided probability value <0.05 was considered statistically significant.

Results

Baseline Characteristics and Procedural Results

A total of 450 patients were enrolled in this study: 225 patients received the rapamycin stent and 225, the paclitaxel stent (Figure 1). As shown in Table 1 and Table 2, the baseline clinical and angiographic features were well matched between the 2 randomized groups. The procedural characteristics are summarized in Table 3. Implantation of the assigned stent was successful in all patients. The number of implanted stents per patient was higher among patients assigned to receive the rapamycin stents. Mean stented length...
was longer among patients assigned to receive paclitaxel stents.

**Angiographic Outcomes**

Follow-up angiography was performed in 183 patients (81.3%) in the rapamycin-stent group and in 181 patients (80.4%) in the paclitaxel-stent group. Figure 1 shows the reasons for not undergoing follow-up angiography. None of the characteristics shown in Table 1 through Table 3 differed significantly between patients who did and those who did not undergo follow-up angiography. With respect to the primary end-point analysis, the mean difference in in-stent late lumen loss between the rapamycin-stent group and the paclitaxel-stent group was 0.002 mm, and the upper limit of the 1-sided 95% confidence interval was 0.10 mm, demonstrating the noninferiority of the rapamycin stent with respect to the paclitaxel stent ($P=0.02$ from test for noninferiority). Figure 2 shows the overlapping cumulative distribution curves of late loss for the 2 stents. Two additional sensitivity analyses were performed to assess the impact on the primary end-point analysis of missing follow-up angiography in 19% of the patients enrolled in this study. When we assigned the lowest in-stent late lumen loss values to patients with missing information in both groups, the mean difference in in-stent late lumen loss between the rapamycin-stent group and the paclitaxel-stent group was 0.009 mm, and the upper limit of the 1-sided 95% confidence interval was 0.09 mm ($P=0.01$ from test for noninferiority). When we assigned the highest in-stent late lumen loss values to patients with missing information in both groups, the mean difference in in-stent late lumen loss between the rapamycin-stent group and the paclitaxel-stent group was 0.002 mm, and the upper limit of

<table>
<thead>
<tr>
<th>Table 1. Baseline Demographic and Clinical Characteristics of the Study Patients</th>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Women, n (%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
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<tr>
<td>Hypercholesterolemia, n (%)</td>
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<tr>
<td>Unstable angina, n (%)</td>
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<tr>
<td>Prior myocardial infarction, n (%)</td>
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<tr>
<td>Prior aortocoronary bypass surgery, n (%)</td>
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<tr>
<td>Left ventricular ejection fraction, %</td>
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<tr>
<td>No. of lesions treated</td>
</tr>
</tbody>
</table>

Plus-minus values are mean±SD.
the 1-sided 95% confidence interval was 0.11 mm ($P=0.02$ from test for noninferiority). All other quantitative parameters of restenosis were also comparable between the 2 groups (Table 4). The incidence of in-segment angiographic restenosis was 14.2% in the rapamycin-stent group and 15.5% in the paclitaxel-stent group ($P=0.73$, Figure 3). In the subset of diabetic patients, in-segment angiographic restenosis was 22.4% in the rapamycin-stent group and 18.8% in the paclitaxel-stent groups ($P=0.64$).

**Clinical Outcomes**

During the first 30 days after randomization, only 1 (0.4%) patient in the paclitaxel-stent group died. Two patients, 1 (0.4%) in the rapamycin-stent group and 1 (0.4%) patient in paclitaxel-stent group, developed a thrombotic stent occlusion. Two patients (0.9%) in the rapamycin-stent group and 1 patient (0.4%) in the paclitaxel-stent group required urgent reintervention because of ischemia. Death or myocardial infarction occurred during the first 30 days in 9 (4.0%) patients in the rapamycin-stent group and in 7 (3.1%) patients in the paclitaxel-stent group ($P=0.64$).

By 9 months, 2 (0.9%) patients in the rapamycin-stent group and 3 (1.3%) in the paclitaxel-stent group had died ($P=0.65$). One (0.4%) patient in the paclitaxel-stent group developed a late thrombotic stent occlusion. The combined 9-month incidence of death or myocardial infarction was comparable between the 2 groups (4.4% in the rapamycin-stent group versus 4.0% in the paclitaxel-stent group, $P=0.81$). Target lesion revascularization rate because of restenosis was 9.3% in both groups ($P=1.0$, Figure 3). None of the patients underwent coronary artery bypass grafting within the 9-month follow-up period.

**Discussion**

In this randomized study, we assessed the relative effectiveness of a nonpolymer-based, on-site–coated, rapamycin-eluting stent and a standard polymer-based, paclitaxel-eluting stent for the prevention of restenosis. The results of this study show that the polymer-free, rapamycin-eluting stent is not inferior to the polymer-based, paclitaxel-eluting stent in reducing neointimal proliferation; the incidence of angiographic and clinical restenosis was virtually the same in both study groups. These findings may be very clinically relevant, with respect to elimination of the potential long-term negative effects of polymers.

The recent emergence of DESs has been perceived as the final solution to the problem of restenosis. Although several DES platforms have been developed, most of them, including the commercially available paclitaxel and sirolimus stents, use a polymer coating for drug storage and adjustment of elution kinetics. Although their efficacy in reducing restenosis rates at midterm follow-up has been well established, there is ongoing debate on the potential of an increased incidence of late stent thrombosis, particularly after discontinuation of thienopyridine therapy, as well as of delayed onset of restenosis with the polymer-based, paclitaxel-eluting

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**TABLE 2. Baseline Angiographic Characteristics of the Study Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Polymer-Free Paclitaxel-Stent Group (n=225)</th>
<th>Polymer-Based Paclitaxel-Stent Group (n=225)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter stenosis before procedure, %</td>
<td>58.3±12.4</td>
<td>58.1±12.7</td>
<td>0.87</td>
</tr>
<tr>
<td>Length of stented segment, mm</td>
<td>21.5±8.2</td>
<td>23.1±8.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Maximal balloon pressure, atm</td>
<td>14.1±2.8</td>
<td>14.3±2.9</td>
<td>0.37</td>
</tr>
<tr>
<td>Balloon-to-vessel ratio</td>
<td>1.13±0.08</td>
<td>1.13±0.10</td>
<td>0.77</td>
</tr>
<tr>
<td>No. of stents per lesion</td>
<td>1.16±0.38</td>
<td>1.08±0.26</td>
<td>0.006</td>
</tr>
<tr>
<td>Minimal lumen diameter after procedure, mm</td>
<td>2.57±0.43</td>
<td>2.59±0.42</td>
<td>0.61</td>
</tr>
<tr>
<td>Diameter stenosis after procedure, %</td>
<td>9.0±5.9</td>
<td>8.7±7.0</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Plus-minus values are mean±SD.
and sirolimus-eluting stents. Previous work has shown that implantation of different types of polymers in porcine coronary arteries evokes a marked inflammatory response, which is characterized by multinucleated giant cells and macrophages and is associated with increased neointimal thickening. Recently, animal and human pathological data have shown that the polymer coatings used with DESs are proinflammatory and prothrombogenic. Sometimes the polymers used may induce a hypersensitivity reaction, which is characterized by an extensive inflammatory infiltrate involving the whole vessel wall and is composed of lymphocytes, plasma cells, macrophages, and neutrophils. This response to polymers may cause late stent thrombosis and even death.

In view of the disadvantages associated with the use of polymers for local drug delivery, other approaches to coating of stents with antirestenotic agents have been proposed, and 1 of these is coating with the drug directly onto the specially treated microporous surface of polymer-free stents. A microporous surface may promote endothelialization without increasing neointimal proliferation, and it has the potential to enhance drug storage capacity and retard the release kinetics. In a preclinical study, we showed that nonpolymer-based, on-site coating of microporous stents with rapamycin solution is feasible and safe and that coated stents effectively inhibit neointimal proliferation. Stent coating was completed on-site by means of a mobile stent-coating platform, which allows for various doses and drugs to be selected without requiring additional polymer use. In a recent study that included 602 patients, we evaluated the antirestenotic efficacy of microporous stents coated with different doses of rapamycin. Rapamycin was chosen because of its proven efficacy in the prevention of restenosis when used both locally and systemically. We found that on-site-coated stents were efficacious in reducing restenosis rates and that their efficacy was dose related. Stents coated with a 2%...
rapamycin solution achieved the maximal restenosis reduction. The large proportion of DESs. The large proportion of DESs. On the other hand, although no direct comparison was included in the present study, the in-stent late lumen loss of 0.48 mm observed in the polymer-free, paclitaxel-stent group seems to be higher than that reported previously for polymer-based stents eluting this drug. This comparison would also have provided more insights into the specific role of the polymer coating. Similar to the comparable antirestenotic efficacy of the 2 DESs, no difference was observed with regard to the safety of these devices. However, with only 3 cases of stent occlusions in the entire study population, 2 among patients who received paclitaxel-eluting stents and 1 among those who received rapamycin-eluting stents, no conclusion can be drawn on the relative safety of these DES platforms.

Two limitations of the present study should be acknowledged. First, follow-up angiography was not available for and precluded the primary end-point analysis of 19% of enrolled patients. However, both the lack of differences in baseline and procedural characteristics between patients with and without follow-up angiography and the consistent results obtained by sensitivity analyses make highly improbable a biasing effect from missing follow-up angiography data on the main results of this study. Second, according to the findings of this study, it should be noted that, although polymer-free DESs are associated with comparable outcomes to their polymer-based counterparts, the presumed advantage deriving from the lack of a polymer coating with the former could not be appreciated. The length of follow-up in our study, though similar to that of other contemporary trials of DESs, was not sufficient to allow detection of any differences in the performance of DESs that could be attributed to the presence of polymers. On the other hand, detection of such differences would be easier in studies including larger numbers of patients.

The results of this study show that nonpolymer-based, rapamycin-eluting stents are not inferior to standard polymer-based, paclitaxel-eluting stents in their capacity to reduce restenosis. Therefore, the rapamycin-eluting stent assessed in this study may represent the first successful nonpolymer approach to DES technology made available to the interventional cardiologist.

Acknowledgment

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Disclosures

Dr. Kastrati reports having received lecture fees from Bristol-Myers Squibb, Lilly, Sanofi, and Cordis. Dr. Wessely reports having received a lecture fee from Lilly. The other authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

Polymer-based drug-eluting stents (DESs) are effective therapy for reducing the risk of restenosis. However, concerns remain regarding the increased inflammatory and thrombogenic responses associated with polymers that may compromise the long-term efficacy of DESs. Polymer-free DESs may represent a safer alternative in the long term, provided that they offer comparable effectiveness to currently used polymer-based DES. The objective of this randomized clinical trial was to assess whether polymer-free stents coated on-site with 2% rapamycin solution are not inferior to polymer-based, paclitaxel-eluting stents for prevention of restenosis. A total of 450 patients with de novo lesions in native coronary vessels were randomly assigned to the polymer-free, rapamycin-coated Yukon DES (rapamycin stent) or the polymer-based, paclitaxel-eluting Taxus stent (paclitaxel stent). The primary end point was late lumen loss. Secondary end points were angiographic restenosis and target lesion revascularization. The noninferiority margin for late lumen loss was set at 0.13 mm. The mean difference in late lumen loss between the rapamycin stent and the paclitaxel stent was 0.002 mm, and the upper limit of the 1-sided 95% confidence interval was 0.10 mm. No significant differences were observed regarding angiographic restenosis (14.2% with the rapamycin stent and 15.5% with the paclitaxel stent) and target lesion revascularization (9.3% in both groups). Thus, the anti-restenotic effect of the polymer-free, rapamycin-coated stent is not inferior to that observed with the polymer-based, paclitaxel-eluting stent. This represents the first successful nonpolymer approach to DES technology now available to the interventional cardiologist.
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