Inhibition of Neointima Formation by a Novel Drug-Eluting Stent System That Allows for Dose-Adjustable, Multiple, and On-Site Stent Coating

Rainer Wessely, Jörg Hausleiter, Cornelia Michaelis, Birgit Jaschke, Michael Vogeser, Stefan Milz, Boris Behnisch, Thomas Schratzenstaller, Magdalena Renke-Gluszko, Michael Stöver, Erich Wintermantel, Adnan Kastrati, Albert Schömig

Objective—The risk of in-stent restenosis can be considerably reduced by stents eluting cytostatic compounds. We created a novel drug-eluting stent system that includes several new features in the rapidly evolving field of stent-based drug delivery.

Methods and Results—The aim of the present study was the preclinical evaluation of a stent-coating system permitting individual, on-site coating of stents with a unique microporous surface allowing for individualizable, dose-adjustable, and multiple coatings with identical or various compounds, designated ISAR (individualizable drug-eluting stent system to abrogate restenosis). Stents were coated with 0.75% rapamycin solution, and high-performance liquid chromatography (HPLC)-based determination of drug release profile indicated drug release for >21 days. Rapamycin-eluting microporous (REMP) stents implanted in porcine coronary arteries were safe. To determine the efficacy of REMP stents, this novel drug-eluting stent platform was compared with the standard sirolimus-eluting stent. At 30 days, in-stent neointima formation in porcine coronary arteries was similar in both groups, yielding a significant decrease of neointimal area and injury-dependent neointimal thickness compared with bare-metal stents.

Conclusion—The ISAR drug-eluting stent platform as a novel concept for stent coating allows for a safe, effective, on-site stent coating process, thus justifying further clinical evaluation to decrease in-stent restenosis in humans. (Arterioscler Thromb Vasc Biol. 2005;25:748-753.)

Key Words: drug-eluting stent ■ rapamycin ■ sirolimus ■ stent platform
coating cartridge including the premounted microporous stent on a balloon-expandable stent system and the coating device.

Materials and Methods
Rapamycin was purchased from the pharmaceutical distribution company “cfm" (Marktredwitz, Germany). The drug was dissolved in 99.5% ethanol (#1.00986; Merck) at 0.75% (7.5 mg/mL).

DES Platform
The ISAR DES platform consists of 2 components, the mobile coating device and the disposable stent cartridge holding a pre-mounted, sandblasted 316L stainless steel microporous stent (Figure 1). The microporous surface of the stent platform allows for drug deposition and retarded drug release without obligate application of a polymer. The roughness of the stent surface as determined by perihometer is 1.96±0.21 μm. The mechanical surface treatment processes do not lead to changes in material composition. For stent coating, the cartridge (15.5 cm length) is dried by sterile pressured air and unlocked for immediate usage. Sterility is maintained throughout the entire coating process.

Pharmacokinetics of Drug-Coated Stents
For determination of pharmacological release kinetics, coated stents (n=3) were deployed ex vivo and submersed in 1 mL PBS at 37°C. Samples harvested at distinct time points were subjected to high-performance liquid chromatography (HPLC)-based analysis. Determination of total rapamycin stent dosage was performed by drug elution in 1.5 mL ethanol 100% overnight at 4°C. After solvent evaporation, rapamycin amounts were quantified by liquid chromatography–tandem mass spectrometry as described previously.10 Measurements of rapamycin blood levels were performed by HPLC as well.

Porcine Coronary Stent Model
One day before percutaneous intervention, juvenile domestic pigs underwent stent implantation of clopidogrel. The antiplatelet therapy of 250 mg aspirin and 75 mg clopidogrel daily was maintained throughout the study. A total of 16 fully anesthetized and ventilated pigs underwent stent implantation in both right coronary artery (RCA) and left anterior descend (LAD) coronary artery. Coronary stenting was performed through a 7-French carotid access under fluoroscopic guidance (GE medical OEC 9800 Plus Cardiac) at a balloon-to-vessel ratio of 1.2:1 with the use of 12-mm-long bare-metal microporous stents (n=8), 13-mm Cypher sirolimus-eluting stents (SES) (Cordis) (n=8), and single-coated (n=8) or double-coated rapamycin-eluting microporous (REMP) stents (n=8) at a length of 12 mm. Stents in each group were equally distributed in the RCA and LAD. At the time of stenting, the animals received 200 units/kg body weight of heparin intravenously. Thirty days after stenting, pigs were sedated and euthanized by a lethal dose of pentobarbital. For determination of rapamycin blood levels in animals who received a rapamycin-coated microporous stent, blood samples were taken at the end of percutaneous coronary intervention (PCI), as well as 4 hours and 24 hours after stenting. For histological analysis, the heart was removed and rinsed through the ostium of the LAD and RCA, respectively, with 250 mL NaCl 0.9% at physiological pressure, followed by perfusion fixation using 4% formaldehyde for each coronary artery. Subsequently, stented artery segments were removed and fixed for another 24 hours in 4% formaldehyde solution. After a dehydration protocol for several days, stented vessels were embedded in methylmethacrylate as previously described.11 For histomorphometric analysis, 100-μm-thick sections were cut with a Leitz saw microtome, stained according to the Gallamin–Giemsa technique, and scanned with a Zeiss Axiophot 100 system. Neointima formation was assessed by histomorphometric measurement of 4 in-stent neointimal areas with 2 mm distance from each other to assure a comprehensive result reflecting the whole stented segment. Morphometric analysis was performed by SigmaScan 5.0 software (SPSS Inc). In addition, injury scores12 and neointimal thicknesses were assessed on an individual strut basis for all stents to evaluate the effectiveness of different stent coatings on the reduction of neointimal thickness at different injury levels. For additional assessment of inflammation, fibrin deposition, and endothelialization, 3 embedded segments of each implanted stent were Paragon-stained according to an established protocol13 and analyzed at a thickness of ≈10 μm according to established scores.14 Assessment score for strut-associated inflammation: 0 = none; 1 = scattered inflammatory cells; 2 = inflammatory cells encompassing 50% of a strut in at least 25% to 50% of the circumference of the artery; and 3 = inflammatory cells surrounding a strut in at least 25% to 50% of the circumference of the artery. Stent endothelialization was defined as the extent of the circumference of the arterial lumen covered by endoluminal: 1 = 25% to 50%; 2 = 75% to 100% coverage. Strut-associated fibrin content was assessed as follows: 0 = no evidence of residual fibrin; 1 = focal regions of residual fibrin deposition adjacent to the strut involving <25% of the circumference of the artery; 2 = moderate fibrin involving >25% of strut struts; and 3 = heavy fibrin deposition involving the majority of strut struts.

To determine rapamycin tissue levels, an additional 2 pigs for each time point were stented in the RCA and LAD and euthanized on days 1, 3, and 6 after stenting. The vascular wall covered by the stent as...
well as perivascular tissue adjacent to the stented vascular wall were harvested under a dissecting microscope and snap-frozen in liquid nitrogen (LN2), weighed, and stored at -70°C. Subsequently, tissue was disaggregated for 10 seconds in 1 mL ice-cold DPBS (#D8537; Sigma-Aldrich) using a MICCRA RT mixer (#ART-MICCRA D-8; Art-Labortechnik). After 3 freeze–thaw cycles, samples were subjected to protein precipitation using an equal volume of a mixture of a methanol/zinc sulfate solution. Thereafter, cleared supernatants were submitted to an on-line solid-phase extraction procedure, followed by analytical chromatography as described.10

Statistical Analysis
Significance of variability among the means of the experimental groups was determined by 1-way or 2-way analysis of variance using SPSS for Windows V10.0 software. Differences among experimental groups were considered to be statistically significant when \( P < 0.05 \). Unless indicated, values are given as mean ± SD.

Results
Rapamycin Concentration on Single-Coated and Dual-Coated Rapamycin-Eluting Microporous Stents
To determine the drug amount on the stent after a single or dual rapamycin coating process, microporous stents were appropriately coated (n=3 each group) and rapamycin concentrations on the stents were determined by HPLC analysis. The drug amount on the stent yielded by single coating was 195±33 mg/cm² stent surface and 317±45 mg/cm² by double coating, respectively. The surface of an uncoated and a rapamycin-coated microporous stent is illustrated in Figure 2.

Pharmacokinetics In Vitro and In Vivo
Time-dependent HPLC-based analysis of rapamycin elution from single-coated and dual-coated REMP stents (n=3 each group) showed sustained rapamycin release for >21 days (Figure 3A), with more than two-thirds of stent-based rapamycin released within the first 6 days. These results were confirmed in a biological assay in which stent-released rapamycin had an impact on mitogen-mediated coronary smooth muscle cell proliferation for >21 days (data not shown). Drug-elution during the first 2 minutes, a timeframe commonly needed between introduction of the stent into the guiding catheter and stent deployment, was determined to be <2% of the total rapamycin dose located on the REMP stent. After 1 hour, ~4.5% of the total dose was released. The relative values were not significantly different for single-coated or dual-coated stents. Blood samples drawn immediately after the intervention and subsequently at 4 hours and 24 hours after stenting showed perceptible rapamycin blood levels only immediately after and 4 hours after stenting. However, 24 hours after PCI, rapamycin blood levels were very low or even undetectable (Figure 3B). To determine rapamycin levels in the vascular wall, the entire stented coronary vascular wall was recovered 1, 3, and 6 days after stent deployment, was disaggregated for 10 seconds in 1 mL ice-cold DPBS (#D8537; Sigma-Aldrich) using a MICCRA RT mixer (#ART-MICCRA D-8; Art-Labortechnik). After 3 freeze–thaw cycles, samples were subjected to protein precipitation using an equal volume of a mixture of a methanol/zinc sulfate solution. Thereafter, cleared supernatants were submitted to an on-line solid-phase extraction procedure, followed by analytical chromatography as described.10

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after stent deployment (n=4 stents for each time point). Intramural rapamycin tissue levels reached their maximum 3 days after stent implantation, but there were substantial rapamycin levels detectable at 6 days after stenting (Figure 3C).

### Safety and Efficacy of REMP Stents Compared With Bare-Metal Microporous and Cypher Stents In Vivo

To determine safety and the impact of the novel drug-eluting stent system on the inhibition of in-stent neointima formation, the pig coronary artery stent model was used. In each group, all animals survived PCI and there was no evidence of acute or subacute stent thrombosis or occurrence of death. Pigs were monitored by veterinarians, reporting no evidence for increased infections or any other serious acknowledgeable side effects that could be attributed to DES. All coronary stents remained patent as assessed by histology. SES, single-coated and dual-coated rapamycin-eluting microporous stents led to a significant reduction of neointimal area and diameter stenosis 30 days after stent deployment (Table 1). Importantly, the mean injury score was not different for all stent groups with the lowest score for bare-metal stents. There was no significant difference between the different DES on the inhibition of neointima formation (Table 1). Determination of injury-dependent neointimal thickness revealed significant attenuation of neointimal thickness for SES and single-coated or dual-coated rapamycin-eluting microporous stents, particularly at higher injury levels (Figure 4A). Thus, in this animal model, drug-eluting stent platforms, SES, and rapamycin-coated microporous stents lead to a comparable degree of limitation of neointimal growth. Assessment of strut-associated inflammation showed a significantly increased score for SES, whereas there was no detectable difference between bare-metal and REMP stents (Table 2). Endothelial coverage and strut-associated fibrin deposition, although somewhat increased in REMP stents, were not significantly different between all stent groups.

### Discussion

For more than a decade, in-stent restenosis has been considered to be the major problem of interventional cardiology. Since the first introduction of a drug-eluting stent platform in clinical medicine in 2001, trials for sirolimus and paclitaxel-eluting stents have convincingly shown that these stents may efficiently inhibit in-stent restenosis in humans. Although robust scientific data are currently not available, there is ongoing discussion whether an increase in rapamycin dosage on DES may lead to a more favorable outcome in certain patients.

#### Table 1. Histomorphometrical Assessment

<table>
<thead>
<tr>
<th></th>
<th>Bare-Metal</th>
<th>SES</th>
<th>Single REMP</th>
<th>Dual REMP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IEL, mm</strong></td>
<td>5.05±0.68</td>
<td>4.49±1.74</td>
<td>4.39±1.31*</td>
<td>4.67±1.46</td>
</tr>
<tr>
<td><strong>Neointimal area, mm</strong>²</td>
<td>2.32±0.95</td>
<td>1.62±0.94*</td>
<td>1.73±0.87*</td>
<td>1.61±0.65*</td>
</tr>
<tr>
<td><strong>DS, %</strong></td>
<td>45.9±17.1</td>
<td>36.2±13.9*</td>
<td>38.4±14.1*</td>
<td>33.5±10.3*</td>
</tr>
<tr>
<td><strong>Mean injury score</strong></td>
<td>1.71±0.62</td>
<td>1.82±0.75</td>
<td>1.98±0.51</td>
<td>1.96±0.51</td>
</tr>
</tbody>
</table>

DS indicates diameter stenosis; IEL, area within internal elastica membrane.

*P<0.05 compared to corresponding bare-metal stent values.

P=NS between all values of the various drug-eluting stent platforms.

Values are mean±SD

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**Figure 4.** Rapamycin-coated microporous stents lead to significant inhibition of strut-associated neointimal thickness in the porcine coronary artery stent model. A, Injury-dependent neointimal thickness is significantly decreased by single or dual rapamycin-eluting microporous (REMP) stents as well as SES (Cypher), particularly at higher injury levels. P<0.05 for all DES groups compared with bare-metal stents at injury scores of ≥1. B, Representative photographs of stented pig coronary arteries 30 days after implantation illustrating decreased neointima formation by both drug-eluting stent platforms, SES and REMP stents (left images). On the right side, images at 100× magnification of representative stent struts. As depicted in Table 2, more strut-associated inflammation was apparent at SES stent struts (arrows), concordant with previously published results in this animal model.
patient subsets. In addition, currently available drug-eluting stent platforms are coated with a polymeric surface. There is evidence that polymeric coating may lead, in some cases, to localized hypersensitivity reactions and even late coronary thrombosis. Further, the steadily increasing availability of various DES in different diameters and lengths together with limited usability because of expiration dates make it costly to secure a constant inventory stock of appropriate DES in the cardiac catheterization laboratory. Therefore, a novel concept for a drug-eluting stent platform, which allows for dose-adjustable, on-site coating of DES without the obligate use of a polymer, might be a valuable addendum to existing stent platforms.

To prove that the ISAR device is capable of reducing neointima formation in vivo, microporous stents were coated with rapamycin, which has been shown to inhibit in-stent restenosis in animal models and humans on the Cypher stent platform. Dose adjustments for ISAR stents might be achieved either by increasing the drug concentration or by repeating the stent-coating processes. Accordingly, we were able to show that a repeated stent-coating process increases absolute rapamycin dosage on the microporous stent and leads to higher concentrations of released rapamycin over time. HPLC-based analysis of rapamycin release from the microporous stent indicated a detectable release for >21 days, with more than two-thirds of the dose released within the first 6 days. Consequently, rapamycin was readily detectable in the pig coronary artery at 6 days after stenting. Peak rapamycin concentrations within the vascular wall were reached 3 days after implantation. This result may be explained by recent observations that pharmacokinetic maximum tissue-loading of rapamycin in the vessel wall takes 60 hours until maximum drug accumulation is reached in an organ bath model. Because release kinetics highly depend on the drug-eluting stent platform, lesion-associated variables, and the compound itself, an optimal release kinetic has not been determined so far for any compound used on DES. However, in the SES first-in-man study, fast-release SES, which liberate sirolimus within 7 days, were as effective and safe at 6 months and 24 months follow-up as slow-release SES, which release most of their compound within 30 days. Additionally, short-term oral treatment with rapamycin has been shown to be effective for the limitation of recurrent in-stent restenosis.

Repeated stent-coating processes may be favorable for increasing the dose of an appropriate drug on the microporous stent and may also allow for on-site coating of a stent with multiple substances. This might be important for future scenarios in which different compounds may be combined on one stent platform, for example one targeting smooth muscle cell proliferation and an additional one promoting re-endothelialization. Thus, physicians may independently choose both drug composition and drug dosage on an individual stent, as they are used to do in their daily clinical practice with systemic application of patient medications.

The pig coronary artery stent model has been shown to be a suitable predictor for stent thrombosis after PCI. In the context of standard combined antiplatelet therapy with aspirin and clopidogrel, there was no event of stent thrombosis in any of the stent groups, indicating an adequate safety profile of the rapamycin-coated stent in this particular animal model.

Stent-based delivery of sirolimus is known to attenuate neointima formation in pigs10 1 month after PCI. Accordingly, our objective was to determine the efficacy of rapamycin-eluting ISAR stents compared with ISAR bare-metal stents on the extent of in-stent neointima formation. In addition, we sought to directly compare the efficacy of rapamycin-coated microporous stents with the established SES platform. Rapamycin-eluting microporous stents significantly inhibited in-stent neointima formation. Notably, in this animal model of vascular injury in the absence of atherosclerotic lesions, there was no statistically significant difference on the magnitude of the inhibition of in-stent neointima formation compared with SES. Both DES maintained similar efficacy by reducing neointimal thickness at moderate and high injury scores as a measure of strut-based vascular injury.

**Study Limitations and Conclusions**

Safety and efficacy of rapamycin-eluting microporous stents were studied in the porcine coronary artery stent model. This particular model is recognized as a standard animal model for the preclinical evaluation of DES.21,22 As is the case with any animal model, in particular in the field of in-stent restenosis, extrapolation of data to the human clinical situation remains indecisive. Pigs were evaluated 4 weeks after stenting because neointimal formation peaks at that time in this particular animal model,22 and studies evaluating stent-based drug delivery in porcine coronaries were performed at identical time points.20,23,24 Despite these limitations, given the significant reduction of neointima formation by rapamycin-eluting microporous stents compared with bare-metal stents, it is suggested that this novel drug-eluting stent concept is effective. The concept of the ISAR coating system constitutes a unique approach for the creation of efficient DES, enabling cardiologists to choose one or several drugs in the desired concentration within a percutaneous coronary interventional procedure at their discretion. Given the results of this preclinical study, this new approach warrants clinical evaluation to decrease in-stent restenosis in human coronary arteries.

| TABLE 2. Assessment of Various Parameters 30 Days After Stenting |
|-----------------------------|------------------|----------------|------------------|------------------|
|                            | Bare-Metal       | SES             | Single REMP      | Dual REMP        |
| Endothelial coverage score  | 2.67±0.49        | 2.52±0.73       | 2.76±0.44        | 2.88±0.33        |
| Inflammation score          | 0.78±1.09        | 1.95±1.00*      | 0.6±0.89         | 0.55±0.79        |
| Strut-associated fibrin score | 0.2±0.41        | 0.16±0.46       | 0.32±0.58        | 0.59±0.51        |

*P<0.05 vs bare-metal and single and dual REMP stents. Values are mean±SD.
Acknowledgments

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References

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In the April 2005 issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, in the article by Wessely et al (*Arterioscler Thromb Vasc Biol*. 2005;25:748–753.), the dosage unit on the stent was incorrectly given in mg (page 750, Results, first paragraph). The correct unit is μg, and the complete corrected paragraph is shown below.

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