Polymer-Free Sirolimus- and Probucol-Eluting Versus New Generation Zotarolimus-Eluting Stents in Coronary Artery Disease

The Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting Versus Zotarolimus-Eluting Stents (ISAR-TEST 5) Trial

Steffen Massberg, MD; Robert A. Byrne, MB BCh; Adnan Kastrati, MD; Stefanie Schulz, MD; Jürgen Pache, MD; Jörg Hausleiter, MD; Tareq Ibrahim, MD; Massimiliano Fusaro, MD; Ilka Ott, MD; Albert Schömig, MD; Karl-Ludwig Laugwitz, MD; Julinda Mehilli, MD; on behalf of the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting Versus Zotarolimus-Eluting Stents (ISAR-TEST 5) Investigators

Background—Durable polymer coatings have been implicated in mid- and long-term adverse events after drug-eluting stent implantation. A polymer-free dual-drug sirolimus- and probucol-eluting stent and a new generation permanent polymer zotarolimus-eluting stent are recently developed technologies demonstrating encouraging results.

Methods and Results—In a clinical trial with minimal exclusion criteria, we randomly assigned 3002 patients to treatment with sirolimus- and probucol-eluting stents versus zotarolimus-eluting stents. The trial was designed to demonstrate noninferiority of the sirolimus- and probucol-eluting stents. The primary end point was the combined incidence of cardiac death, target-vessel–related myocardial infarction, or target-lesion revascularization at 1-year follow-up. Follow-up angiography was scheduled at 6 to 8 months.

The sirolimus- and probucol-eluting stent was noninferior to the zotarolimus-eluting stent in terms of occurrence of the primary end point (13.1% versus 13.5%, respectively, \( P_{\text{noninferiority}} = 0.006; \) hazard ratio = 0.97, 95% confidence interval, 0.78 to 1.19; \( P_{\text{superiority}} = 0.74 \)). The incidence of definite/probable stent thrombosis was low in both groups (1.1% versus 1.2%, respectively; hazard ratio = 0.91 [95% confidence interval, 0.45 to 1.84], \( P = 0.80 \)). With regard to angiographic efficacy, there were no differences between the sirolimus- and probucol-eluting stent and the zotarolimus-eluting stent in terms of either in-segment binary angiographic restenosis (13.3% versus 13.4% respectively; \( P = 0.95 \)) or in-stent late luminal loss (0.31 ± 0.58 mm versus 0.29 ± 0.56 mm, respectively; \( P = 0.46 \)).

Conclusion—In this large-scale study powered for clinical end points, a polymer-free sirolimus- and probucol-eluting stent was noninferior to a new generation durable polymer-based zotarolimus-eluting stent out to 12 months.

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier NCT 00598533.

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Key Words: drug-eluting stents ■ probucol ■ sirolimus ■ randomized clinical trial ■ zotarolimus

Numerous pathological studies have identified persistent inflammatory response to nonerodable polymer coatings as a key causal factor in delayed arterial healing after drug-eluting stent implantation.\(^1\)\(^2\) However, because modulation of drug-release kinetics is a crucial factor in the determination of the antirestenotic efficacy of drug-eluting stent (DES) platforms, the elimination or modification of durable polymer coatings has proved difficult to achieve without compromise in antirestenotic efficacy.\(^2\)\(^3\)

Clinical Perspective on p 632

The new generation zotarolimus-eluting stent (Resolute, Medtronic Cardiovascular, Santa Clara, CA) represents a potential forward step in drug-eluting stent therapy. A novel...
3-component durable polymer combines hydrophilic surface elements with a hydrophobic core and offers potentially improved biocompatibility with enhanced drug-release kinetics. Initial studies demonstrated high antirestenotic efficacy with a favorable safety profile out to 3 years, and a recent large-scale clinical trial demonstrated clinical outcomes comparable to the everolimus-eluting Xience stent. Polymer-free drug-eluting stents represent an alternative approach to improve DES biocompatibility. In the setting of the industry-independent Intracoronary Stenting and Angiographic Results (ISAR) stent project, we developed a polymer-free dual-drug sirolimus- and probucol-eluting stent using a commercially available microporous metal stent backbone (Yukon, Translumina, Hechingen, Germany). In an earlier randomized trial the sirolimus- and probucol-eluting stent demonstrated high angiographic antirestenotic efficacy, comparable to that of the sirolimus-eluting Cypher stent and superior to that of the zotarolimus-eluting Endeavor stent. In the current study, we compared the efficacy and safety of the sirolimus- and probucol-eluting stent to that of the new generation zotarolimus-eluting stent in a large-scale randomized trial powered for clinical end points.

Methods

Study Population, Device Description, and Trial Protocol

Between February 2008 and August 2009, patients >18 years of age with ischemic symptoms or evidence of myocardial ischemia (inducible or spontaneous) in the presence of ≥50% de novo stenosis located in native coronary vessels were considered eligible provided that written informed consent by the patient or her/his legally authorized representative for participation in the study was obtained. Patients with a target lesion located in the left main stem, cardiogenic shock, malignancies, or other comorbid conditions with life expectancy <12 months or that may result in protocol noncompliance, known allergy to the study medications (probucol, sirolimus, zotarolimus) or pregnancy (present, suspected, or planned) were considered ineligible for the study. The study was conducted in accordance with the provisions of the Declaration of Helsinki and with the International Conference on Harmonization of Good Clinical Practices. The trial protocol was approved by the institutional ethics committee of the 2 participating centers: Deutsches Herzzentrum and 1. Medizinische Klinik, Klinikum rechts der Isar, both in Munich, Germany.

In each participating center, allocation to treatment was made by means of sealed opaque envelopes containing a computer-generated sequence; randomization was performed immediately after crossing the lesion with a guide wire. Patients who met all of the inclusion criteria and none of the exclusion criteria were randomized in the order that they qualified. Randomization was stratified only according to participating center. Balance was achieved between groups using randomly permuted blocks. Patients were assigned to receive polymer-free sirolimus- and probucol-eluting stents or permanent polymer zotarolimus-eluting stents (Resolute, Medtronic Cardiovascular) in a 2:1 allocation. Both treatment groups were studied concurrently. Time zero was defined as the time of randomization, and at this time point patients were considered enrolled in the study and eligible for the final intention-to-treat analysis. The same randomly assigned stent had to be implanted in all lesions in those patients who required stenting in multiple lesions. The use of >1 stent per lesion was also allowed.

The polymer-free stent platform consists of a premounted, sandblasted, 316L stainless steel microporous stent that is coated on site with a mixture of sirolimus, probucol, and shellac resin (a biocompatible resin widely used in the coating of medical tablets). A detailed description for creating the micropores and its rationale, the specifics of the coating process, and the sirolimus- and probucol-release profile of the platform have been reported previously. Description of stent platforms and elution characteristics of the zotarolimus-eluting stent are reported elsewhere. The polymer-free sirolimus- and probucol-eluting stent was available in diameters of 2.0, 2.5, 3.0, and 3.5 mm and lengths of 8, 12, 18, 23, and 25 mm for each diameter. The zotarolimus-eluting stent was available in diameters of 2.25, 2.5, 2.75, 3.0, 3.5, and 4.0 mm and lengths of 8 and 14 mm (for stent diameters ≤2.75 mm), 9 and 15 mm (for stent diameters ≥3.00 mm), and 12, 18, 24, and 30 mm for all diameters.

An oral loading dose of 600-mg clopidogrel was administered to all patients at least 2 hours before the intervention, regardless of whether the patient was taking clopidogrel before being admitted. During the procedure, patients were given intravenous aspirin, heparin, or bivalirudin; glycoprotein IIb/IIIa inhibitor usage was at the discretion of the operators. After the intervention, all patients, irrespective of treatment allocation, were prescribed 200 mg/d aspirin indefinitely, clopidogrel 150 mg for the first 3 days (or until discharge) followed by 75 mg/d for at least 6 months and other cardiac medications according to the judgment of the patient’s physician (eg, β-blockers, angiotensin-converting enzyme inhibitors, or statins). After enrollment, patients remained in hospital for at least 48 hours. Blood samples were drawn every 8 hours for the first 24 hours after randomization and daily afterward for the determination of myocardial injury markers. Daily recording of ECG tracings was also performed until discharge. All patients were evaluated at 1 and 12 months by phone or office visit. Repeat coronary angiography was scheduled at 6 to 8 months.

Data Management, End Points, and Definitions

Relevant data were collected and entered into a computer database by specialized personnel of the Clinical Data Management Centre (ISARESEARCH Center, Munich, Germany). All events were adjudicated and classified by an event adjudication committee blinded to the treatment groups. All events were reported to the Data Safety and Monitoring Board, which monitored the overall rate of events in the study. Baseline, postprocedural, and follow-up coronary angiograms were digitally recorded and assessed off-line in the quantitative angiographic core laboratory (ISARESEARCH Center, Munich, Germany) with an automated edge-detection system (CMS version 7.1, Medis Medical Imaging Systems) by 2 independent experienced operators unaware of the treatment allocation. Measurements were performed on cineangiograms recorded after the intracoronary administration of nitroglycerine using the same single worst-view projection at all times. The contrast-filled nontapered catheter tip was used for calibration. Quantitative analysis was performed on both the in-stent and in-segment area (including the stented segment, as well as both 5-mm margins proximal and distal to the stent). Intra- and interobserver variability was calculated at 0.09±0.07 mm and 0.08±0.06 mm, respectively, for the measurement of vessel size. Qualitative morphological lesion characteristics were characterized by standard criteria.

The primary end point of the study was the device-oriented composite of cardiac death, myocardial infarction related to the target vessel, or target lesion revascularization at 12 months post index intervention. Secondary end points were all-cause mortality, incidence of definite/probable stent thrombosis (by Academic Research Consortium definition), in-segment binary restenosis at follow-up angiography, and in-stent late lumen loss (defined as the difference between the minimal luminal diameter at the end of the procedure and the minimal luminal diameter at follow-up angiography). Cardiac death was defined as death due to any of the following: acute myocardial infarction; cardiac perforation/pericardial tamponade; arrhythmia or conduction abnormality; stroke within 30 days of the procedure or stroke suspected of being related to the procedure; death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery; or any death in which a cardiac cause cannot be excluded. Spontaneous myocardial infarction was defined as any creatine kinase MB or troponin increase with or without the development of Q waves on ECG.
Details relating to the adjudication of myocardial infarction related to percutaneous intervention or to bypass surgery are as reported previously in detail. Target lesion revascularization was defined as any ischemia-driven repeat percutaneous coronary intervention of the target lesion or bypass surgery of the target vessel. Ischemia-driven was defined by diameter stenosis ≥50% (on in-segment quantitative angiographic analysis) at follow-up angiography and positive functional study corresponding to the area served by the target lesion or ischemic symptoms and ECG changes at rest referable to the target lesion; or diameter stenosis ≥70% at follow-up angiography in the absence of documented clinical or functional ischemia. In patients with multilesion intervention target-lesion revascularization was defined as a reintervention in at least 1 of the lesions treated during the index procedure.

Statistical Analysis
The objective of the study was to assess the noninferiority of the sirolimus- and probucol-eluting stent compared with the polymer-based zotarolimus-eluting stent. The null hypothesis was that the sirolimus- and probucol-eluting stents were inferior to the polymer-based zotarolimus-eluting stent. Sample size calculation was based on an assumed incidence of the primary composite end point of 10% in both groups. The chosen margin of noninferiority was 3%, which was based on the assumption that any absolute difference in the primary end point <3% was considered to be of no clinical relevance. This threshold is in keeping with that used in recent drug-eluting stent comparative efficacy studies8,14,15 and allows for preservation of 80% of the reduction in the incidence of the primary end point observed previously with current available drug-eluting stents compared to bare-metal stents.16,17 With a power of 80%, a 1-sided α-level of 0.05, and a randomization sequence of 2:1 it was estimated that 2783 patients (1855 receiving sirolimus- and probucol-eluting stents and 928 receiving zotarolimus-eluting stents) were needed to show the noninferiority of the sirolimus- and probucol-eluting stent. To account for possible losses to follow-up, it was planned to enroll a total of 3000 patients. Sample size calculation was performed with nQuery Advisor (Statistical Solutions, Cork, Ireland) according to the method described by O’Brien and Muller.18

Continuous data are presented as mean (SD) or median 25th–75th percentiles. Categorical data are presented as counts or proportions (%). Data distribution was tested for normality using the Kolmogorov-Smirnov test for goodness of fit. For patient level data differences between groups were checked for significance using generalized estimating equations for nonnormally distributed data in order to address intrapatient correlation in patients who underwent multilesion intervention.19 The noninferiority hypothesis relative to the primary end point was tested with EquivTest (Statistical Solutions) according to the methods described by Hauck and Anderson.20 Noninferiority was considered to be demonstrated if the upper 1-sided 95% confidence interval (CI) surrounding the difference between the test treatment and the standard treatment was lower than the prespecified threshold. After the determination of noninferiority, we performed standard superiority testing including calculation of 95% CIs for relative risk with a 2-tailed P value <0.05 considered statistically significant.

Event-free survival was assessed using the methods of Kaplan–
end points was planned to be performed on an intention-to-treat basis. Although there are alternative opinions preferring a per protocol analysis in trials with a noninferiority design, in view of the absence of crossover, this issue is of no relevance to the current study. Analysis of the primary outcome was also performed for prespecified subsets of interest: old and young patients (above and at or below the median age), men and women, diabetic and nondiabetic patients, small and large vessels (below and at or above the median value). Interaction between treatment effect and these covariates was assessed with Cox proportional hazards models. Statistical software S-PLUS, version 4.5 (S-PLUS, Insightful Corp, Seattle, WA) was used for analysis.

## Results

### Patients

A total of 3002 patients were enrolled and randomized to receive either polymer-free sirolimus- and probucol-eluting (n=2002) or permanent polymer zotarolimus-eluting (n=1000) stents (see Figure 1). A total of 2227 patients were enrolled at Deutsches Herzzentrum, with 775 patients at 1. Medizinische Klinik, Klinikum rechts der Isar. As shown in Table 1, the groups were well matched in terms of baseline patient characteristics. The total number of treated lesions was 4391 (sirolimus- and probucol-eluting stent, n=2912; zotarolimus-eluting stent, n=1479). More than one lesion was treated in 35.7% of patients in the sirolimus- and probucol-eluting stent group versus 37.8% in the zotarolimus-eluting group (P=0.26). Baseline lesion and procedural characteristics were also similar between the 2 groups (Table 2), with the exception of minimal luminal diameter post procedure (P=0.04) and total stent length (P=0.01), both of which were marginally higher in the zotarolimus-eluting stent group. During the procedure, 2611 patients (87.0%) were

### Table 2. Angiographic and Procedural Characteristics

<table>
<thead>
<tr>
<th>Sirolimus- and Probucol-Eluting Stent (n=2912)</th>
<th>Zotarolimus-Eluting Stent (n=1479)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target vessel</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Left anterior descending vessels</td>
<td>1315 (45.2)</td>
<td>666 (45.0)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>711 (24.4)</td>
<td>386 (26.1)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>886 (30.4)</td>
<td>427 (28.9)</td>
</tr>
<tr>
<td>Chronic total occlusion</td>
<td>174 (6.0)</td>
<td>76 (5.1)</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>798 (27.4)</td>
<td>427 (28.9)</td>
</tr>
<tr>
<td>Ostial</td>
<td>583 (20.0)</td>
<td>305 (20.0)</td>
</tr>
<tr>
<td>Complex morphology, B2/C</td>
<td>2164 (74.3)</td>
<td>1088 (73.6)</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>16.4 ± 9.6</td>
<td>16.9 ± 10.0</td>
</tr>
<tr>
<td>Vessel size, mm</td>
<td>2.78 ± 0.50</td>
<td>2.80 ± 0.50</td>
</tr>
<tr>
<td>Minimal lumen diameter, pre, mm</td>
<td>0.91 ± 0.50</td>
<td>0.90 ± 0.50</td>
</tr>
<tr>
<td>Balloon diameter, mm</td>
<td>3.07 ± 0.52</td>
<td>3.08 ± 0.53</td>
</tr>
<tr>
<td>Balloon pressure, max, atm</td>
<td>15.6 ± 3.2</td>
<td>15.4 ± 3.2</td>
</tr>
<tr>
<td>Minimal lumen diameter, post, mm</td>
<td>2.54 ± 0.48</td>
<td>2.58 ± 0.49</td>
</tr>
<tr>
<td>Stented length, mm</td>
<td>25.9 ± 12.2</td>
<td>26.8 ± 12.4</td>
</tr>
<tr>
<td>% Diameter stenosis, post</td>
<td>12.1 ± 7.4</td>
<td>11.7 ± 8.2</td>
</tr>
</tbody>
</table>

Data shown as mean ± SD or n (%). B2/C indicates complex lesion morphology as assessed by American Heart Association/American College of Cardiology criteria.

### Table 3. Clinical Results at 1 Year

<table>
<thead>
<tr>
<th>Sirolimus- and Probucol-Eluting Stent (n=2002)</th>
<th>Zotarolimus-Eluting Stent (n=1000)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device-oriented outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac death, MI related to target vessel, or target lesion revascularization</td>
<td>258 (13.1)</td>
<td>132 (13.5)</td>
<td>0.97 (0.78–1.19)</td>
</tr>
<tr>
<td>Cardiac death or MI related to target vessel</td>
<td>81 (4.1)</td>
<td>43 (4.3)</td>
<td>0.94 (0.65–1.35)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>37 (1.9)</td>
<td>18 (1.8)</td>
<td>1.02 (0.58–1.80)</td>
</tr>
<tr>
<td>MI related to target vessel</td>
<td>49 (2.4)</td>
<td>28 (2.8)</td>
<td>0.87 (0.55–1.39)</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>200 (10.3)</td>
<td>100 (10.4)</td>
<td>0.99 (0.78–1.26)</td>
</tr>
<tr>
<td>Patient-oriented outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>71 (3.6)</td>
<td>47 (4.7)</td>
<td>0.75 (0.52–1.08)</td>
</tr>
<tr>
<td>Any MI</td>
<td>78 (3.9)</td>
<td>38 (3.8)</td>
<td>1.02 (0.69–1.51)</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>289 (14.9)</td>
<td>149 (15.4)</td>
<td>0.95 (0.78–1.16)</td>
</tr>
<tr>
<td>Nontarget vessel revascularization</td>
<td>245 (12.5)</td>
<td>117 (12.1)</td>
<td>1.04 (0.83–1.29)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>10 (0.5)</td>
<td>4 (0.4)</td>
<td>1.24 (0.39–3.97)</td>
</tr>
<tr>
<td>Probable</td>
<td>12 (0.6)</td>
<td>8 (0.8)</td>
<td>0.75 (0.31–1.83)</td>
</tr>
<tr>
<td>Possible</td>
<td>11 (0.6)</td>
<td>3 (0.3)</td>
<td>1.82 (0.51–6.52)</td>
</tr>
<tr>
<td>Definite or probable</td>
<td>22 (1.1)</td>
<td>12 (1.2)</td>
<td>0.91 (0.45–1.84)</td>
</tr>
</tbody>
</table>

Data shown as n (%) by Kaplan–Meier analysis; hazard ratios and P values were calculated from Cox proportional hazard methods. CI indicates confidence interval; MI, myocardial infarction.
treated with heparin, with 391 patients (13.0%) receiving bivalirudin.

**Clinical Outcomes**

One-year follow-up was complete on all but 57 patients (1.9%), without any significant difference between the 2 study groups (43 patients [2.1%] in the sirolimus- and probucol-eluting stent group and 14 patients [1.4%] in the zotarolimus-eluting stent group, \( P = 0.16 \)). In patients without 1-year follow-up, median duration of follow-up was 6.0 [0.6 to 7.7] months.

The results of 1-year follow-up are shown in Table 3. With regard to the primary end point of cardiac death, myocardial infarction related to target vessel and target lesion revascularization, the sirolimus- and probucol-eluting stent was noninferior to the zotarolimus-eluting stent (13.1% versus 13.5% respectively, \( P_{\text{noninferiority}} = 0.006 \); hazard ratio = 0.97, 95% CI, 0.78 to 1.19; \( P_{\text{superiority}} = 0.74 \)). Figure 2A shows survival analysis curves for the occurrence of the primary end point.

With regard to clinical antirestenotic efficacy, the rate of target lesion revascularization was also similar between the sirolimus- and probucol-eluting stent and the zotarolimus-eluting stent (10.3% versus 10.4%, respectively; hazard ratio = 0.99 [95% CI, 0.78 to 1.26]; \( P = 0.94 \); Figure 2B).

In terms of safety end points, the sirolimus- and probucol-eluting stent in comparison with the zotarolimus-eluting stent showed similar rates of all-cause mortality (3.6% versus 4.7%, respectively; hazard ratio = 0.75 [95% CI, 0.52 to 1.08]; \( P = 0.13 \)), cardiac death or myocardial infarction related to target vessel (4.1% versus 4.3%, respectively; hazard ratio = 0.94 [95% CI, 0.65 to 1.36]; \( P = 0.72 \)), and definite/probable stent thrombosis (1.1% versus 1.2% respectively; hazard ratio = 0.91 [95% CI, 0.45 to 1.84]; \( P = 0.80 \); Figure 3). Early definite stent thrombosis occurred at a rate of 0.4% in both treatment groups (\( P > 0.99 \)).

There was no evidence of interaction between treatment effect and membership to each of the prespecified subgroups of age, sex, diabetes mellitus, and vessel size (Figure 4). In
addition, there was no interaction between outcome and enrolling center (P=0.38) or periprocedural antithrombotic therapy received (P=0.47).

### Angiographic Surveillance

Follow-up angiography at 6 to 8 months was performed in 76.3% of patients with no difference in rates of surveillance between the 2 treatment groups (P=0.53). Median time to angiographic follow-up in both groups was 202 days. In terms of angiographic end points, there were no significant differences between the sirolimus- and probucol-eluting stent and the zotarolimus-eluting stent in terms of in-segment binary angiographic restenosis (13.3% versus 13.4%, respectively; P=0.95), in-stent minimum lumen diameter (2.23±0.70 mm versus 2.28±0.68 mm; P=0.07), or in-stent late luminal loss (0.31±0.58 mm versus 0.30±0.56 mm, respectively; P=0.50; Figure 5).

### Discussion

The results of the ISAR-TEST 5 trial demonstrate that in the setting of a large-scale randomized control trial with broad inclusion criteria, polymer-free sirolimus- and probucol-eluting dual-drug stents were not inferior to new generation permanent polymer-based zotarolimus-eluting stents in terms of the occurrence of clinical and angiographic end points. Furthermore, both stent platforms were associated with low and comparable rates of stent thrombosis out to 1 year. This is the first demonstration of clinical efficacy of a novel DES which uses a dual-drug combination and no polymer.

Although the pathogenesis of delayed healing of the stented arterial segment after DES implantation is not fully understood, persistent inflammatory response to residue from nonerodable polymer coatings seems to play an important role. In recent years, many efforts have been made to avoid the use of polymers in DES. However, the control of release kinetics of the eluted drug appears to be the crucial step in determination of the antirestenotic efficacy of DES platforms. In this respect, the elimination or modification of durable polymer coatings has proved difficult to achieve without compromising antirestenotic efficacy.

The zotarolimus-eluting Resolute stent is based on the same stent backbone as the Endeavor stent and is coated with zotarolimus at a similar concentration. The key difference in comparison with the earlier Endeavor stent is its polymer coating, a mixture composed of 3 different hydrophilic and hydrophobic polymeric elements. This platform has demonstrated high biocompatibility, superior drug-release kinetics, and enhanced antirestenotic efficacy in comparison with its predecessor. Recently, it was demonstrated to be noninferior to the everolimus-eluting Xience stent in a large-scale randomized trial. The current study provides further encouraging data supporting high clinical safety and efficacy outcomes. In particular, in comparison with the Resolute All Comers study, the safety composite of cardiac death and myocardial infarction related to the target vessel was similar in both studies whereas the rate of definite stent thrombosis

**Figure 3.** Time-to-event curve for incidence of definite or probable stent thrombosis. Hazard ratios and P values are derived from Cox proportional hazard methods. HR indicates hazard ratio; CI, confidence interval.

**Figure 4.** Treatment effect for sirolimus- and probucol-eluting versus zotarolimus-eluting stents for the primary end point in the overall study population and in prespecified subgroups. Observed differences in proportions between sirolimus- and probucol-eluting stent and zotarolimus-eluting stents are displayed with upper 95% CIs according to the methods of Hauck-Anderson; P values for interaction are derived from Cox proportional hazard methods; the null difference margin is shown by a red dashed line; the boundary of noninferiority is shown by the black dashed line. CI indicates confidence interval.
was lower in the current study (at 0.4% after 12 months). Furthermore, in patients undergoing angiographic surveillance, the mean late loss seen in our study of 0.30 mm in the Resolute group is comparable to that of 0.27 mm (Resolute All Comers trial9) and 0.30 mm (Resolute US registry23) recently reported with this stent in nonselected patient cohorts.

The stent backbone used in the polymer-free sirolimus- and probucol-eluting dual-drug stent described in this study is a commercially available thin-strut stainless steel platform with surface micropores that facilitate drug-loading and may promote more rapid endothelial overgrowth.24 The availability of on-site coating technology has enabled the investigation of a variety of drug and polymer coatings in preclinical studies11,12,25 and clinical trials.9,10,13,26,27 The current device iteration is coated with a mixture of sirolimus and probucol. Probucol is a potent antioxidant, which has proven effects in reducing restenosis and promoting endothelialization.28–30 In addition, its high lipophilicity facilitates retardation of sirolimus release in a manner similar to that achieved by polymer coating. Prior studies confirmed an optimal drug-release profile without recourse to polymer coating, and an earlier randomized clinical trial, ISAR-TEST 2, demonstrated a device efficacy comparable to that of the sirolimus-eluting Cypher stent and superior to that of the zotarolimus-eluting Endeavor stent in a study powered for an angiographic end point.9,10 The current report extends the encouraging results seen with this technology to the setting of a large-scale clinical trial powered for clinical end points. The demonstration of excellent clinical outcomes in a broadly inclusive patient population without recourse to durable polymer coatings may represent an important development in DES technology. In particular, the very low rate of definite stent thrombosis at 1 year may be seen as an encouraging safety signal. Nevertheless, the hypothesized benefit of high-efficacy polymer-free DES platforms, particularly in relation to delayed adverse events such as very late stent thrombosis, can only be adjudicated on following long-term follow-up of large numbers of treated patients. Likewise, potential benefits in terms of a requirement for a shorter duration of dual antiplatelet therapy remain to be proven.

Some limitations of the current study should be highlighted. Firstly, although the current trial employed broad inclusion criteria and enrolled a very high proportion of patients who were eligible for inclusion, it should be acknowledged that patients undergoing percutaneous intervention for left main stem stenosis, drug-eluting stent restenosis, and cardiogenic shock, who were triaged for enrolment in concurrent clinical trials, are not represented in the current study. Secondly, angiographic surveillance was scheduled for all patients in the trial protocol. This feature is recognized to increase the absolute rates of repeat revascularization though relative differences between study arms are unlikely to be impacted.31 Furthermore, although the proportion of patients with angiographic follow-up is considerable (76%), this rate is somewhat lower than that considered optimal for surveillance angiography.32 Thirdly, there were some differences in the available stent diameter and length between the comparator test groups. This may have contributed to the observed marginal differences in baseline procedural characteristics. Fourthly, in the current study, clopidogrel therapy was maintained for at least 6 months. It should be acknowledged that the optimal duration of such therapy after drug-eluting stent implantation remains unknown and is the subject of a number of ongoing large randomized trials. Finally, we also performed exploratory testing of the noninferiority hypothesis in the prespecified subgroups. Although noninferiority was not demonstrated in certain subgroups, most notably in female patients, at least 2 reasons argue against the relevance of this observation. Firstly, there was no statistical interaction between treatment effect and membership to each of the subgroups. Secondly, none of the subgroups was sufficiently powered for noninferiority testing. For this reason, these observations might be regarded as hypothesis generating at best though they may warrant further investigation in future studies.
In conclusion, polymer-free sirolimus- and probucol-eluting stents were demonstrated to be noninferior to durable polymer-based zotarolimus-eluting stents in terms of 12-month clinical outcomes. Furthermore, both sirolimus- and probucol-eluting stents and zotarolimus-eluting stents showed high clinical and angiographic antirestenotic efficacy and very low rates of stent thrombosis.

**Appendix**

**Study Organization**

**Steering Committee**
A. Kastrati (Chair), J. Mehilli (Principal Investigator), Josef Dirschinger.

**Participating Centers**
Deutsches Herzzentrum, Technische Universität, Munich, Germany, and I. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität, Munich, Germany.

**Data Safety Monitoring Board**
J. Mann (Chair), F. Hoffmann, K. Ulm (biostatistician).

**Clinical Event Adjudication Committee**
D. Hall (Chair)*, G. Ndreppea, D. Poci.

**Data Coordination**

**Sources of Funding**
This was an investigator-initiated industry-independent trial. There was no remuneration for investigators or subjects. Study design and analysis were performed by Deutsches Herzcentrum, Munich. Funding was provided in part by the Bavarian Research Foundation (BFS-ISAR Aktenzeichen AZ: 668/05) and by the European Union FP7 (PRESTIGE 260309). This Institute: R.A. Byrne, S. Pinieck, A. Bergbauer, D. Blersch, S. Hurt, S. Ranftl.

**Disclosures**
The microporous metal stent platform used in the polymer-free DES is produced by Translumina, Hechingen, Germany, which had no input into the study design, conduct, or funding. Dr Kastrati and Dr Schömig hold a patent related to the polymer-free sirolimus and probucol coating. Dr Kastrati reports having received honoraria from Abbott, Biosensors, Biotronik, Cordis, and Medtronic. The remaining authors report no conflicts.

**References**


*Deceased.*
Polymer coatings are a key component of drug-eluting stent technology because they allow tight control of drug-release kinetics and thereby permit effective inhibition of coronary restenosis. However, concerns have long existed about the negative vascular effects of durable polymer, which remains permanently embedded in the vessel wall and has been implicated in delayed arterial healing and late adverse events after stenting. The zotarolimus-eluting (Resolute) stent employs a novel high-biocompatibility polymer composed of hydrophobic and hydrophilic elements and has demonstrated excellent performance in recent clinical trials. We developed a polymer-free drug-eluting stent, which is coated with a mixture of 2 drugs, sirolimus and probucol, and shows high-antirestenotic efficacy. The Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting Versus Zotarolimus-Eluting Stents (ISAR-TEST 5) trial is one of the largest clinical trials involving new-generation drug-eluting stents. In this study with inclusive enrollment criteria and powered for clinical end points, 3002 patients were randomized to receive either polymer-free sirolimus- and probucol-coated or novel polymer-based zotarolimus-eluting stents. The primary finding was that both stents showed high efficacy in prevention of restenosis as well as low rates of stent thrombosis out to 1 year. This represents the first successful translation of polymer-free drug-eluting stent technology based on a combination of drugs to treat a real-life patient population with coronary artery disease.
Steffen Massberg, Robert A. Byrne, Adnan Kastrati, Stefanie Schulz, Jürgen Pache, Jörg Hausleiter, Tareq Ibrahim, Massimiliano Fusaro, Ilka Ott, Albert Schömig, Karl-Ludwig Laugwitz and Julinda Mehilli

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