Clinical Outcomes After Sirolimus-Eluting, Paclitaxel-Eluting, and Bare Metal Stents (from the First Phase of the Prospective Multicenter German DES.DE Registry)

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The prospective multicenter German Drug-Eluting Stent (DES.DE) registry is an observational study to analyze and evaluate the therapeutic principle of the differential drug-eluting stents (sirolimus- and paclitaxel-eluting stents) and bare metal stents under real world conditions in the context of the German healthcare system. The baseline clinical and angiographic characteristics and follow-up events for 1 year were recorded for all enrolled patients. In addition, a health economics assessment was performed at 3, 6, 9, and 12 months after initial stent placement. The composite of death, myocardial infarction, and stroke, defined as major adverse cardiac and cerebrovascular events, and target vessel revascularization were used as the primary objectives. From October 2005 to October 2006, 6,384 patients were enrolled (sirolimus-eluting stents, n = 2,137; paclitaxel-eluting stents, n = 2,740; bare metal stents, n = 485) at 98 Deutsches Drug-Eluting Stent Register sites. With similar baseline clinical and descriptive morphology of coronary artery disease between both drug-eluting stent groups, no differences were present at 1 year of follow-up in the rates of overall mortality (3.8% vs 4.1%), target vessel revascularization (10.4% vs 10.4%), overall stent thrombosis (3.6% vs 3.8%), and major adverse cardiac and cerebrovascular events (8.1% vs 8.0%). Compared with the bare metal stent group, patients treated with drug-eluting stents had significantly lower rates of myocardial infarction (3.2% vs 6.0%; p <0.01), stroke (1.2% vs 2.7%; p <0.05), and target vessel revascularization (10.4% vs 14.9%; p <0.01) without any difference in the stent thrombosis rate (3.7% vs 4.3%; p = 0.57) or mortality rate (4.0% vs 5.2%; p = 0.21). In conclusion, the data generated from the German Drug-Eluting Stent registry revealed no differences between patients receiving a paclitaxel-eluting stent and sirolimus-eluting stent in a "real-world" setting with regard to the clinical outcomes at 1 year. **(Am J Cardiol 2009;104:1362–1369)**

The large prospective multicenter German Drug-Eluting Stent (DES.DE) registry was designed to compare the effects of the paclitaxel-eluting stent (PES; Taxus, Boston Scientific, Natick, Massachusetts), sirolimus-eluting stent (SES; Cypher, Cordis, Miami Lakes, Florida), and various bare metal stents (BMSs) in a "real-world" setting, with respect to the 1-year clinical outcomes and differences in mortality, clinically diagnosed myocardial infarction (MI), target vessel revascularization, stroke, and stent thrombosis.

Methods

The prospective multicenter German DES.DE registry was initiated in October 2005 as an observational registry study by the Deutsche Gesellschaft für Kardiologie (German Cardiac Society), Bundesverband Niedergelassener Kardiologen (German Society of Cardiologists in Private Practice), and Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (The Working Group of Leading Hospital Cardiologists) to analyze and evaluate the therapeutic principle of drug-eluting stents (DESs) in real-world conditions in the context of the German healthcare system. The participating DESs in the DES.DE had to meet certain quality criteria orchestrated and confirmed by the DES.DE steering committee and partly adopted from the European Society of Cardiology percutaneous coronary intervention guideline criteria for DESs.[1] In the first phase of the registry (October

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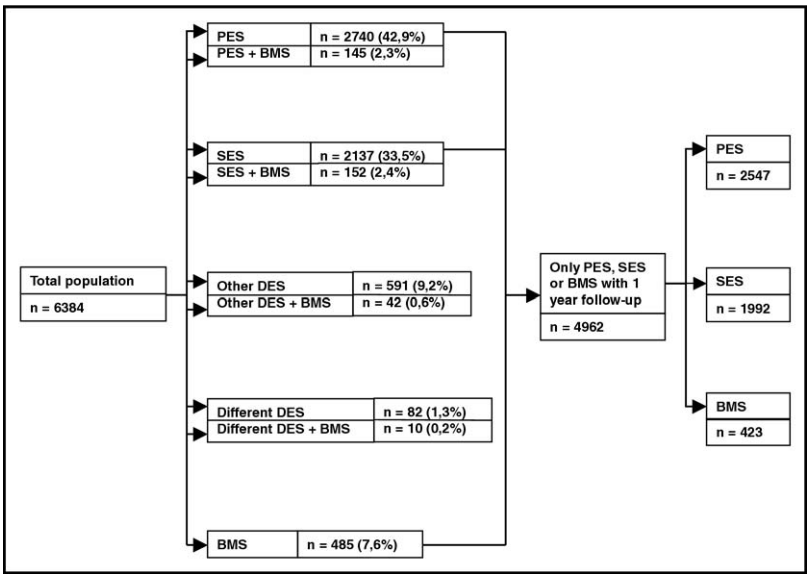

Figure 1. Distribution of total patient population in phase I of DES.DE. Patients receiving either a combination of different stent types or other stents than accepted in phase I were excluded from the present analysis.

Table 1
Baseline demographics of patients receiving paclitaxel-eluting (PES), sirolimus-eluting (SES), or bare metal stent (BMS)

Variable	PES	SES	BMS	p Value	
				PES vs SES	DES vs BMS
Patients (n)	2,740	2137	485		
Men	73.7%	75.7%	73.8%	0.12	0.71
Age ± SD (years)	65.3 ± 10.4	64.7 ± 10.6	67.2 ± 11.0	<0.05	<0.0001
Body mass index (kg/m^2)	27.5	27.3	27.5	<0.01	0.8
Diabetes mellitus	33.7%	28.9%	32.4%	<0.001	0.7
Dietary control	4.5%	4.2%	4.5%	0.68	0.84
Oral hypoglycemic agents	15.5%	14.8%	16.9%	0.49	0.3
Insulin	12.8%	8.9%	9.9%	<0.0001	0.42
Dyslipidemia	79.8%	81.8%	76.8%	0.08	<0.05
Renal insufficiency	12.8%	11.8%	14.3%	0.29	0.21
History of heart failure	15.5%	15.8%	17.7%	0.8	0.24
Hypertension	83.3%	84.4%	83.2%	0.33	0.73
Atrial fibrillation	8.0%	7.5%	13.9%	0.82	<0.0001
Smoker					
Current	21.4%	23.2%	25.4%	0.15	0.13
Previous	51.4%	56.5%	47.0%	<0.001	<0.01
Family history of coronary artery disease	34.0%	38.3%	29.3%	<0.01	<0.01
Previous known myocardial infarction	29.7%	31.2%	25.2%	0.25	<0.05
Previous known PCI	45.5%	45.9%	34.6%	0.75	<0.0001
Previous known CABG	15.1%	13.4%	16.2%	0.09	0.27
Previous known stroke	4.3%	4.4%	3.0%	0.99	0.16
Ejection fraction					
>50%	70.3%	67.8%	65.2%	0.0002	0.06
41–50%	19.2%	18.3%	18.5%		
31–40%	6.8%	10.8%	10.1%		
<30%	3.8%	3.2%	6.2%		
Acute coronary syndrome					
ST-elevated myocardial infarction	11.3%	14.2%	21.5%	<0.0001	<0.0001
Non–ST-elevated myocardial infarction	13.8%	10.8%	21.1%	<0.0001	<0.0001
Unstable angina pectoris	16.7%	14.0%	18.6%	0.15	<0.05
Elevated cardiac markers	27.2%	24.2%	38.0%	<0.05	<0.0001

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

2005 to October 2006), only the 2 Food and Drug Administration-approved DESs, Taxus and Cypher, met the quality criteria of the registry. It was intended to collect data from ≥2,000 Taxus, ≥2,000 Cypher, and ≥500 BMSs at German sites with access to both DESs. To avoid bias in selecting patients for a DES versus a BMS, an attempt was made to identify patients with a BMS to match the baseline characteristics of patients receiving a DES. Patients receiving a BMS had to have met ≥1 of the following criteria: diabetes mellitus, acute coronary syndrome, previous revascularization (either percutaneous coronary intervention or coronary artery bypass grafting) and/or previously diagnosed coronary three-vessel disease. In all cases, the interventional strategy, including choice of stent, use of intravascular ultrasonography, and the choice of periprocedural adjunctive therapy was at the discretion of the responsible physician.

Data were collected using an Internet platform by the Institut für Klinische Kardiovaskuläre Forschung (Institute for Clinical Cardiovascular Research) of the German Cardiac Society. The European Cardiology Audit and Registration Standards (CARDS) standard was adapted for both patient and lesion data. All patients were required to provide written informed consent for processing the data at the Institut für Herzinfarktforschung (Institute of Myocardial Infarction Research Ludwigshafen) and Institut für Klinische Kardiovaskuläre Forschung. The baseline clinical and angiographic characteristics and certain procedural and clinical in-hospital events were recorded for all enrolled patients. Paper-based clinical and health economics follow-up assessments were performed at 3, 6, 9, and 12 months after the initial stent placement, and the data were analyzed at the Institute for Social Medicine, Epidemiology and Health Economics, Charite University Medical Center Berlin. Relevant events were forwarded to the 2 independent critical event committees and adjudicated.

The primary objective in the DES.DE was to evaluate the occurrence of target vessel revascularization and major adverse cardiac and cerebrovascular events, defined as the composite of death (cardiac and noncardiac), MI, and stroke. Death was defined as all causes of mortality. Myocardial infarction was defined as either as ST-elevation MI (ST-elevation of ≥1 mm in ≥2 standard leads or ≥2 mm in ≥2 contiguous precordial leads, or the development of new left bundle branch block on the electrocardiogram) or non–ST-elevation MI (a pathologic increase in cardiac-specific enzymes, with creatinine kinase-MB >1.5 times the normal limits, troponin T or I greater than ninety-ninth percentile of the normal value). target vessel revascularization was defined as a repeat procedure, either percutaneous coronary intervention or coronary artery bypass grafting, in the target vessel. The definitions for major adverse cardiac events and MI were not the standardized ones. In a number of major adverse cardiac events definitions, different types of death (either cardiac or total death rate) and revascularization parameters such as target vessel revascularization have been used. Because the use of different definitions of major adverse cardiac events can cause confusion when comparing rates between trials, the steering committee decided to use only major adverse cardiac and cerebrovascular events as defined in the present report. Routine angiography was not a part of the protocol in DES.DE for any subgroup of patients; therefore, all reinterventions were clinically driven. Stent thrombosis was classified as definitive (presence of angiographic thrombus with complete occlusion), probable (unexplained sudden death within 30 days after stent graft placement or Q-wave myocardial infarction in the distribution of the stented artery), and possible (unexplained death 30 days after percutaneous coronary intervention) according to the definitions proposed by the Academic Research Consortium and was stratified as acute (<24 hours), subacute (24 hours to 30 days), late (1 to 12 months), and very late (>12 months).[2] The details of the health economics assessment will be reported separately.

Table 2
Descriptive morphology of coronary artery disease in patients receiving paclitaxel-eluting (PES), sirolimus-eluting (SES), or bare metal stent (BMS)

Variable	PES	SES	BMS	p Value	
				PES vs SES	DES vs BMS
Vessel disease				0.82	0.004
Single	28.2%	28.7%	24.3%		
Double	33.2%	32.6%	29.7%		
Triple	37.3%	38.1%	45.6%		
Target coronary artery				0.95	<0.0001
Left anterior descending	48.9%	48.0%	28.3%		
Left circumflex	21.9%	22.1%	28.7%		
Right	26.3%	27.1%	42.6%		
Left main	2.9%	2.9%	0.6%		
Bypass graft	5.0%	4.8%	8.0%		
AHA/ACC lesion score				0.0004	<0.0001
A	11.2%	14.8%	19.6%		
B	61.5%	57.3%	53.6%		
C	27.3%	27.9%	26.8%		
TIMI flow				<0.001	<0.0001
0	11.9%	12.6%	18.6%		
1	11.0%	7.4%	8.5%		
2	22.7%	21.0%	25.4%		
3	54.4%	59.0%	47.5%		
Chronic total occlusion	3.3%	3.3%	0.9%	0.94	<0.01
In-stent restenosis	14.3%	19.4%	2.1%	<0.0001	<0.0001
Bifurcation	13.8%	16.6%	11.4%	<0.01	<0.05

AHA/ACC = American Heart Association/American College of Cardiology; TIMI = Thrombolysis In Myocardial Infarction.

Statistical analysis was performed using the Statistical Analysis Systems statistical package, version 9.1 (SAS Institute, Cary, North Carolina). The demographic characteristics, pre-existing risk factors, procedure-related variables, and 1-year outcomes were summarized using the mean value with the SD for continuous variables and frequencies and percentages for categorical variables. Differences in the baseline, procedural, and angiographic characteristics, in-hospital and follow-up data were compared between the PESs and SESs and between DESs and BMSs using the chi-square test, and continuous variables were compared using the Wilcoxon rank sum test. The 1-year event-free survival rates for major adverse cardiac and cerebrovascular events and target vessel revascularization were demonstrated using the Kaplan-Meier curves and were compared using the log-rank test. p Values <0.05 were considered

Table 3
Procedural characteristics of patients receiving paclitaxel-eluting (PES), sirolimus-eluting (SES), or bare metal stent (BMS)

Variable	PES	SES	BMS	p Value	
				PES vs SES	DES vs BMS
Patients (n)	2,740	2137	485		
Total lesions (n)	2,953	2,377	538	<0.01	<0.0001
Stents implanted	98.7%	98.5%	98.9%	0.41	0.53
Total implanted stents (n)	3,486	2,755	652	<0.01	<0.0001
Stenosis degree ± SD	87.3 ± 10.8%	87.0 ± 11.2%	89.1 ± 9.8%	0.49	<0.0001
Lesion diameter (mm)	3.0 ± 0.8	3.1 ± 0.8	3.2 ± 0.9	<0.05	<0.0001
Lesion length (mm)	19 ± 12	20 ± 13	16 ± 10	<0.001	<0.0001
Stent diameter (mm)	2.9 ± 0.4	3.0 ± 0.4	3.2 ± 0.5	<0.05	<0.0001
Stent length (mm)	19 ± 7	20 ± 7	16 ± 6	<0.0001	<0.0001
Device use					
Intravascular ultrasonography	1.3%	1.9%	0%	0.10	<0.05
Rotablation	0.5%	0.4%	0.2%	0.52	0.32
Cutting balloon	0.5%	0.2%	0%	0.05	0.18
Direct stenting	39.5%	46.2%	45.7%	<0.0001	0.11
Residual stenosis ± SD	1.3 ± 7.0%	2.5 ± 8.7%	1.6 ± 6.9%	<0.0001	0.29
Postprocedural TIMI class III	97.5%	98.4%	96.6%	<0.05	0.06
Lesion complication					
Abrupt closure	0.2%	0.2%	0%	0.73	0.31
Side-branch occlusion	0.4%	0%	0%	<0.01	0.27
Persistent flow reduction	0.1%	0.2%	0.2%	0.76	0.84
Clopidogrel loading dose (mg)					
300	42.9%	27.3%	35.8%	<0.0001	0.85
600	42.8%	60.4%	53.5%	<0.0001	0.42
Glycoprotein IIb/IIIa antagonist	14.5%	16.9%	25.2%	<0.05	<0.0001

Abbreviation as in Table 2.

significant and were the results of 2-tailed tests. Stepwise multivariate logistic regression analysis was used to estimate the adjusted odds ratios with 95% confidence intervals for major adverse cardiac and cerebrovascular events and target vessel revascularization outcomes by DES treatment strategy. Because of the lack of differences in the outcomes between the PESs and SESs and the small number of BMS patients, we decided to perform a multivariate analysis just for the overall DES group. The variables entered into the multivariate models for major adverse cardiac and cerebrovascular events were female gender, age >75 years, body mass index >25 kg/m^2, diabetes mellitus, hypertension, dyslipidemia, smoker, family history of coronary artery disease, renal insufficiency, previous percutaneous coronary intervention, previous MI, previous coronary arterial bypass grafting, previous stroke, peripheral arterial vascular disease, ST-elevation MI, non–ST-elevation MI, unstable angina pectoris, heart failure, moderate to severe impairment of left ventricular ejection fraction (<40%), triple-vessel disease, and cardiogenic shock. Assessing the multivariate models for target vessel revascularization, additional variables such as bifurcation lesion, in-stent restenosis, chronic total occlusion, vessel diameter <3 mm, long lesion (>15 mm), and type C lesion were used.

Results

From October 2005 and October 2006, 6,384 patients were enrolled at 98 sites in the prospective DES.DE. The present analysis included 2,740 patients (42.9%) who received only a PES, 2,137 (33.5%) who received only a SES, and 485 patients (7.6%) who received only a BMS, constituting 84% of the entire study cohort in phase I. The remaining 16% of patients received either a combination of PES, SES, and/or BMS, or a DES other than SES or PES and were excluded from the present analysis. The study population and baseline characteristics are presented in Figure 1 and listed in Table 1.

Overall, approximately 1/2 of the patients in all 3 groups were admitted with an acute coronary syndrome. Although SESs were used preferentially in the setting of ST-elevation MI (14.2% vs 11.3%, p <0.0001) and PESs were used preferentially for non–ST-elevation MI (13.8% vs 10.8%; p <0.0001), difference in the outcomes was not significant. More DESs were implanted during complex procedures. Thus, of 174 patients with chronic total occlusion, 169 (97.1%) received a DES and 5 (2.9%) a BMS. Similarly, 788 (92.8%) of 849 patients with a bifurcation lesion and 873 (98.8%) of 884 with in-stent restenosis received a DES. Lesions in the left main coronary artery were treated predominantly with a DES (2.9% vs 0.6%; p <0.01); of the 157 patients with significant left main coronary artery stenosis, 154 (98.1) received a DES and 3 (1.9%) a BMS (Table 2).

Procedural information is listed in Table 3. Overall, 6,893 stents were implanted for 5,868 lesions in 5,342 patients (1.29/patient and 1.17/lesion), with a procedural success rate of 97%. Stents were deployed in >98% of the cases. The numbers of stents per patient and per lesion were equally distributed, with 1.38 stents/patient and 1.18 stents/lesion in the PES group, 1.29 stents/patient and 1.16 stents/lesion in the SES group, and 1.34 stents/patient and 1.21

Table 4
In-hospital and 1-year clinical follow-up of patients receiving paclitaxel-eluting (PES), sirolimus-eluting (SES), or bare metal stent (BMS)

Variable	PES	SES	BMS	p Value	
				PES vs SES	DES vs BMS
In-hospital follow-up					
Death	0.7%	0.2%	0.8%	<0.05	0.32
Myocardial infarction	1.4%	0.9%	1.7%	0.13	0.32
Stroke	0.6%	0.3%	0.6%	0.09	0.65
Major adverse cardiac and cerebrovascular events	2.5%	1.4%	2.5%	<0.01	0.43
Repeat urgent revascularization					
Percutaneous coronary intervention	0.7%	0.7%	1.0%	0.87	0.37
Coronary artery bypass grafting	0%	0.1%	0%	0.42	0.58
Repeat elective revascularization					
Percutaneous coronary intervention	2.3%	2.2%	3.9%	0.81	<0.05
Coronary artery bypass grafting	0.7%	0.5%	1.6%	0.31	<0.01
Renal failure	1.5%	1.2%	1.2%	0.46	0.82
Severe bleeding complications	0.6%	0.4%	1.1%	0.28	0.12
Hospitalization >3 days	30.8%	33.7%	41.0%	<0.05	<0.0001
Aspirin + clopidogrel + oral anticoagulation	2.6%	2.9%	2.9%	0.57	0.82
1-Year follow-up					
Clinical follow-up	93.6%	93.4%	87.9%	0.85	<0.0001
Death	4.1%	3.8%	5.2%	0.58	0.21
Myocardial infarction	3.2%	3.2%	6.0%	0.99	<0.01
Stroke	1.0%	1.5%	2.7%	0.19	<0.05
Major adverse cardiac and cerebrovascular events	8.0%	8.1%	13.0%	0.97	<0.001
Target vessel revascularization	10.4%	10.4%	14.9%	0.82	<0.01
Overall stent thrombosis	3.8%	3.6%	4.3%	0.78	0.57
Definitive	0.7%	0.6%	0.7%	0.62	0.8
Aspirin	94.7%	93.8%	91.2%	0.24	<0.05
Clopidogrel	57.9%	53.1%	37.0%	<0.01	<0.0001
Oral anticoagulation	7.5%	8.7%	12.9%	0.2	<0.01
Bleeding					
Major	1.3%	1.1%	0.5%	0.53	0.25
Minor	50.4%	47.7%	39.0%	0.08	<0.001

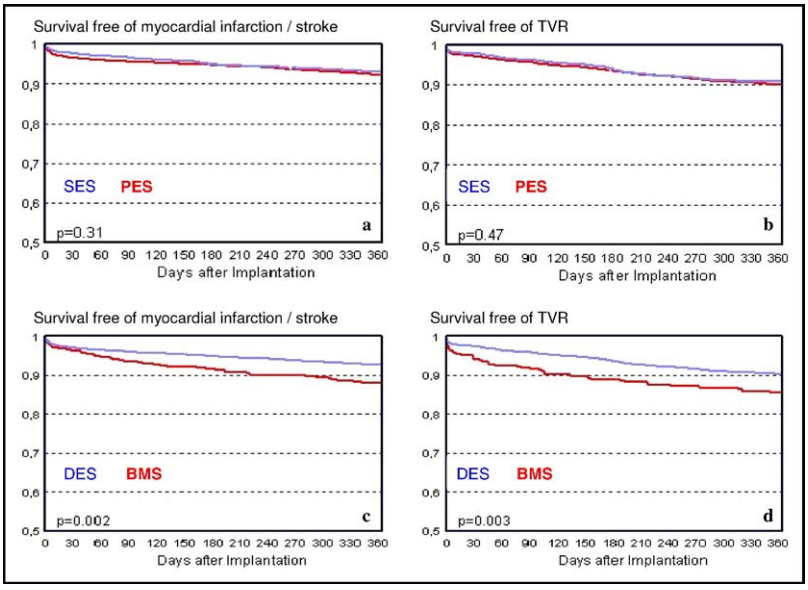

Figure 2. Overall 1-year Kaplan-Meier curves for composite of MI/stroke and target vessel revascularization between *(a,b)* SES and PES and *(c,d)* composite of DES and BMS. No significant difference were found between the 2 DESs. In contrast, the differences between the overall DES group and BMS group were significant.

stents/lesion in the BMS group. Direct stenting was performed in <1/2 of the DES and BMS population (42.5% and 45.7%, respectively), with no significant differences among the groups. SESs were usually longer than the PESs (20 ± 7 mm vs 19 ± 7 mm; p <0.0001), but both were longer than the BMSs (16 ± 6 mm; p <0.0001). In contrast,

Table 5
Multivariate predictors of major adverse cardiac and cerebrovascular events and target vessel revascularization in overall drug-eluting stent (DES) group during follow-up

Variable	OR	95% CI	p
Major adverse cardiac and cerebrovascular events			
Age >75 years	1.767	1.250–2.498	0.0013
Smoker	1.568	1.100–2.237	0.0130
Renal insufficiency	1.942	1.321–2.855	0.0007
Previous known coronary artery bypass grafting	1.492	1.023–2.174	0.0375
Peripheral arterial vascular disease	1.866	1.238–2.811	0.0029
ST-elevated myocardial infarction	2.025	1.449–2.831	<0.0001
Impaired left ventricular function (<40%)	1.926	1.318–2.934	0.0016
Heart failure	1.680	1.190–2.373	0.0032
Target vessel revascularization			
Previous known percutaneous coronary intervention	1.669	1.267–2.198	0.0003
ST-elevated myocardial infarction	1.688	1.211–2.352	0.0020
Unstable angina pectoris	1.640	1.112–2.418	0.0125
Impaired left ventricular function (<40%)	1.628	1.208–2.246	0.0008
Type C lesion	1.388	1.069–1.803	0.0139
Vessel diameter <3 mm	1.316	1.026–1.689	0.0306

CI = confidence interval; OR = odds ratio.

the diameter was, on average, smaller in the PES group than in the SES group (2.9 ± 0.4 mm vs 3.0 ± 0.4 mm; p <0.05). Compared to BMSs (3.2 ± 0.5 mm), the DESs had a significantly smaller diameter (p <0.0001).

The overall in-hospital major adverse cardiac and cerebrovascular event rate was 2.0% in the DES group and 2.5% in the BMS group. Likewise, the rates of postprocedural MI, death, stroke, urgent revascularization, and severe bleeding complications were low, with no significant differences among the PES, SES, and BMS groups (Table 4). The medications at discharge included aspirin in 98%, clopidogrel in 99%, and dual antiplatelet therapy combined with oral anticoagulation in 2.8%, β-blocking agents in 89%, angiotensin-converting enzyme blocking agents in 75%, and statins in 89%.

The clinical outcomes after a mean follow-up of 12.4 months (Table 4) were obtained for 93.5% of the PES group, 93.3% of the SES group, and 87.9% of the BMS group (p <0.0001 comparing DESs and BMSs). No significant differences were noted between PESs and SESs in the incidence of death, MI, stroke, target vessel revascularization, and stent thrombosis during the follow-up period. Compared to the BMS group, the patients treated with DESs had significantly lower MI (3.2% vs 6.0%; p <0.01), stroke (1.2% vs 2.7%; p <0.05), and target vessel revascularization (10.4% vs 14.9%; p <0.01) rates. Similarly, the cumulative major adverse cardiac and cerebrovascular event rates (8.1% vs 13.0%; p <0.001) were reduced in the DES group at 1 year of follow-up (Figure 2). The rates of overall stent thrombosis according to the Academic Research Consortium criteria were in the expected range and were not significantly different statistically between the DES and BMS patients (3.7% vs 4.3%; p = 0.57), with the proportion of definitive stent thrombosis of 0.6% and 0.7%, respectively (p = 0.8). At 1 year of follow-up, the antiplatelet medication was significantly different. Aspirin use was present more in the DES than in the BMS group (94.3% vs 91.2%; p <0.05) with no differences between the PES and SES groups. Similarly, more patients with DES were taking clopidogrel (55.8% vs 37%; p <0.0001), and oral anticoagulation was used more in the BMS group (12.9% vs 8.0%; p <0.01; Table 4). Concomitant medication with β-blocking agents, angiotensin-converting enzyme receptor blocking agents, and statin were equally administered in all 3 groups.

The effect of DES implantation on the risk of subsequent, clinically driven, target vessel revascularization and major adverse cardiac and cerebrovascular event in the specific subsets is listed in Table 5.

Discussion

DESs have been shown to markedly decrease the incidence of in-stent restenosis in the context of randomized trials.[3–6] However, such randomized studies have enrolled patient populations with noncomplex cases referred for elective intervention. Thus, the findings from randomized studies are difficult to extrapolate to everyday practice with complex, nonselected cases being the rule, rather than the exception. With the prospective multicenter DES.DE, the clinical outcomes in patients receiving 2 commercial DESs (PES and SES) and BMS are now available in the German healthcare system with about 42% DES penetration. The present analysis has described the 1-year clinical outcomes in a "real-world" population of patients with a high rate of so-called off-label indications, as reflected by the proportions of patients with acute coronary syndrome (45.5%), diabetes mellitus (31.7%), mild to severe impaired left ventricular function (31.2%), atrial fibrillation (8.3%), multivessel disease (71%), left main stenosis (1%), bypass graft intervention (5.2%), type B/C lesion according to the American College of Cardiology/American Heart Association classification (86.5%), in-stent restenosis (15.2%), bifurcation lesion (14.7%), and a mean stent length of 20 ± 9 mm. Most of these parameters were assigned as exclusion criteria in the randomized Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting stent (TAXUS) and Sirolimus-Coated Stents in De Novo Coronary Lesions (SIRIUS) trials.[3–6] As expected, very few of the baseline and procedural characteristics differed or were numerically small between the PES and SES groups. These differences, however, were significant between the DES and BMS groups, with more use of BMSs in the patients with acute coronary syndrome (61.1% vs 40.8%; p <0.0001), atrial fibrillation (13.9% vs 7.8%; p <0.0001), severe impaired left ventricular function (6.2% vs 3.5%; p <0.05), type A lesions (19.6% vs 12.8%; p <0.0001), and a culprit lesion located in a bypass graft (8.0% vs 4.9%; p <0.01) or in the right coronary artery (42.6% vs 26.6%; p <0.0001). In contrast to these indications, DESs were implanted predominantly in patients with previous known coronary artery disease, left anterior descending or left main target coronary artery, type B/C lesions, chronic total occlusion, in-stent restenosis, and bifurcation lesions. Even though PES and

SES rely on different antiproliferatory concepts, the clinical outcomes at 1 year in the present large comparison have indicated that, in "real-world" practice, the selection of either SES or PES resulted in almost identical clinical results, with a target vessel revascularization rate of 10.4% and a major adverse cardiac and cerebrovascular event rate of 8.1% in the 2 groups. Furthermore, from a safety standpoint, no difference was found in the rate of death, MI, or stent thrombosis between the 2 DES groups during the 1-year follow-up period.

Similar results with no difference in the clinical findings between patients implanted with SESs and PESs followed sequentially over time were reported in the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) and Taxus-Eluting STent Evaluated AT Rotterdam Hospital (T-SEARCH) registry with a 1-year, clinically driven, target vessel revascularization rate of 5.1% and 7.3% ($p = 0.3$), an overall major adverse cardiac event rate of 13.9% and 10.5% ($p = 0.1$), and a mortality rate of 5.3% and 3.4%, respectively.[7] Additional randomized trials such as the REALITY[8] and the Danish Organization on Randomized Trials with Clinical Outcome II (SORT OUT II)[9] and "real-world" registries such as Strategic Transcatheter Evaluation of New Therapies (STENT)[10] and DEScover,[11] revealed no differences in outcomes for either commercial DES. In contrast to our findings, recent meta-analyses have suggested lower clinical event rates with SESs than with PESs[12,13]; those meta-analyses, however, also recruited data from 1- or 2-center studies that had focused on late-lumen loss on angiographic follow-up. The effect of these surrogate parameters on the clinical end points are not known, and mandatory angiographic follow-up, as prescribed in randomized clinical trials, is likely to overestimate the need for relevant revascularization because of the "oculostenotic" reflex.[14] The reduction of adverse events after DES implantation in the DES.DE was lower than that observed in randomized trials such as RAVEL[15] and others, in which no binary angiographic restenosis was diagnosed. The explanation lies in the proportion of patients with an "off-label" indication and angiographic baseline parameters reflecting advanced coronary disease. Currently, approximately 25% of the patients are treated with a DES in "off-label" situations.[16] In our registry, some of these "off-label" indications were identified as predictors for major adverse cardiac and cerebrovascular events and target vessel revascularization, underlining the need for continued clinical follow-up. Conceptually, the antiproliferative properties of DESs are associated with delayed healing, setting the stage for prolonged biologic interactions between the vessel wall and the DES surface eluting the drug. Side effects such as hypersensitivity reactions, acquired late malapposition, and, most importantly, late stent thrombosis have been associated with delayed healing in both animal experiments and human observations.[17–20]

The results from the DES.DE have confirmed, in a large, real-world population, that the safety profile of DESs, at least with the current antiplatelet therapy regimen, does not differ significantly from that of BMSs. In contrast to the initial randomized controlled trials in which clopidogrel was recommended for 3 to 6 months, in the DES.DE 55.8% of DES patients and 37% of BMS patients were receiving dual antiplatelet therapy at 1 year of follow-up, reflecting the caution expressed in the ongoing debate concerning late stent thrombosis. A recent meta-analysis showed that the rate of stent thrombosis was not significantly increased with DESs during 4 years of follow-up, and the rate of target vessel revascularization was reduced.[21] The maximal difference in target vessel revascularization had occurred by 1 year, with the hazard curves remaining parallel between 1 and 4 years, confirming clinical efficacy over time in contradistinction to the "catch-up" phenomenon of late restenosis noted after coronary brachytherapy.[22] Additionally, in DES.DE, the rate of major adverse cardiac and cerebrovascular event was significantly reduced by use of DESs compared to BMSs (8.0% vs 13.0%; $p < 0.001$). The increased rate of MI in patients treated with BMSs in the DES.DE might be explained by the elevated rates of target vessel revascularization after BMS implantation. Previous data have shown that in-stent restenosis can present as acute coronary syndrome in 3.5% to 19.4% of patients and, thus, is not a benign process.[23,24] With the inclusion of clinical bleeding parameters into major adverse cardiac and cerebrovascular events, no difference was noted. A likely explanation was the twice as high acute coronary syndrome prevalence in the BMS group that also required dual antiplatelet therapy (with 100 mg aspirin and 75 mg clopidogrel for $\geq$9 months). Recently, the long-term outcome of unselected patients from the Drug-Eluting Stents in the Real World Registry (DESIRE) showed that the use of first-generation SESs was associated with a very low incidence of acute and long-term (2.6 ± 1.2 years) major adverse cardiac events (8.5%) and that the incidence of stent thrombosis was very low (1.6%) and did not seem to differ from that in initial reports of randomized controlled trials of DESs and historical series of BMSs.[25] Similar results were reported from the REgistro AngiopLastiche dellÈmilia Romagna (REAL) registry, including a total of 10,629 patients (3,064 treated with DES and 7,565 with BMS) treated in 13 centers in Italy.[26] In that nonrandomized registry, patients with DES experienced less frequent major adverse cardiac events (16.9% vs 21.8%; $p < 0.0001$) and target lesion revascularization (5.8% vs 9.9%, $p < 0.0001$), with similar rates of documented stent thrombosis (1% with DESs vs 0.6% with BMSs), thus corroborating the findings in the DES.DE.

The present analysis had the inherent limitations of any nonrandomized multicenter registry. The registry findings can be limited by low rates of enrollment and under-reporting of events, although reflecting the real world better than controlled randomized studies. With >20,000 entries within a record time, however, this problem was unlikely. Moreover, DES.DE was closely monitored by a critical event committee and steering committee, despite its comprehensive structure. Finally, the number of BMS patients, which was not risk adjusted, was relatively small compared to the numbers in the DES groups; thus, the data might lack precision for uncommon clinical events, including stent thrombosis. In the present trial, however, the target vessel revascularization and major adverse cardiac and cerebrovascular event rates were clinically driven and thus were as close to reality as possible. Finally, the percutaneous coronary intervention-associated increase in cardiac enzymes by

1.5 times the normal limits might have been too sensitive and have identified even irrelevant procedure-related enzyme leakage.

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