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ORIGINAL PAPER

Comparison between on-label versus off-label use of drug-eluting coronary stents in clinical practice: results from the German DES.DE-Registry

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Abstract
Background Observational studies from the USA have demonstrated that off-label use of drug-eluting stents (DES) is common. Data on off-label use in Western Europe are limited.
Methods We analyzed the data of consecutive patients receiving DES prospectively enrolled in the multicenter German DES.DE registry (Deutsches Drug-Eluting Stent Register) between October 2005 and October 2006. Off-label use was defined in the presence of one of the following criteria: ST-elevation myocardial infarction, in-stent stenosis, chronic total occlusion, lesions in a bypass graft, in bifurcation or left main stem, stent length per lesion $\geq$32 mm, and vessel diameter $<$2.5 or $>$3.5 mm.
Results Overall, 4,295 patients were included in this analysis and divided into two groups: 2,366 (55.1%) received DES for off-label and 1,929 (44.9%) for on-label indications. There were substantial differences in the rates of off-label use at the participating hospitals. Patients with off-label DES more often presented with high-risk features such as acute coronary syndrome, cardiogenic shock, congestive heart failure, and more complex coronary anatomy. Among hospital survivors, the incidence of the composite endpoint of death, myocardial infarction and stroke (MACCE) (9.2 vs. 7.4%, $p < 0.05$), and target vessel revascularization (TVR) (11.3 vs. 9.1%, $p < 0.05$) was increased in the off-label group at the 1-year follow-up. However, in the multivariate analysis off-label use was not linked with an elevated risk for MACCE (hazard ratio 0.86, 95% confidence interval 0.62–1.18) and TVR (hazard ratio 1.05, 95% confidence interval 0.78–1.42).

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Conclusions In clinical practice, DES was very frequently used off-label. After adjustment for confounding variables, off-label use was not associated with an increase of adverse events.

Keywords Drug-eluting stents · Off-label · Outcome · Clinical practice

Introduction

There is convincing evidence that drug-eluting stents (DES) reduce the incidence of in-stent restenosis in comparison to bare-metal stents (BMS). The first successful trial led to approval of the sirolimus-eluting Cypher™ stent in Europe in 2002 [1]. After a larger pivotal trial, the Cypher stent received the US Food and Drug Administration (FDA) approval in 2003 [2]. Soon thereafter, a series of trials of the paclitaxel-eluting Taxus™ stent led to FDA approval in 2004 [3]. However, these approvals were restricted to rather low-risk clinical scenarios with specially defined patients and lesions. Since then, the use of DES has dramatically increased. In 2007, two observational studies from the USA demonstrated that off-label use is very common and carries an increased risk of adverse events such as stent thrombosis, target vessel revascularization (TVR), myocardial infarction (MI), and mortality [4, 5]. Investigations that are more recent suggest that off-label use of both BMS and DES has an elevated risk. However, DES seemed to have similar or improved rates of death or MI compared with BMS, and consistently reduced need for TVR. Overall, the data support the use of DES for unapproved reasons [6–18].

Data on off-label use in Western Europe are limited. Within the large prospective multicenter German DES.DE (Deutsches Drug-Eluting Stent Register) registry, this study aimed to compare on-label with off-label use, with respect to clinical and lesion characteristics, as well as hospital and 1-year clinical outcomes.

Methods

The DES.DE registry

The prospective multicenter German DES.DE registry was initiated in October 2005 as an observational registry study by "Deutsche Gesellschaft für Kardiologie" (DGK, German Cardiac Society), "Bundesverband Niedergelassener Kardiologen" (BNK, German Society of Cardiologists in Private Practice), and "Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte" (ALKK, The Working Group of Leading Hospital Cardiologists) to analyze and evaluate the therapeutic principle of DES under real-world conditions in the context of the German Health System [19, 20]. The participating drug-eluting stents in DES.DE had to meet certain quality criteria orchestrated and confirmed by the DES.DE steering committee (SC) and partly adopted from European Society of Cardiology (ESC) PCI guideline criteria for DES [21]. In phase I of the registry (October 2005 to October 2006), only the two FDA-approved DES, Taxus™ (Boston Scientific Corp., Natick, Massachusetts) and Cypher™ (Cordis Corp., Miami Lakes, Florida), met the quality criteria of the registry.

For the present analysis, patients receiving DES were divided into two groups according to on-label and off-label criteria. Patients with more than one treated segment, hybrid stenting (DES and BMS, two different DES) or missing follow-up were excluded.

Data collection

Data were collected via Internet platform by the "Institut für Klinische Kardiovaskuläre Forschung" (IKKF Institute for Clinical Cardiovascular Research) of the German Cardiac Society. The European CARDS standard was adapted for both patient and lesion data [22]. Written informed consent for processing data at the "Institut für Herzinfarktforschung" (IHF Institute of Myocardial Infarction Research, Ludwigshafen) and IKKF was required. Baseline clinical and angiographic characteristics, certain procedural and clinical in-hospital events were recorded for all enrolled patients. Paper-based clinical follow-up assessment was performed at 3, 6, 9, and 12 months after initial stent placement and analyzed at the Institute for Social Medicine, Epidemiology, and Health Economics, Charite University Medical Center, Berlin.

Definitions

Off-label use was defined in the presence of one of the following criteria: ST-elevation myocardial infarction (STEMI), in-stent stenosis, chronic total occlusion (CTO), lesions in a bypass graft, in bifurcation or left main stem, stent length per lesion $\geq$32 mm, and vessel diameter $<$2.5 or $>$3.5 mm. In 2005, at the time of registry entry, this was the generally accepted definition [23]. Any patient who did not meet these criteria was included in the on-label group.

Major adverse cardiac and cerebrovascular events (MACCE) were classified as the composite of death (cardiac and non-cardiac), myocardial infarction, and stroke. Death was defined as all causes of mortality, whereas myocardial infarction either as STEMI (ST-elevation at least 1 mm in two or more standard leads or at least 2 mm in two or more contiguous precordial leads, development of new left bundle branch block on the ECG) or non-ST-

elevation myocardial infarction (NSTEMI, pathological increase of cardiac specific enzymes with creatininkinase-MB > 1.5 times of normal limits, Troponin T or I > 99 percentile of normal value). A neurological deficit of cerebrovascular cause that persisted beyond 24 h was diagnosed as stroke. Target vessel revascularization (TVR) was defined as repeat procedure, either PCI or CABG, in the target vessel. Routine angiography was not part of the protocol in DES.DE for any subgroup of patients; therefore, all re-interventions can be considered clinically driven. Stent thrombosis (ST) was classified as definitive (presence of angiographic thrombus with a complete occlusion), probable (unexplained sudden death within 30 days after stent graft placement or Q-wave MI in the distribution of the stented artery), and possible (unexplained death 30 days after PCI) according to definitions proposed by the Academic Research Consortium (ARC) [24].

Statistical methods

Statistical analysis was performed using the SAS-statistical package, version 9.1 (Cary, NC). Demographic characteristics, pre-existing risk factors, procedure-related variables, and 1-year outcomes were summarized using mean value with standard deviation for continuous variables, and frequency and percentage for categorical variables. Differences in baseline, procedural, and angiographic characteristics; and in-hospital and follow-up data were compared between on-label and off-label uses by chi-square test, while continuous variables were compared by Wilcoxon rank sum test. One-year event-free survivals for MACCE and TVR were demonstrated by Kaplan–Meier curves and were compared using log rank test. The effect of different demographic, clinical, and interventional variables on MACCE and TVR was evaluated by using Cox regression analysis and calculating hazards (HR), 95% confidence intervals (CI) and p values. The multivariate analyses were performed with adjustment for the following parameters: off-label use, age >75 years, prior myocardial infarction (MI), prior coronary artery bypass grafting (CABG), prior stroke, congestive heart failure, diabetes mellitus, renal insufficiency, peripheral artery disease (PAD), STEMI, NSTEMI, cardiogenic shock, 3-vessel disease, use of glycoprotein (GP) IIb/IIIa antagonists, in-stent stenosis, CTO, PCI of bypass grafts, bifurcation lesions or left main stem.

Results

Baseline characteristics

For the present analysis, patients were divided into two categories: 1,929 patients (44.9%) receiving DES for on-label and 2,366 patients (55.1%) for off-label indications. There were substantial differences in the rates of off-label use at the participating hospitals (range 25–86%) (Fig. 1). The baseline characteristics of the patients are shown in Table 1. Patients with DES for unapproved reasons more often had a history of coronary artery disease, and congestive heart failure. Patients with off-label DES were more likely to undergo PCI for ACS (43.9 vs. 34.9%, $p < 0.0001$) and more often presented with cardiogenic shock (2.0 vs. 0.3%, $p < 0.0001$).

Angiographic and interventional characteristics

In the off-label group, coronary angiography revealed more severe CAD and more complex lesions as compared to the on-label group. In comparison to patients with on-label DES, implanted stents were longer in the off-label group. Procedural success was similar in both cohorts (Table 2).

Medical treatment

Patients with off-label DES were more likely to receive GP IIb/IIIa receptor blockers. At discharge, medical therapy was adherent to current guidelines in both groups. The percentage of patients taking phenprocoumon, beta-blocker, and ACE inhibitor was slightly higher in the off-label group. After 3 (>96%) and 6 months (>92%), there were no relevant differences in dual-antiplatelet therapy between the two groups. After 9 (76.0 vs. 71.6%, $p < 0.01$) and 12 months (58.9 vs. 51.2%, $p < 0.0001$), more patients with off-label-DES additionally took clopidogrel. No other major differences could be observed at the 1-year follow-up (Table 3).

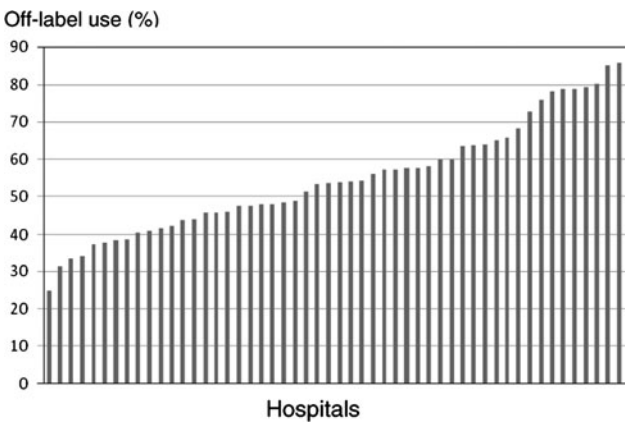

Fig. 1 Proportion of off-label use (%) at participating hospitals (>20 patients included)

Table 1 Baseline characteristics of patients receiving DES for on-label and off-label indications

	On-label $n = 1,929$	Off-label $n = 2,366$	p value
Demographics			
Age (years)	65.2 ± 10.1	65.2 ± 10.7	0.49
Men	1,427 (74.0%)	1,779 (75.2%)	0.36
BMI (kg/m^2)	27.4 (24.9–30.2)	27.5 (24.8–30.1)	0.96
History Relevant to CAD			
History of myocardial infarction	467/1,852 (25.2%)	779/2,238 (34.8%)	<0.0001
Prior PCI	686/1,898 (36.1%)	1.259/2,332 (54.0%)	<0.0001
Prior CABG	165/1,916 (8.6%)	460/2,352 (19.6%)	<0.0001
Congestive heart failure	239/1,804 (13.2%)	362/2,130 (17.0%)	<0.0001
History of stroke	79/1,886 (4.2%)	95/2,289 (4.2%)	0.95
Peripheral vascular disease	145/1,812 (8.0%)	233/2,173 (10.7%)	<0.01
Chronic renal failure	214/1,893 (11.3%)	305/2,318 (13.2%)	0.07
Risk factors			
Hypertension	1,599/1,913 (83.6%)	1,956/2,336 (83.7%)	0.90
Diabetes mellitus	607/1,909 (31.8%)	714/2,348 (30.4%)	0.33
Hypercholesterolemia	1.453/1,853 (78.4%)	1,884/2,286 (82.4%)	<0.01
Current/former smoker	1,260/1,716 (73.4%)	1,581/2,070 (76.4%)	0.09
Diagnosis			
STEMI	–	438/2,356 (18.6%)	<0.0001
Post STEMI	47/1,929 (2.4%)	32/2,356 (1.4%)	<0.01
NSTEMI	278/1,929 (14.4%)	244/2,356 (10.3%)	<0.01
Unstable Angina	350/1,929 (18.1%)	321/2,356 (13.6%)	<0.0001
Cardiogenic shock	5/1,929 (0.3%)	48/2,356 (2.0%)	<0.0001
Elective PCI	1,177/1,929 (61.0%)	1,250/2,356 (53.1%)	<0.0001
Ejection fraction ≤40%	142/1,517 (9.3%)	256/1,846 (13.8%)	<0.0001

Hospital outcome

The overall in-hospital MACCE rate was 2.2% in the off-label and 1.7% in the on-label group. Likewise, the rates of post-procedural MI (1.1 vs. 0.9%), stroke (0.3 vs. 0.7%), urgent revascularization (0.9 vs. 0.4%), and severe bleeding complication (0.6 vs. 0.3%) were low with no significant differences between the two groups. However, hospital mortality was significantly increased among those with off-label DES (0.8 vs. 0.2%, $p < 0.01$).

1-year outcome

Clinical outcomes of hospital survivors after a mean follow-up of 12.4 months are summarized in Table 4. Significant differences were noted between on-label and off-label uses with respect to the incidences of resuscitation, MI, MACCE, and TVR (Figs. 2 and 3). The incidence of death also tended to be higher in patients with off-label DES, but missed the level of significance. Rates of definitive ST did not differ between the two groups. However, the composite of definite, probable and possible ST occurred more frequently among patients with off-label use.

Multivariate analysis

After adjustment for confounding variables, off-label DES use was not linked with an increased risk for MACCE and TVR. The multivariate analysis revealed the following independent determinants for MACCE in decreasing order of importance (using odd ratios): cardiogenic shock, PAD, STEMI, congestive heart failure, chronic renal insufficiency, age >75 years and in-stent restenosis. The use of GP IIb/IIIa antagonists and congestive heart failure also were independent predictors for TVR (Table 5).

Discussion

This analysis of the contemporary multicenter DES.DE registry compared on-label with off-label DES use, with respect to clinical and lesion characteristics as well as hospital and 1-year clinical outcomes. In clinical practice, DES was used in 55% for unapproved indications. Considerable differences in the rates of off-label use at the participating hospitals could be observed. Patients with off-label DES more often presented with high-risk features. After adjustment for confounding variables, the use of DES

Table 2 Angiographic and interventional characteristics of patients treated with on-label and off-label DES

	On-label $n = 1,929$	Off-label $n = 2,366$	p value
Stenosed vessels (≥50%)			
1-vessel disease	596/1,929 (30.9%)	691/2,366 (29.2%)	0.23
2-vessel disease	687/1,929 (35.6%)	707/2,366 (29.9%)	<0.001
3-vessel disease	645/1,929 (33.4%)	924/2,366 (39.1%)	<0.001
Left main disease	1/1,929 (0.1%)	44/2,366 (1.9%)	<0.0001
Treated vessels			
LAD	997/1,929 (51.7%)	1,139/2,366 (48.1%)	<0.05
LCX	432/1,924 (22.5%)	462/2,358 (19.6%)	<0.05
RCA	500/1,929 (25.9%)	639/2,366 (27.0%)	0.42
Left main stem	–	126/2,366 (5.3%)	<0.0001
Bypass graft	–	227/2,366 (9.6%)	<0.0001
Lesion characteristics			
Type C	296/1,863 (15.9%)	805/2,151 (37.4%)	<0.0001
In-stent restenosis	–	723/2,314 (31.2%)	<0.0001
Bifurcation	–	610/2,295 (26.6%)	<0.0001
Chronic total occlusion	–	142/2,225 (6.4%)	<0.0001
TIMI flow before PCI			
TIMI 3	1,200/1,900 (63.2%)	1,070/2,162 (49.5%)	<0.0001
TIMI 0	66/1,900 (3.5%)	423/2,162 (19.6%)	<0.0001
Stent details			
Cypher™	872/2,218 (39.3%)	1,286/2,989 (43.0%)	<0.01
Taxus™	1,346/2,218 (60.7%)	1,580/2,989 (57.0%)	<0.0001
Length (mm)	16 (13–20)	20 (16–28)	<0.0001
Diameter (mm)	3.0 (2.5–3.0)	3.0 (2.8–3.0)	<0.0001
Procedural success			
TIMI 3 flow after PCI	1,893/1,920 (98.6%)	2,242/2,300 (97.5%)	<0.05
Stenosis after PCI (%)	1.7 ± 7.1	1.8 ± 7.2	0.10

Table 3 Medication during PCI, at discharge and at 1-year follow-up in patients receiving DES for on-label and off-label indications

	On-label $n = 1,929$	Off-label $n = 2,366$	p value
GP IIb/IIIa antagonist	162/1,921 (8.4%)	467/2,354 (19.8%)	<0.0001
At discharge			
ASA	1,893/1,929 (98.1%)	2,313/2,366 (97.8%)	0.39
Clopidogrel	1,918/1,929 (99.4%)	2,340/2,366 (98.9%)	0.06
Phenprocoumon	62/1,929 (4.2%)	104/2,366 (6.4%)	<0.05
Beta-Blocker	1,675/1,929 (86.8%)	2,138/2,366 (90.4%)	<0.001
ACE inhibitor	1,354/1,929 (70.2%)	1,872/2,366 (77.2%)	<0.001
Sartan	276/1,929 (14.3%)	274/2,366 (11.6%)	<0.01
Statin	1,704/1,929 (88.3%)	2,127/2,366 (89.9%)	0.10
At 1-year follow-up			
ASA	1,649/1,759 (93.7%)	2,006/2,116 (94.8%)	0.16
Clopidogrel	822/1,604 (51.2%)	1,151/1,954 (58.9%)	<0.0001
Phenprocoumon	123/1,547 (8.0%)	155/1,879 (8.2%)	0.75
Beta-Blocker	769/1,832 (42.0%)	952/2,224 (42.8%)	0.59
ACE inhibitor	641/1,832 (35.0%)	874/2,224 (39.3%)	<0.01
Sartan	497/1,832 (27.1%)	572/2,224 (25.7%)	0.31
Statin	1,648/1,832 (90.0%)	2,039/2,224 (91.7%)	0.06

Table 4 1-year clinical follow-up data of hospital survivors treated with on-label and off-label DES

	On-label $n = 1,927$	Off-label $n = 2,348$	p value
Death	71/1,927 (3.7%)	109/2,348 (4.6%)	0.12
Resuscitation	24/1,815 (1.3%)	48/2,188 (2.2%)	<0.05
ST (definite, probable and possible)	61/1,927 (3.2%)	114/2,348 (4.9%)	<0.01
Definite ST	14/1,897 (0.7%)	18/2,285 (0.8%)	0.85
Myocardial infarction	48/1,866 (2.6%)	89/2,258 (3.9%)	<0.05
Stroke	27/1,869 (1.4%)	22/2,264 (1.0%)	0.16
MACCE	142/1,927 (7.4%)	217/2,348 (9.2%)	<0.05
CABG	43/1,869 (2.3%)	64/2,261 (2.8%)	0.29
Coronary angiography	832/1,859 (44.8%)	1,009/2,255 (44.7%)	0.99
PCI	79/1,886 (4.2%)	95/2,289 (4.2%)	0.95
TVR	169/1,852 (9.1%)	253/2,241 (11.3%)	<0.05

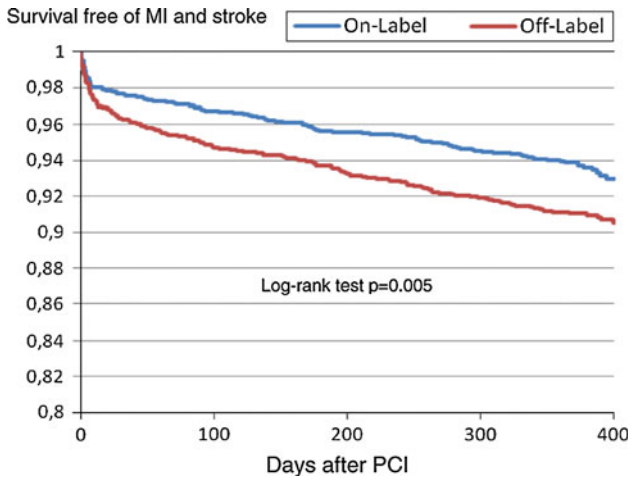

Fig. 2 Overall 1-year Kaplan–Meier survival curves: survival free of myocardial infarction (MI) and stroke in on-label and off-label use. The impaired outcome associated with off-label use of DES is mainly determined by clinical variables (please see Table 5) and not by DES off-label use as such

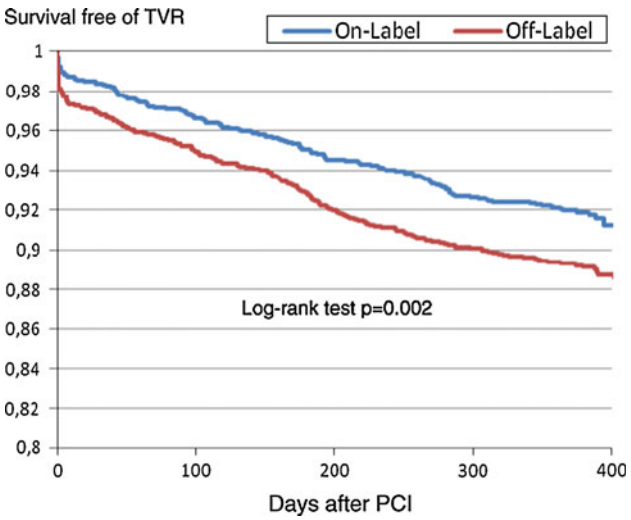

Fig. 3 Overall 1-year Kaplan–Meier survival curves: survival free of target vessel revascularization (TVR) in on-label and off-label use. The impaired outcome associated with off-label use of DES is mainly determined by clinical variables (please see Table 5) and not by DES off-label use as such

for unapproved reasons was not associated with an increase of adverse events and TVR rates.

Our investigation revealed the following off-label indications in decreasing order of frequency: in-stent stenosis (31.2%), bifurcated lesions (26.6%), stent length ≥32 mm (20.0%), acute STEMI (18.6%), bypass grafts (9.6%), vessel diameter <2.5 or >3.5 mm (9.0%), CTO (6.4%) and left main stem (5.3%). The majority of these parameters were assigned as exclusion criteria in the randomized trials examining paclitaxel-eluting or sirolimus-coated stents [1–3]. However, in Germany the definition of off-label use is different nowadays. In the meantime, several randomized trials have been published and the application of DES in in-stent stenosis, CTO and acute STEMI has been approved [25]. Of note, the definitions of on-label and off-label vary between different countries.

In the DES.DE registry, DES was very often used for off-label indications. Approximately, 55% of the patients were treated with DES in off-label situations. In the German Cypher Stent Registry, a significant trend to implant DES in more complex lesions were already observed between 2002 and 2005 [26]. This is in accordance with data from North America and Sweden. Off-label use of DES accounted for between 24 and 60% in previous observational studies [4, 5, 7, 8, 14, 15, 17].

One of the most interesting aspects of this analysis is that the strategy of the individual institution had a major impact on the rates of off-label use. There were large differences at the participating hospitals with a range from 25 to 86%; one can only speculate as to the reasons. Patient selection of the interventional centers, personal preferences of the policy makers, financial aspects, etc., could have played a role.

Table 5 Independent determinants for MACCE and TVR [HR (95% CI) and *p* value] at 1 year in the entire study population

	MACCE HR (95% CI)	MACCE *p* value	TVR HR (95% CI)	TVR *p* value
Off-label	0.86 (0.62–1.18)	0.35	1.05 (0.78–1.42)	0.73
Age >75 years	*1.46 (1.12–1.90)*	*0.005*	1.03 (0.78–1.35)	0.84
Prior MI	1.16 (0.90–1.49)	0.26	*0.78 (0.61–0.99)*	*0.046*
Prior CABG	1.38 (0.93–2.05)	0.11	1.35 (0.93–1.96)	0.12
Congestive heart failure	*1.75 (1.34–2.29)*	*<0.001*	*1.41 (1.07–1.85)*	*0.016*
Prior stroke	1.22 (0.75–1.99)	0.43	*0.39 (0.17–0.88)*	*0.024*
Chronic renal insufficiency	*1.56 (1.16–2.10)*	*0.003*	1.16 (0.84–1.58)	0.37
PAD	*1.91 (1.41–2.60)*	*<0.001*	1.21 (0.86–1.69)	0.28
Diabetes	1.02 (0.80–1.30)	0.86	0.98 (0.78–1.23)	0.85
STEMI	*1.86 (1.37–2.53)*	*<0.001*	1.21 (0.89–1.63)	0.22
NSTEMI	1.15 (0.80–1.67)	0.45	1.17 (0.84–1.63)	0.35
Shock	*2.09 (1.08–4.08)*	*0.030*	1.57 (0.79–3.13)	0.20
3-vessel disease	0.91 (0.70–1.18)	0.47	1.04 (0.82–1.32)	0.74
Left main stem treated	0.73 (0.34–1.54)	0.40	0.81 (0.42–1.59)	0.54
Bypass graft treated	1.48 (0.87–2.52)	0.15	1.11 (0.64–1.92)	0.71
In-stent restenosis	*1.43 (1.03–1.99)*	*0.034*	1.34 (0.98–1.82)	0.06
CTO	0.58 (0.24–1.44)	0.24	1.15 (0.64–2.05)	0.64
Bifurcation	1.00 (0.70–1.44)	0.98	1.05 (0.76–1.45)	0.76
GP IIb/IIIa antagonist	1,21 (0.88–1.66)	0.23	*1.52 (1.14–2.02)*	*0.004*

Significant values $p \leq 0.05$

Off-label indications may per se represent a high-risk group of patients. As expected, clinical, angiographic, and procedural characteristics differed significantly between the two groups. In concordance with previous observational studies, patients receiving DES for off-label indications more likely had renal insufficiency and a history of prior myocardial infarction, previous PCI/CABG and congestive heart failure [4, 5, 7, 8, 14]. Considering the fact that STEMI was an off-label criterion altogether, more patients with off-label DES were suffering from ACS and cardiogenic shock. Finally, coronary atherosclerosis and lesions characteristics were more severe among patients receiving DES for off-label indications. Nevertheless, despite the more complex anatomy, procedural success was as high as in on-label use.

Differences in adjunctive medical treatment were found between the two groups. In consequence of the increased rate of high-risk procedures GP IIb/IIIa receptor blockers were more often used among patients receiving DES for unapproved indications. There was also a trend towards a higher use of beta-blocker and ACE-inhibitor/sartan at discharge, most likely due to the greater incidence of congestive heart failure among patients with off-label DES. One of the main strengths of the DES.DE registry is the closed meshed follow-up, which included documentation of the patient's pharmacotherapy. Many previous studies could not provide data on the length of dual-antiplatelet therapy [4, 8, 14]. In our analysis, the duration of dual-antiplatelet therapy was significantly longer among those with off-label DES. The probable explanation lies in the higher proportion of patients with ACS and the fear of ST.

Hospital complications were fairly low in both groups. Despite this high-risk profile in the off-label group, the rates of post-procedural MI, stroke, urgent revascularization, and severe bleeding complication were not significantly increased. However, hospital mortality was considerably higher among those with off-label DES (0.8 vs. 0.2%, $p < 0.01$). At 1-year follow-up use of DES for unapproved reasons was associated with a significant increase of MACCE (9.2 vs. 7.4%, $p < 0.05$) and TVR (11.3 vs. 9.1%, $p < 0.05$) rates among hospital survivors. However, all these differences in event rates were most likely related to clinical or specific procedural characteristics that predispose a patient to adverse outcomes. After adjustment for confounding risk factors, these differences between on-label and off-label uses were no longer present. It appears that DES are safe and effective, even in subsets of patients and lesions that were not a proven indication at that time [6, 8, 9, 11, 13–15, 17]. Our results suggest that DES were adequately selected and physicians used off-label DES for lesions at high risk for restenosis.

Implantation of DES might be associated with an increased risk of ST. In a meta-analysis by Bavry et al. evaluating sirolimus and paclitaxel-eluting stents there was a small but statistically higher risk of ST after the first year, compared to BMS, whereas no significant differences were found in a meta-analysis by Settler et al. [27, 28]. ST often causes MI and death and the risk of ST after implantation

of DES might be increased in off-label situations [5, 29]. On the contrary, in a German observational study, the use of DES outside of FDA-approved indications was not found to be no independent predictor for definite ST [30]. In the DES.DE registry, the risk for definite ST was rather low after 1 year with no significant differences between on-label and off-label uses. The long duration of dual-antiplatelet therapy (in particular among patients receiving DES for unapproved indications) could have played a role.

Limitations

As the nature of the study is exploratory, the findings should be interpreted cautiously. In the DES.DE registry, the treatment was left to the discretion of the physician. This could result in selection bias, which cannot be fully eliminated by using a multivariate analysis. Moreover, the PCI associated increase in cardiac enzymes by 1.5 normal limits may indeed be too sensitive and identify even irrelevant procedure-related enzyme leakage.

Conclusions

The DES.DE registry gives a consistent overview of DES implantations for unapproved indications in a large Western European real-world population. Off-label use was very common. There were substantial differences in the rates of off-label situations at the participating hospitals. At the 1-year follow-up, use of DES for unapproved reasons was not associated with an increase of adverse events and TVR rates.

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