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Complete List of Authors:	Jeschke, Elke; Research Institute of the Local Health Care Funds (WIdO), Searle, Julia; CharitT Berlin CVK, Cardiology Emergency Medicine Guenster, Christian; Research Institute of the Local Health Care Funds (WIdO), , Health Services and Quality Research Baberg, Henning; Helios Klinikum, Berlin-Buch, Department of Cardiology and Nephrology Dirschedl, Peter; Medical Service of the Health Funds (MDK) Baden-Württemberg Levenson, Benny; German Society of Cardiologists in Private Practise (BNK) Malzahn, Juergen; Federal Association of the Local Health Care Funds (AOK), Mansky, Thomas; Technische Universität Berlin, Faculty of Economics and Management Mockel, Martin; Charité University Medicine, Division of Emergency Medicine CVK, CCM and Department of Cardiology CVK
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Drug eluting stents in clinical routine: A 1-year follow-up analysis based on German health insurance administrative data from 2008-2014.

Elke Jeschke[1], Julia Searle[2], Christian Günster[1], Henning Thomas Baberg[3], Peter Dirschedl[4], Benny Levenson[5], Jürgen Malzahn[6], Thomas Mansky[7], Martin Möckel[2]

[1]Research Institute of the Local Health Care Funds (WIdO), 10178 Berlin, Germany, Elke Jeschke, Epidemiologist, Christian Günster, Head of Department Quality and Health Care Research; [2]Department of Cardiology and Division of Emergency Medicine and Chest Pain Units, Campus Virchow Klinikum and Campus Charité Mitte, Charité – Universitätsmedizin Berlin, 13353 Berlin, Germany, Julia Searle, Senior Research Associate, Martin Möckel, Medical Head of Division and Professor of Medicine; [3]Department of Cardiology and Nephrology, Helios Klinikum, Berlin-Buch, 13125 Berlin, Germany, Henning Thomas Baberg, Medical Head of Department; [4]Medical Service of the Health Funds (MDK) Baden-Württemberg, 77933 Lahr, Germany, Peter Dirschedl, Deputy Medical Head; [5]German Society of Cardiologists in Private Practice (BNK), Bundesverband niedergelassener Kardiologen), 80805 München, Germany, Benny Levenson, Executive Board; [6]Federal Association of the Local Health Care Funds (AOK), 10178 Berlin, Germany, Jürgen Malzahn Head of Division Inpatient Treatment and Rehabilitation; [7]Faculty of Economics and Management, Division for Structural Development and Quality Management in Healthcare, Technische Universität Berlin, 10623 Berlin, Germany, Thomas Mansky, Head of Division.

Correspondence to:

Martin Möckel, MD, FESC, FAHA (martin.moeckel@charite.de)

Charité - Universitätsmedizin Berlin

Charitéplatz 1, 10117 Berlin, Germany

Abstract

Objectives: To describe of the use of DES in the population of the largest statutory health insurance members in Germany, including newly developed bio-resorbable vascular scaffolds (BVS) and to evaluate 1-year complication rates of DES as compared to BMS treatment in this cohort.

Design: Routine data analysis of statutory health insurance claims data from the years 2008 to 2014.

Setting: The AOK provides nationwide health care insurance for approximately 30% of the German population and is the largest provider of statutory health care insurance in Germany.

Participants and interventions: We included all patients with a claims record for a percutaneous coronary intervention (PCI) with either DES or bare metal stent (BMS) and additionally, from 2013, BVS. Patients with acute myocardial infarction (AMI) were excluded. **Main outcome measure:** Major adverse cerebro- and cardiovascular events (MACCE, defined as mortality, AMI, stroke and transient ischemic attack (TIA)), bypass surgery, PCI and coronary angiography) at one year after the intervention.

Results: A total of 243,581 PCI cases were included (DES excluding BVS: 143,765; BVS: 1,440; BMS: 98,376). The 1-year MACCE rate was 7.42% in the DES subgroup excluding BVS and 11.29% in the BMS subgroup. The adjusted odds ratio (OR) for MACCE was 0.72 (95% CI: 0.70 to0.75) in DES patients excluding BVS as compared to BMS patients. In the BVS-group, the proportion of 1-year MACCE was 5.0%.

Conclusion: The analyses demonstrate a lower MACCE rate for the PCI with DES. BVS are used in clinical routine in selected cases and seem to provide a high safety, but data are still sparse.

Key words: drug eluting stents, administrative data, MACCE, safety, healthcare research, bio-resorbable vascular scaffolds

Article summary:

- This study assesses the safety of DES in clinical routine in Germany within the first year after index PCI, using statutory health insurance claims data from the largest health insurance in Germany covering around 30% of the German population.
- Up until now, publication on current use and time trends regarding routing PCI practice are sparse.
- The analysis was performed on the basis of changing conditions and patient populations for PCI treatment, to assess the clinical routine of coronary revascularization with PCI.
- AOK patients form a large group within Germany with 24 million insured persons and around one third of all inpatient hospital cases, but still external validity of our data on PCI utilization and MACCE-rates is limited due to the fact that AOK insured persons differ in their age and comorbidity profile when compared to other health insurances in Germany
- Data were generated as routine data for billing of claims. Thus, data were not generated for research purposes; Inaccuracies of coding cannot be excluded and important variables may be missing.

Introduction

Percutaneous coronary interventions (PCI) are a commonly and increasingly used revascularization strategy in patients with coronary artery disease (CAD). In Germany, 361.377 PCIs were performed in 2014[1]. Germany is a model region with respect to early availability of new treatment options. For example, the mean time from approval to market for new medical drugs is 3.5 months compared to 5.8 months in the Netherlands and 16 months in Spain (Dtsch Arztebl 2017; 114(13): A-606).

In recent years, case numbers for PCI have been stable on a high level. Still, the utilization pattern of PCI changed dramatically over time with a distinct increase of PCIs in patients over the age of 70 years and in patients with comorbidities like diabetes mellitus and chronic kidney disease, as compared to 2008[1]. Additionally, materials used in PCIs have changed. Whilst in the early years uncoated stents made of differing metal alloys (bare metal stents, BMS) were used, stents coated with pharmaceutical drugs and polymer (drug eluting stents, DES) are on the rise. DES were developed to prevent scarring and re-stenosis of the treated coronary vessel by releasing active agents over a defined period of time. Drugs commonly used in these stents inhibit cell growth, e.g. immunosuppressant drugs like Everolimus, Zotarolimus, Sirolimus or the cytostatic drug Paclitaxel - although Paclitaxel is used increasingly less - all in combination with different carrier materials (polymer). The latest development are bio-resorbable vascular scaffolds (BVS) which support the vessel over a certain period of time after which they dissolve. The safety and efficacy of BVS has been challenged recently[2].

DES have led to a significant reduction of in-stent-re-stenoses (ISR)[3-6]. Still, particularly in the days of first generation DES in the mid-2000s, there were considerable safety concerns, as a number of studies reported increased rates of late in-stent thromboses compared to BMS[7-11]. This argument is still being used to favour BVS. For the second generation DES these concerns seem not to apply[12] and current guidelines recommend DES for most patients

although very recent data show that BMS may still have their place e.g., patients with recent bleeding or a need for concomitant anticoagulation therapy[13 14].

This analysis of German statutory health insurance claims data was performed on the basis of changing conditions and patient populations for PCI treatment, to assess the clinical routine of coronary revascularization with PCI in Germany. Up until now, the only publication from Germany uses data from the German DES Registry, in which 98 hospitals participated[15]. We aimed to test the following hypotheses: a) DES are the new clinical standard for PCI in Germany and b) DES are effective and safe with respect to repeat-revascularisation and major adverse cerebro- and cardiovascular events (MACCE) within 1-year after the initial PCI and c) BVS are increasingly used in clinical routine with a safe outcome.

Methods

Nation-wide, anonymous billing data of the statutory health insurance company AOK (Allgemeine Ortskrankenkasse) were used for all 24 Mio AOK-insured persons in Germany,. The AOK provides nationwide health care insurance for approximately 30% of the German population and is the largest provider of statutory health care insurance in Germany. Every person is allowed to enrol in the AOK regardless of age, comorbidity, income or type of employment. Data were derived from billing data for inpatient hospital treatment. They comprise of a unique identification number, age, sex, main diagnosis and comorbidities, procedures, length of stay, patient survival and insurance status. Diagnoses were coded according to the 10th revision of the International Classification of Diseases (ICD-10)[16]. Procedures were documented using the German version of the International Classification of Procedures in Medicine (ICPM)[17], the "Operationen- und Prozedurenschlüssel" (OPS). Health care providers and health care insurances jointly issue binding guidelines for coding of diagnoses and procedures in hospital claims[18]. Hospital claims data in Germany are

thoroughly checked against these guidelines and for plausibility by the Medical Review Board of the Social Health Insurance Funds and are returned to hospitals for correction if necessary. Corrections are included in the claims data used in this analysis.

We included all AOK cases from 2008 until 2014, with a claim of inpatient treatment with DES or BMS. Cases were identified by OPS-codes (DES excluding BVS: 8-837.m; BVS: 8-83d.0; BMS: 8-837.k). The hospitalization during which this PCI was performed is referred to as the index hospitalisation.

We excluded all cases with acute myocardial infarction (AMI) and patients with an age below 20 years as well as patients with cardiac surgery or PCI in the year before the index hospitalisation, independent of whether this was done as an inpatient or outpatient treatment as the outcome of these patients depends on other strong factors than the type of stent.

For the analysis we formed three subgroups, patients with DES excluding BVS, patients with BVS and patients with BMS treatment. Data for BVS were available only for the years 2013 and 2014.

If patients had multiple stenting during the index hospitalisation with combined DES and BMS stenting, he/she was assigned to the DES group. This applies to n= 5.986 (2.46%) of cases.

First, we performed a descriptive analysis on the development of BMS and DES treatment over the pre-defined 5-year period. Cochrane-Armitage Trend Test was used to analyse trends over these years. In the DES-group, we analysed subgroups according to the pharmaceutical drug and carrier material as indicated in the OPS-code (OPS: 8-83b). We then analysed events during the 1-year follow-up period for the DES and BMS subgroups. Primary endpoint was the one-year MACCE-rate (mortality, AMI, stroke and TIA; ICD10: I21, I22, I63, G45). Additionally we assessed CABG surgery (OPS: 5-361, 3-362, 5-363), PCI (OPS: 8-837, 8-83d) and coronary angiographies (OPS: 1-275) during different time frames within the 1-year follow-up period. To evaluate the association of PCI treatment (DES excluding BVS vs.

BMS) with outcomes we used multivariable logistic regression models. Adjustment was made for age, sex, co-morbidities according to Elixhauser classification[19], shock, NYHA class (I vs. II, III or IV), left main disease, multi-vessel disease (2 or 3 vessels), number of PCI (one coronary artery vs. a minimum of two) at index hospitalisation, AMI and dialysis in the year preceding admission and year of treatment. Comorbidities were defined using the Elixhauser measure. The definition includes 31 acute and chronic comorbidities: congestive heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation disorders, peripheral vascular disease, hypertension uncomplicated, hypertension complicated, diabetes uncomplicated, diabetes complicated (i.e. coma, ketoacidosis, vascular disease), renal failure, liver disease, coagulopathy, blood loss anemia, deficiency anemia, hypothyroidism, peptic ulcer disease excluding bleeding, chronic pulmonary disease (COPD), obesity (BMI $\geq$ 30 kg/m²), weight loss, solid tumor without metastasis, metastatic cancer, lymphoma, fluid and electrolyte disorders, rheumatoid arthritis/collagen vascular diseases, paralysis, other neurological disorders, alcohol abuse, drug abuse, psychoses, depression, AIDS/HIV. Comorbidities were identified using the coding algorithm by Quan et al. based on the ICD-10 coding[20]. AMI, cardiogenic shock, NYHA class (I vs. II, III or IV), left main disease, multi-vessel disease (2 or 3 vessels), which are not included in the Elixhauser measure, were also analysed because they are potential risk factors and differ between the analysed groups ($p < 0.005$). Patients in whom the insurance status with the AOK ended before the end of the 1-year follow-up period were censored resulting in differing case numbers for different follow-up periods. All analyses were performed using STATA 11.2 (StataCorp, College Station, Texas).

Ethics

The present study is based on data provided by hospitals for health insurance accounting. The recommendations for good practice in secondary data analysis developed by the German Working Group on the Collection and Use of Secondary Data[21] were applied in full. This type of analysis requires no formal ethics committee approval.

Results

The analysis included 243.581 cases with PCI, 143,765 (59.02%) in the DES excluding BVS group, 1,440 (0.59%) in the BVS group and 98.376 (40.39%) in the BMS group. In total, 37.0% of all eligible cases (N= 659.067) with PCI were included. Cases were excluded according to the exclusion criteria (AMI at the index hospitalisation, cardiac surgery or PCI in the year before the index hospitalisation or age below 20 years).

Time trends in percutaneous coronary interventions

Figure 1 shows the frequency of PCI-treatment in AOK-patients over time. The proportion of DES increased from 33.6% in the year 2008 (n=10,843) to 84.2% in 2014 (n=30,181), including 2.3% BVS in 2014 (n=856). The proportion of BMS decreased accordingly.

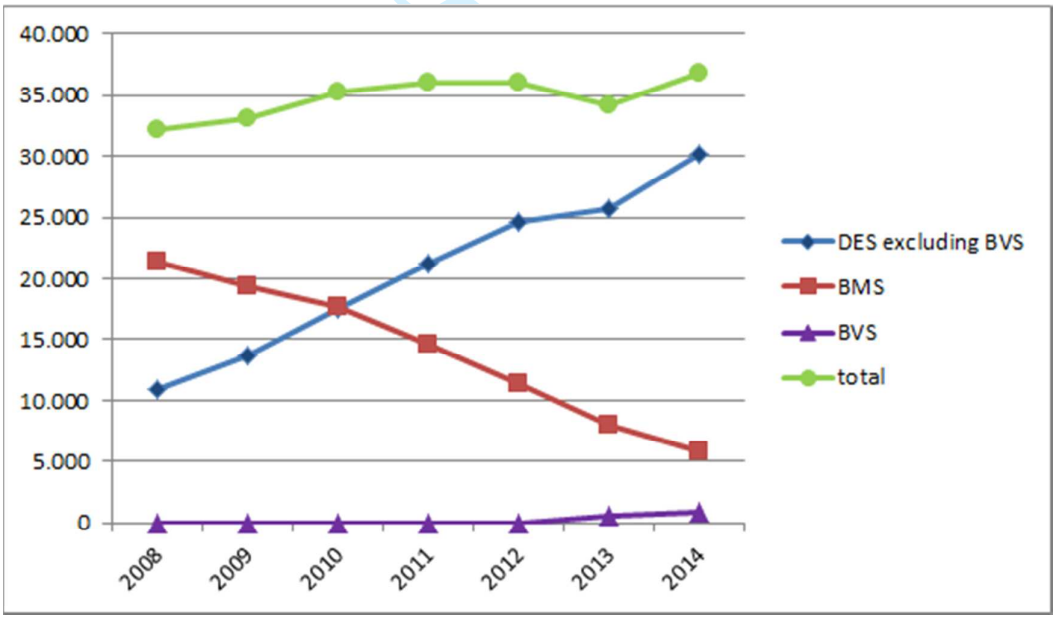

Figure 1: Frequency of drug eluting stents (DES) and bare metal stents (BMS) utilization over time (2008-2014). BVS bio-resorbable vascular scaffolds.

Figure 2 shows the development of DES treatment over the pre-defined 7-year period according to pharmaceutical drug and carrier materials used. The proportion of Everolimus-eluding stents with polymer increased markedly (2008: 25.5%; 2014: 46.4%). The same is true for the proportion of Zotarolimus- and Biolimus-eluding stents with polymer (2008:

17.7%; 2014: 25.5% and 2008: 5.8%; 2014: 12.4%, respectively). The use of all other stents decreased over this time period, most prominently Paclitaxel-eluding stents with polymer (2008: 29.7%; 2014: 1.5%). Very rarely used stents with case numbers below 100 over the five-year period are not shown. Drugs used in BVS are not sufficiently coded in the data set.

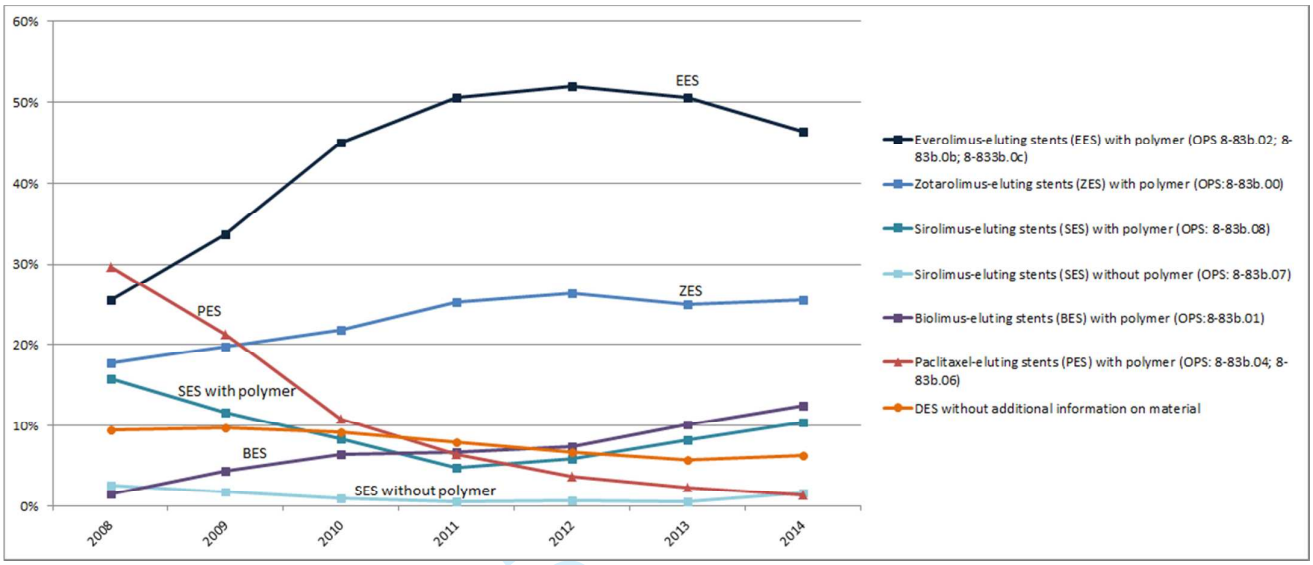

Figure 2: Frequency of the different drug eluting stent (DES) used over time (2008-2014) according to active drug component and carrier material (groups > 1% only) * Multiple selections possible due to implantation of different stent types during index procedure. BVS were not included. OPS "Operationen- und Prozedurenschlüssel" (OPS) German version of the International Classification of Procedures in Medicine (ICPM) [17]

Study population

Table 1 shows basic characteristics of our study population. Patients in the DES excluding BVS group were in median 2 years younger than patients in the BMS-group (70 vs. 72 years). The proportion of patients with prior MI, coronary 3-vessel disease, left main disease and diabetes was higher in the DES excluding BVS group as was the proportion of patients with multiple stenting (PCI-number >1; DES: 18.5% vs. BMS: 6.3%). In the BMS-group, the proportion of patients with heart failure, NYHA-class >1, cardiac arrhythmia, valvular disease, and COPD was higher. The median age of the BVS group was 64 years and the proportion of patients with concomitant diseases was lower than in the other groups.

The age of patients increased in all groups over time, but more prominently in the BMS-group (Median age in years: DES-group excluding BVS 2008: 68; 2014: 71; BMS-group 2008: 70; 2014: 75). The proportion of patients with an age above 70 years in 2014 was 53.80% in the DES excluding BVS-, 69.60% in the BMS-, and 35.96 in the BVS-group. Likewise, the proportion of co-morbidities increased over time, this was also most prominent in patients of the BMS-group with heart failure, cardiac arrhythmia, valvular diseases, and chronic kidney disease. The proportion of patients with cardiac arrhythmia, for example, increased by 8.5% (2008: 16.0%; 2014: 24.5%) in the DES excluding BVS-group and by 28.2% (2008: 24.3%; 2014: 52. 5%) in the BMS-group.

	Total	**DES not including BVS**	**BMS**	**BVS**
Number [N]	**243.581**	**143.765**	**98.376**	**1.440**
Age [Median (IQR)]	71 (62-77)	70 (61-76)	72 (65-78)	64 (55-73)
Female patients [%]	32.23%	31.52%	33.31%	28.47%
Diagnoses at the index hospital stay [%]*				
Cardiovascular diseases				
Prior MI	9.60%	10.34%	8.55%	7.50%
Stroke	0.48%	0.40%	0.59%	0.28%
TIA	0.27%	0.21%	0.35%	0.14%
Intracerebral bleeding	0.04%	0.03%	0.06%	0.00%
Congestive heart failure	26.69%	25.45%	28.53%	25.21%
NYHA-stage > 1	22.07%	21.02%	23.62%	21.67%
Coronary 2-vessel disease	31.54%	31.63%	31.39%	32.15%
Coronary 3-vessel disease	37.63%	40.36%	33.73%	30.49%
Left main CAD	3.77%	4.68%	2.47%	1.46%
Shock	0.55%	0.49%	0.64%	0.14%
Arterial hypertension	78.63%	79.52%	77.34%	77.92%
Cardiac arrhythmia	25.30%	20.48%	32.44%	17.29%
Valvular disease	10.11%	8.75%	12.14%	7.43%
Peripheral vascular disorders	11.56%	11.25%	12.06%	8.06%
Other concomitant diseases				

Diabetes mellitus	33.51%	35.22%	31.07%	28.75%
COPD	9.55%	8.76%	10.71%	9.31%
CKD	19.48%	18.70%	20.73%	12.15%
ESRD	3.92%	3.91%	3.97%	2.26%
Hypothyroidism	7.22%	7.54%	6.71%	9.44%
Obesity (BMI ≥ 30 kg/m²)	12.00%	12.03%	11.93%	13.96%
Interventions at index hospital stay [%]				
PCI > 1 coronary artery**	13.52%	18.45%	6.32%	12.57%
Pacemaker	1.20%	1.04%	1.45%	0.63%
ICD-implantation	0.79%	0.70%	0.93%	0.28%
Dialysis	1.75%	1.59%	2.00%	0.69%

Table 1: **Patient characteristics, for all patients and for the subgroups of patients with DES not including BVS, BMS and BVS**

*other analysed comorbidities according to Elixhauser et al. with frequency <5% are not shown (pulmonary circulation disorders, liver disease, blood loss anemia, deficiency anemia, peptic ulcer disease excluding bleeding, coagulopathy, weight loss, solid tumor without metastasis, metastatic cancer, lymphoma, rheumatoid arthritis/collagen, paralysis, other neurological disorders, alcohol abuse, drug abuse, psychoses, depression, AIDS/HIV) **At least two stents in one or more coronary arteries during index hospitalisation.

Abbreviations: DES drug eluting stent; BMS bare metal stent; BVS bio-resorbable vascular scaffolds; IQR interquartile range; MI myocardial infarction; TIA transient ischaemic attack; CKD chronic kidney disease; ESRD end stage renal disease; COPD chronic obstructive pulmonary disease; PCI percutaneous coronary intervention; ICD implantable cardioverter defibrillator

MACCE und repeat-revascularisation within one year

Table 2 shows event rates for the DES excluding BVS and BMS groups over the whole study period and for the respective years of the study period. In total, the proportion of MACCE during the one-year period after the index PCI was 7.4% in the DES excluding BVS-group and 11.3% in the BMS-group. Repeat coronary procedures occurred more frequently in the DES excluding BVS-group. The proportion of repeat coronary angiographies, for example, was 3.4% higher in the DES excluding BVS-group (DES excluding BVS-group: 34.5%; BMS-group: 31.1%). In the BVS-group (data available only for 2013 and 2014) the proportion of 1-year MACCE was 5.0% and the 1-year mortality was 2.5%. Repeat coronary

procedures within one-year occurred more frequently in BVS patients (PCI 25.8%; repeat coronary angiographies 39.6%).

In the DES excluding BVS-group, there was a small increase with respect to 1-year MACCE over time (p > 0.001, trend test). One-year mortality increased (2008: 3.6%; 2014: 5.1%; p<0,001), whereas the proportion of AMI decreased slightly over time (2008: 2.5%; 2014: 2.2%; p=0.013). In the BMS-group, the proportion of 1-year MACCE increased by 5.3% (2008: 9.6%; 2012: 14.9%; p<0.001). This is mostly driven by an increased mortality (2008: 5.3%; 2014: 10.8%; p<0.001).

Looking at repeat coronary procedures over time, data show a decrease, particularly of coronary angiographies, (DES excluding BVS: 2008: 40.81%, 2014: 30.69%; BMS: 2008: 33.66%, 2014: 26.53%; p<0.001 for both) but also of CABG surgery (DES excluding BVS: 2008: 1.94%, 2014: 0.90%; BMS: 2008: 2.15%, 2014: 1.28%, p<0,001 for both).

	Total [%]	2008 [%]	2009 [%]	2010 [%]	2011 [%]	2012 [%]	2013 [%]	2014 [%]
DES excluding BVS (N=143,765)								
Mortality during index hospitalisation	**0.57**	0.41	0.42	0.50	0.44	0.56	0.60	0.83
MACCE (1y)	**7.42**	7.04	7.60	7.21	7.01	7.17	7.53	8.28
Mortality	**4.22**	3.59	3.53	3.94	3.88	4.07	4.43	5.10
AMI	**2.22**	2.52	2.52	2.14	2.16	2.18	2.09	2.19
Stroke	**1.06**	1.05	1.01	1.13	1.10	0.93	1.07	1.13
TIA	**0.55**	0.50	0.44	0.61	0.48	0.60	0.60	0.55
CABG after index hospitalisation (1y)	**1.20**	1.94	1.44	1.52	1.22	1.04	1.02	0.90
- of those within 30d	**0.09**	0.11	0.08	0.11	0.10	0.11	0.09	0.08
- of those within 31-365d	**1.10**	1.83	1.36	1.41	1.12	0.93	0.93	0.81
PCI after index hospitalisation (1y)	**21.40**	22.50	22.86	22.46	21.80	21.09	20.65	20.32
- of those within 90d	**12.59**	11.62	12.18	12.37	12.75	12.91	12.75	12.76
- of those within 91-365d	**8.52**	10.68	10.44	9.83	8.79	7.90	7.55	7.20
Coronary angiography after index hospitalisation (1y)	**34.49**	40.81	39.13	37.50	35.02	33.19	32.49	30.69
BMS (N=98.376)								

Mortality during index hospitalisation	**0.97**	0.64	0.83	0.95	1.00	1.23	1.51	1.33
MACCE (1y)	**11.29**	9.58	10.33	11.05	11.32	12.68	14.10	14.93
Mortality	**7.08**	5.26	6.15	6.76	7.32	8.60	9.64	10.80
AMI	**3.33**	3.44	3.26	3.38	3.19	3.20	3.47	3.35
Stroke	**1.44**	1.36	1.26	1.42	1.47	1.51	1.75	1.72
TIA	**0.72**	0.61	0.82	0.70	0.62	0.81	0.87	0.74
CABG after index hospitalisation (1y)	**1.70**	2.15	1.97	1.66	1.39	1.28	1.40	1.25
- of those within 30d	**0.14**	0.13	0.12	0.14	0.15	0.11	0.14	0.23
- of those within 31-365d	**1.56**	2.01	1.84	1.51	1.24	1.16	1.25	1.00
PCI after index hospitalisation (1y)	**19.90**	21.22	20.00	20.22	19.67	19.50	18.08	17.37
- of those within 90d	**10.17**	10.55	10.02	10.28	10.42	10.28	9.44	8.99
- of those within 91-365d	**9.38**	10.43	9.66	9.61	8.85	8.79	8.16	7.84
Coronary angiography after index hospitalisation (1y)	**31.14**	33.66	32.21	31.84	30.26	28.71	28.29	26.53

Table 2: Event rates during the 5-year observation period and during the individual years (claims data of the German local healthcare funds 2008-2014)

Patients in whom the insurance status with the AOK ended before the end of the 1-year follow-up period were censored resulting in differing case numbers for different follow-up periods. Abbreviations: DES drug eluting stent; BVS bio-resorbable vascular scaffolds; MACCE major cerebro- and cardiovascular events; AMI acute myocardial infarction; TIA transient ischaemic attack; CABG coronary artery bypass graft; PCI percutaneous coronary intervention; BMS bare metal stent.

Table 3 shows odds ratios for DES excluding BVS compared to BMS treatment, risk-adjusted for patient characteristics and year of treatment. After risk-adjustment, the DES excluding BVS-group had a lower risk for 1-year MACCE (OR= 0.72; 95% CI: 0.70-0.75), and particularly for 1-year mortality (OR = 0.70; CI: 0.67-0.74), 1-year CABG surgery (OR = 0.69; CI: 0.63-0.75), and repeat PCI within days 91-365 after the index PCI (OR = 0.87; CI: 0.81-0.93). The DES excluding BVS-group had a higher risk of PCI within 90 days after the index PCI (OR = 1.14; CI: 1.07-1.21) and of repeat coronary angiography within 1 year (OR = 1.14; CI: 1.06-1.23).

Like DES excluding BVS, the odds ratios for BVS compared to BMS were lower for 1-year MACCE (OR= 0.59; 95% CI: 0.46-0.74) and for 1-year mortality (OR = 0.55; CI: 0.41-0.74). The BVS-group also had a higher risk of PCI within 90 days after the index PCI (OR = 1.83; CI: 1.51-2.22) and of repeat coronary angiography within 1 year (OR = 1.64; CI: 1.33-2.02).

	Adjusted OR* (95% CI)	**Crude OR (95% CI)**
Mortality during index hospitalisation	**0.70 (0.61-0.80)**	**0.59 (0.53-0.66)**
MACCE (1y)	**0.72 (0.70-0.75)**	**0.63 (0.61-0.65)**
- of this mortality (1y)	**0.70 (0.67-0.74)**	**0.58 (0.55-0.61)**
CABG after index hospitalisation (1y)	**0.69 (0.63-0.75)**	**0.70 (0.65-0.76)**
- of these within 30d	**0.60 (0.47-0.76)**	**0.68 (0.54-0.87)**
- of these within 31-365d	**0.70 (0.64-0.77)**	**0.70 (0.65-0.77)**
PCI after index hospitalisation (1y)	0.99 (0.94-1.04)	**1.11 (1.04-1.15)**
- of these within 90d	**1.14 (1.07-1.21)**	**1.27 (1.20-1.35)**
- of these within 91-365d	**0.87 (0.81-0.93)**	**0,90 (0,84-0.96)**
Coronary angiography after index hospitalisation (1y)	**1.14 (1.06-1.23)**	**1.16 (1.09-1.25)**

Table 3: Uni- and multivariable logistic regression analysis of the effect of PCI-treatment - DES excluding BVS vs. BMS (reference) - on event rates (claims data of the German local healthcare funds 2008-2014) *Risk adjustment included age, sex, co-morbidities according to Elixhauser classification, shock, NYHA class (I vs. II, III or IV), left main disease, multi-vessel disease (2 or 3 vessels), number of PCI (one coronary artery vs. a minimum of two) at index hospitalisation, AMI and dialysis in the year preceding admission and year of treatment. Significant odds ratios are highlighted in bold. Abbreviations: DES drug eluting stent; BMS bare metal stent; BVS bio-resorbable vascular scaffolds; OR odds ratio; CI confidence interval; MACCE major cerebro- and cardiovascular events; CABG coronary artery bypass graft; PCI percutaneous coronary intervention.

Influence of DES stent type

Table 4 shows the comparison of newer versus first generation (Paclitaxel) DES. Bioresorbable stents were excluded as the respective code was only available for 2013 and 2014.

		Adjusted OR (95%-CI)*				
	OPS	**Mortality in hospital**	**MACCE 1 year**	**Bypass-surgery 1 year**	**PCI 1 year**	**Repeat CA 1 year**
Paclitaxel-eluting stents (PES) with polymer	558b.04 558b.06	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Everolimus-eluting stents (EES) with polymer	883b.02 883b.0b 883b.0c	0.81 (0.61-1.07)	0.97 (0.90-1.04)	**0.81 (0.68-0.95)**	1.01 (0.96-1.05)	0.97 (0.94-1.01)
Zotarolimus-eluting (ZES) stents with polymer	558b.00	1.10 (0.82-1.46)	1.05 (0.97-1.13)	0.90 (0.76-1.07)	1.00 (0.95-1.04)	0.98 (0.94-1.03)
Sirolimus-eluting stents (SES) mit Polymer	558b.08	**0.64 (0.43-0.95)**	0.99 (0.90-1.08)	0.93 (0.75-1.14)	1.02 (0.96-1.08)	**1.07 (1.01-1.12)**
Sirolimus-eluting stents (SES) without polymer	558b.07	1.09 (0.54-1.11)	1.27 (1.06-1.53)	1.17 (0.76-1.80)	**1.36 (1.20-1.54)**	**1.67 (1.50-1.86)**
Biolimus-eluting stents (BES) with polymer	558b.01	0.76 (0.52-1.11)	1.06 (0.96-1.16)	**0.75 (0.60-0.94)**	1.04 (0.98-1.10)	**0.89 (0.85-0.94)**

Table 4: Multivariable logistic regression analyses of the effect of DES type on event rates (claims data of the German local healthcare funds 2008–2014) *risk adjusted for age, sex, co-morbidities according to Elixhauser classification, shock, NYHA class (I vs. II, III or IV), left main disease, multi-vessel disease (2 or 3 vessels), number of PCI (one coronary artery vs. a minimum of two) at index hospitalisation, AMI and dialysis in the year preceding admission. Significant odds ratios are highlighted in bold. BVS were not included. Abbreviations: DES drug eluting stent; BMS bare metal stent; BVS bio-resorbable vascular scaffolds; OR odds ratio; CI confidence interval; MACCE major cerebro- and cardiovascular events; CABG coronary artery bypass graft; PCI percutaneous coronary intervention; CA coronary angiography.

Discussion

This study assesses the safety of DES in clinical routine in Germany within the first year after index PCI, using statutory health insurance claims data from the largest health insurance in Germany covering around 30% of the German population. Additionally, we analysed the consequences of changes in DES-utilization over a 7-year time period. Our data show that the use of DES increased over time and that DES are associated with a decreased risk of 1-year MACCE compared to BMS.

Limitations

Our analyses included AOK-patients only. Even though AOK patients form a large group within Germany with 24 million insured persons and around one third of all inpatient hospital cases, external validity of our data on PCI utilization and MACCE-rates is limited due to the fact that AOK insured persons differ in their age and comorbidity profile when compared to other health insurances in Germany[22]. Comparing AOK cases to all German patients with coronary angiography and PCI in 2013, there are slight differences to our study population (female sex 39.8% (AOK) vs. 35.4% (Germany), age ≥ 70 years 52.7% (AOK) vs. 51.8% (Germany))[23]. For the risk-adjusted analyses of outcomes, patient characteristics were considered.

Data were generated as routine data for billing of claims. Inaccuracies of coding cannot be excluded and important variables may be missing. For example, we are not able to assess whether a repeat-revascularisation was performed in the same vessel as the index PCI. Additionally, we are unable to differentiate re-stenoses and stent-thromboses, therefore we chose mortality, AMI and repeat coronary procedures as endpoints.

It also has to be noted that due to missing POA-indexing (present on admission) of AMI, stroke and TIA, these diagnoses cannot be included in MACCE during the index hospitalisation. The proportion of these diagnoses after PCI has been reported as around 0.3%[23].

Time trends in percutaneous coronary interventions

Whilst the utilization of PCI has stabilized on a high level over the past years, the proportion of DES doubled during the study period from 33.6% in the year 2008 to 84.2% in 2014, the proportion of BMS was accordingly quartered during this time. Case numbers for 2014 confirm published data for Germany of 85.9% for DES[1], although these include patients with AMI. For 2013, an increase of DES utilization to 79% was reported[1]. In our analysis, immunosuppressive drugs with polymer cover 83.1% of DES in 2014 (Everolimus: 45.5%, Zotarolimus: 23.9%, Sirolimus: 8.7 and Biolimus: 8.0%). The increase of DES can be explained by recent reports of clinical trials on their efficacy and safety[24-26].

Study population

Our data show a distinct change in patient characteristics over the study time period 2008-2014. The proportion of patients with an age above 70 years increased as it has been previously reported for PCI-patients in Germany (German Heart Report: relative increase by 14.4% in men and 6.1% in women). The proportion of patients with diabetes was 34% and of patients with chronic kidney disease 19% (German Heart Report: 27% und 23% in 2014)[1]. Patients in the BMS-group were slightly older and had more co-morbidities like valvular diseases, atrial fibrillation and coagulopathies indicating a need for chronic anticoagulation or an increased tendency to bleed. For these patients, treatment seems to follow the current guideline recommendations[14]. Our data show a significant increase of these co-morbidities in the BMS-group over time. In the DES excluding BVS-group, the proportion of patients with multiple-vessel CAD, left main disease, previous AMI and diabetes was higher. Additionally in this group, multiple stenting occurred more frequently. These observations confirm study results and recommendations of Medical Societies on an advantage of DES in patients with an increased risk for re-stenosis or left main stenosis[25 27 28]. BMS-treatment is currently recommended for patients with an increased risk of stent thrombosis and in patients with

expected complications regarding dual anti-platelet therapy, e.g. due to planned elective surgery or anticipated compliance issues[27].

MACCE und repeat-revascularisation within one year

The one-year MACCE-rate in our cohort was 7.4% in the DES excluding BVS and 11.3% in the BMS-group. In the DES excluding BVS-group, the MACCE-rate remained nearly stable over time, despite the extended utilization in elder patients and despite the increase of complex procedures. Considering this, the slight increase in mortality is hardly surprising, especially as some patients who would have been candidates for CABG-surgery in earlier days (e.g. patients with left main disease) are increasingly treated with PCI. The decreasing proportion of AMI can be explained by the progress of DES-development and the use of modern anti-platelet agents like Prasugrel and Ticagrelor[14]. Die proportion of coronary angiographies during the one-year follow-up markedly decreased over time. This could be explained by an increasing perception of DES as a safe and routinely used treatment option.

Our finding of a distinctly increased 1-year MACCE rate in the BMS-group as compared to the DES-group has to be discussed considering the higher proportion of patients with an age over 70 years and with co-morbidities in the DES-group. One-year mortality in the BMS-group was double as high, and the proportion of AMI by a third higher than in the DES excluding BVS-group. In total, the proportion of MACCE in the BMS-group increased significantly over the observed time frame.

The adjusted odds ratio for the DES excluding BVS-group as compared to the BMS-group for 1-year MACCE is 0.72 (95%-CI: 0.70-0.75). It has to be considered that DES-treatment is not suitable for all patients and that the probability of ISR is higher in the „rest of patients" for whom DES treatment is not suitable. Clinical trials recently showed similar risks for DES and BMS in patients with STEMI with respect to mortality and repeat-AMI but advantages of DES with respect to repeat-revascularization[17 29]. A Canadian registry study, on the other hand, reported a reduced 3-year mortality of the DES-group in 2007[5].

Finally, DES technology improved over recent years[18 30]. With new developments and increased safety, further patient groups will profit from this treatment.

Conclusions

In summary, our analyses show that DES-treatment over a 7-year observation period evolved as the current standard of care. Despite the increased utilization of DES, 1-year MACCE are consistently less frequent than with BMS over the whole observation period with a small increase in the last two years indicating broader use. The frequency of repeat-coronary diagnostics and procedures decreased over time as DES are increasingly perceived as safe. BVS are used in clinical routine in selected cases with high safety, but with a high repeat-coronary angiography rate.

What is already known on this subject

- Drug eluting stents (DES) are recommended in current guidelines for most patients, but bare metal stents (BMS) may be recommendable in specific subgroups. Bio-resorbable vascular scaffolds (BVS) are the latest development in PCI, their safety and efficacy is still unclear.
- PCI is increasingly being used in higher risk patients. At the same time the stent materials used during PCI have evolved.
- With the rapidly evolving changes regarding patients and PCI materials, there is a lack of data for Europe describing effectiveness and safety of the different PCI materials and their application over recent years.

What this study adds

- In this analysis of German routine statutory health insurance claims data, application of DES during PCI increased from 33.6% in the year 2008 to 84.2% in 2014, including 2.3% BVS in 2014. The application of BMS decreased accordingly.
- Age of patients and their number of comorbidities increased over time in both, the DES and the BMS group. Patients with BMS were older than patients with DES.
- The one-year MACCE-rate in this cohort was 7.4% in the DES excluding BVS and 11.3% in the BMS-group.
- After risk-adjustment, the DES (excluding BVS) group had a lower risk for 1-year MACCE (OR= 0.72; 95% CI: 0.70-0.75), and particularly for 1-year mortality (OR = 0.70; CI: 0.67-0.74), 1-year CABG surgery (OR = 0.69; CI: 0.63-0.75), and repeat PCI within days 91-365 after the index PCI (OR = 0.87; CI: 0.81-0.93) as compared to the BMS group.
- Our study shows that DES can be used safely in clinical routine for the majority of patients

Data sharing statement

Raw data and code are accessible at the WIdO under data protection provisions.

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Competing interests:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest

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Authorship / Contributorship

EJ, MM and JS have drafted the manuscript, the other authors revised it critically for important intellectual content. All authors contributed to the conception and design of the research. EJ and CG contributed to the acquisition of the data. EJ and MM analyzed the data. All authors contributed to the interpretation of the results. All authors have approved of final the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration:

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. *Deutsche Herzstifung e.V. (Hrsg). 27. Deutscher Herzbericht 2015*. Frankfurt 2015.

2. Schuetz P, Batschwaroff M, Dusemund F, et al. Effectiveness of a procalcitonin algorithm to guide antibiotic therapy in respiratory tract infections outside of study conditions: a post-study survey. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 2010;**29**(3):269-77.

3. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. The New England journal of medicine 2003;**349**(14):1315-23.

4. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. The New England journal of medicine 2004;**350**(3):221-31.

5. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in Ontario. The New England journal of medicine 2007;**357**(14):1393-402.

6. Valgimigli M, Sabate M, Kaiser C, et al. Effects of cobalt-chromium everolimus eluting stents or bare metal stent on fatal and non-fatal cardiovascular events: patient level meta-analysis. Bmj 2014;**349**:g6427.

7. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;**369**(9562):667-78.

8. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. Journal of the American College of Cardiology 2006;**48**(1):193-202.

9. Lagerqvist B, James SK, Stenestrand U, et al. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. The New England journal of medicine 2007;**356**(10):1009-19.

10. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. Journal of the American College of Cardiology 2006;**48**(12):2584-91.

11. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004;**109**(6):701-5.

12. Bangalore S, Amoroso N, Fusaro M, et al. Outcomes with various drug-eluting or bare metal stents in patients with ST-segment-elevation myocardial infarction: a mixed treatment comparison analysis of trial level data from 34 068 patient-years of follow-up from randomized trials. Circulation Cardiovascular interventions 2013;**6**(4):378-90.

13. Bønaa KH MJ, Wiseth R, Aaberge L, Myreng Y, Nygård O, Nilsen DW, Kløw NE, Uchto M, Trovik T, Bendz B, Stavnes S, Bjørnerheim R, Larsen AI, Slette M, Steigen T, Jakobsen OJ, Bleie Ø, Fossum E, Hanssen TA, Dahl-Eriksen Ø, Njølstad I, Rasmussen K, Wilsgaard T, Nordrehaug JE; NORSTENT Investigators. Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease. N Engl J Med 2016;**375(13)**:1242-52.

14. Authors/Task Force m, Windecker S, Kolh P, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). European heart journal 2014;**35**(37):2541-619.

15. Akin I, Nienaber CA, Richardt G, et al. Risk factors for clinical events at 1-year follow-up after drug-eluting stent implantation: results from the prospective multicenter German DES.DE registry. Clinical research in cardiology : official journal of the German Cardiac Society 2014;**103**(5):363-72.

16. International Statistical Classification of Diseases and Related Health Problems 10th Revision. German Modification. Version 2012: Köln: DIMDI, 2012.

17. Sethi A, Bahekar A, Bhuriya R, et al. Drug-eluting stents versus bare metal stents in ST elevation myocardial infarction at a follow-up of three years or longer: A meta-analysis of randomized trials. Experimental and clinical cardiology 2012;**17**(4):169-74.

18. Byrne RA, Serruys PW, Baumbach A, et al. Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary. European heart journal 2015;**36**(38):2608-20.

19. Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. Medical care 1998;**36**(1):8-27.

20. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical care 2005;**43**(11):1130-9.

21. Arbeitsgruppe Erhebung und Nutzung von Sekundardaten der Deutschen Gesellschaft fur Sozialmedizin und P, Arbeitsgruppe Epidemiologische Methoden der Deutschen Gesellschaft fur Epid e m, Deutschen Gesellschaft fur Medizinische Informatik BuE, et al. [Good practice of secondary data analysis, first revision]. Gesundheitswesen 2008;**70**(1):54-60.

22. Hoffmann F, Icks A. [Structural differences between health insurance funds and their impact on health services research: results from the Bertelsmann Health-Care Monitor]. Gesundheitswesen 2012;**74**(5):291-7.

23. AQUA-Institut für angewandte Qualitätsförderung und Forschung im Gesundheitswesen GmbH. [Bundesauswertung zum Verfahrensjahr 2013. Koronarangiographie und PCI.] Göttingen: 2014. .

24. *Deutsche Herzstifung e.V. (Hrsg). 25. Deutscher Herzbericht 2013*. Frankfurt 2013

25. Kedhi E, Gomes ME, Lagerqvist B, et al. Clinical impact of second-generation everolimus-eluting stent compared with first-generation drug-eluting stents in diabetes mellitus patients: insights from a nationwide coronary intervention register. JACC Cardiovascular interventions 2012;**5**(11):1141-9.

26. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. The New England journal of medicine 2010;**363**(2):136-46.

27. Scheller B, Levenson B, Joner M, et al. Arbeitsgruppe Interventionelle Kardiologie (AGIK) der Deutschen Gesellschaft für Kardiologie (DGK). [Medikamente freisetzende Koronarstents und mit Medikamenten beschichtete Ballonkatheter. Positionspapier der DGK 2011]. Kardiologe 2011(5):411-35.

28. Wang XZ, Xu K, Li Y, et al. Comparison of the efficacy of drug-eluting stents versus bare-metal stents for the treatment of left main coronary artery disease. Chinese medical journal 2015;**128**(6):721-6.

29. Cho YK, Hur SH, Park NH, et al. Long-term outcomes of intravascular ultrasound-guided implantation of bare metal stents versus drug-eluting stents in primary percutaneous coronary intervention. The Korean journal of internal medicine 2014;**29**(1):66-75.

30. Tada T, Byrne RA, Simunovic I, et al. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. JACC Cardiovascular interventions 2013;**6**(12):1267-74.

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Drug eluting stents in clinical routine: A 1-year follow-up analysis based on German health insurance administrative data from 2008-2014

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Drug eluting stents in clinical routine: A 1-year follow-up analysis based on German health insurance administrative data from 2008-2014.

Elke Jeschke[1], Julia Searle[2], Christian Günster[1], Henning Thomas Baberg[3], Peter Dirschedl[4], Benny Levenson[5], Jürgen Malzahn[6], Thomas Mansky[7], Martin Möckel[2]

[1]Research Institute of the Local Health Care Funds (WIdO), 10178 Berlin, Germany, Elke Jeschke, Epidemiologist, Christian Günster, Head of Department Quality and Health Care Research; [2]Department of Cardiology and Division of Emergency Medicine and Chest Pain Units, Campus Virchow Klinikum and Campus Charité Mitte, Charité – Universitätsmedizin Berlin, 13353 Berlin, Germany, Julia Searle, Senior Research Associate, Martin Möckel, Medical Head of Division and Professor of Medicine; [3]Department of Cardiology and Nephrology, Helios Klinikum, Berlin-Buch, 13125 Berlin, Germany, Henning Thomas Baberg, Medical Head of Department; [4]Medical Service of the Health Funds (MDK) Baden-Württemberg, 77933 Lahr, Germany, Peter Dirschedl, Deputy Medical Head; [5]German Society of Cardiologists in Private Practice (BNK), Bundesverband niedergelassener Kardiologen), 80805 München, Germany, Benny Levenson, Executive Board; [6]Federal Association of the Local Health Care Funds (AOK), 10178 Berlin, Germany, Jürgen Malzahn Head of Division Inpatient Treatment and Rehabilitation; [7]Faculty of Economics and Management, Division for Structural Development and Quality Management in Healthcare, Technische Universität Berlin, 10623 Berlin, Germany, Thomas Mansky, Head of Division.

Correspondence to:

Martin Möckel, MD, FESC, FAHA (martin.moeckel@charite.de)

Charité - Universitätsmedizin Berlin

Charitéplatz 1, 10117 Berlin, Germany

Abstract

Objectives: To describe the use of drug eluting stents (DES) in the largest population of statutory health insurance members in Germany, including newly developed bio-resorbable vascular scaffolds (BVS), and to evaluate 1-year complication rates of DES as compared to bare metal stents (BMS) in this cohort.

Design: Routine data analysis of statutory health insurance claims data from the years 2008 to 2014.

Setting: The German healthcare insurance Allgemeine Ortskrankenkasse (AOK) covers approximately 30% of the German population and is the largest nationwide provider of statutory health care insurance in Germany.

Participants and interventions: We included all patients with a claims record for a percutaneous coronary intervention (PCI) with either DES or BMS and additionally, from 2013, BVS. Patients with acute myocardial infarction (AMI) were excluded. **Main outcome measure:** Major adverse cerebro- and cardiovascular events (MACCE, defined as mortality, AMI, stroke and transient ischemic attack (TIA)), bypass surgery, PCI and coronary angiography) at one year after the intervention.

Results: A total of 243,581 PCI cases were included (DES excluding BVS: 143,765; BVS: 1,440; BMS: 98,376). The 1-year MACCE rate was 7.42% in the DES subgroup excluding BVS and 11.29% in the BMS subgroup. The adjusted odds ratio (OR) for MACCE was 0.72 (95% CI: 0.70 to0.75) in DES patients excluding BVS as compared to BMS patients. In the BVS group, the proportion of 1-year MACCE was 5.0%.

Conclusion: The analyses demonstrate a lower MACCE rate for PCI with DES. BVS are used in clinical routine in selected cases and seem to provide a high degree of safety, but data are still sparse.

Key words: drug eluting stents, administrative data, MACCE, safety, healthcare research, bio-resorbable vascular scaffolds

Strengths and Limitations:

- Data of the largest provider of statutory health care insurance in Germany were used, which covers around 30% of the German population (24 million people).
- 243,581 PCI cases were included and time trends in PCI utilization over a 7-year time period were analysed. Data on newly developed BVS are also presented.
- MACCE, bypass surgery, PCI and coronary angiography within one year after the intervention were analysed.
- Multivariable logistic regression models were used to evaluate the association of PCI treatment (DES excluding BVS, BMS) on outcome.
- A subgroup analysis according to the pharmaceutical drug and carrier material was performed.
- The external validity of the data on PCI utilization is limited due to slight differences between AOK insurance members and German patients overall with regard to age and comorbidity profile
- Data were generated as routine data for billing of claims. Thus, coding inaccuracies cannot be ruled out and important variables may be missing. For example, it was not possible to assess whether a repeat revascularisation was performed in the same vessel as the index PCI

Introduction

Percutaneous coronary interventions (PCI) are a commonly and increasingly used revascularization strategy in patients with coronary artery disease (CAD). In Germany, 361,377 PCIs were performed in 2014 [1]. Germany is a model region with respect to early availability of new treatment options. For example, the mean time from approval to market for new medical drugs is 3.5 months compared to 5.8 months in the Netherlands and 16 months in Spain [2].

In recent years, case numbers for PCI have been stable on a high level. Still, the utilization pattern of PCI has changed dramatically over time with a distinct increase of PCIs in patients over the age of 70 years and in patients with comorbidities like diabetes mellitus and chronic kidney disease, as compared to 2008 [1]. Additionally, materials used in PCIs have changed. Whilst in the early years uncoated stents made of differing metal alloys (bare metal stents, BMS) were used, stents coated with pharmaceutical drugs and polymer (drug eluting stents, DES) are on the rise. DES were developed to prevent scarring and re-stenosis of the treated coronary vessel by releasing active agents over a defined period of time. Drugs commonly used in these stents inhibit cell growth, e.g. immunosuppressant drugs like Everolimus, Zotarolimus, Sirolimus or the cytostatic drug Paclitaxel - although Paclitaxel is used increasingly less - all in combination with different carrier materials (polymer). The latest development are bio-resorbable vascular scaffolds (BVS) which support the vessel over a certain period of time after which they dissolve. The safety and efficacy of BVS has been challenged recently [3].

DES have led to a significant reduction of in-stent re-stenoses (ISR) [4-7]. Still, particularly in the days of first-generation DES in the mid-2000s, there were considerable safety concerns, as a number of studies reported increased rates of late in-stent thromboses compared to BMS [8-12]. This argument is still being used to favour BMS. For the second-generation DES these concerns seem not to apply [13] and current guidelines recommend DES for most patients

although very recent data show that BMS may still have their place, e.g. patients with recent bleeding or a need for concomitant anticoagulation therapy [14 15]. The ESC guidelines mention BVS as a "promising" option without a clear recommendation [15]. A recent meta-analysis on the use of the "ABSORB" stent, which is the momentarily most used BVS, resulted in the conclusion that "BVS had increased definite/probable ST and MI during follow-up compared with DES [16].

This analysis of German statutory health insurance claims data was performed on the basis of changing conditions and patient populations for PCI treatment, to assess the clinical routine of coronary revascularization with PCI in Germany. Up until now, the only publication from Germany uses data from the German DES Registry, in which 98 hospitals participated [17]. We aimed to test the following hypotheses: a) DES are the new clinical standard for PCI in Germany and b) DES are effective and safe with respect to repeat revascularisation and major adverse cerebro- and cardiovascular events (MACCE) within 1-year after the initial PCI and c) BVS are increasingly used in clinical routine with a safe outcome.

Methods

Nationwide, anonymous billing data of the statutory health insurance company AOK (Allgemeine Ortskrankenkasse) were used for all 24 million AOK-insured persons in Germany. The AOK provides health care insurance for approximately 30% of the German population and is the largest nationwide provider of statutory health care insurance in Germany. Every person is allowed to enrol with the AOK regardless of age, comorbidity, income or type of employment. Data were derived from billing data for inpatient hospital treatment. They comprise ~~of~~ a unique identification number, age, sex, principal diagnosis and other diagnoses, procedures, length of stay, patient survival and insurance status. Diagnoses were coded according to the 10th revision of the International Classification of Diseases

(ICD-10) [18]. Procedures were documented using the German version of the International Classification of Procedures in Medicine (ICPM) [19], the "Operationen- und Prozedurenschlüssel" (OPS). Health care providers and health care insurances jointly issue binding guidelines for coding of diagnoses and procedures in hospital claims [20]. Hospital claims data in Germany are thoroughly checked against these guidelines and for plausibility by the Medical Review Board of the Social Health Insurance Funds and are returned to hospitals for correction if necessary. Corrections are included in the claims data used in this analysis.

We included all AOK cases from 2008 until 2014 with a claim for inpatient treatment with DES or BMS. Cases were identified by OPS codes (DES excluding BVS: 8-837.m; BVS: 8-83d.0; BMS: 8-837.k). The hospitalisation during which this PCI was performed is referred to as the index hospitalisation.

We excluded all cases with acute myocardial infarction (AMI) and patients with an age below 20 years as well as patients with cardiac surgery or PCI in the year before the index hospitalisation, independent of whether the latter was performed as an inpatient or outpatient treatment, as the outcome of these patients is strongly dependent on other factors than the type of stent.

For the analysis we formed three subgroups: patients with DES excluding BVS, patients with BVS and patients with BMS treatment. Data for BVS were available only for the years 2013 and 2014.

If patients had multiple stenting during the index hospitalisation with combined DES and BMS stenting, they were assigned to the DES group. This applies to n= 5.986 (2.46%) of cases.

First, we performed a descriptive analysis on the development of BMS and DES treatment over the pre-defined 5-year period. Cochrane-Armitage Trend Test was used to analyse trends over these years. In the DES group, we analysed subgroups according to the pharmaceutical

drug and carrier material as indicated within the OPS code 8-83b. We then analysed events during the 1-year follow-up period for the DES and BMS subgroups. Primary endpoint was the one-year MACCE rate (mortality, AMI, stroke or transient ischemic attack (TIA); ICD10: I21, I22, I63, G45), which is the proportion of patients who had one or more of these events during the follow-up year. These events are not ordered hierarchically, i.e. the MACCE rate is the proportion of patients who had at least one of these events within the follow-up year. In addition, we assessed coronary artery bypass graft CABG surgery (OPS: 5-361, 3-362, 5-363), PCI (OPS: 8-837, 8-83d) and coronary angiographies (OPS: 1-275) for different time frames within the 1-year follow-up period. To evaluate the association of PCI treatment (DES excluding BVS vs. BMS) with outcomes we used multivariable logistic regression models. Adjustment was made for age, sex, co-morbidities according to the Elixhauser classification [21], shock, NYHA class (I vs. II, III or IV), left main coronary artery disease (CAD), multi-vessel disease (2 or 3 vessels), number of PCIs (one coronary artery vs. a minimum of two) at index hospitalisation, AMI and dialysis in the year preceding admission, and year of treatment. Comorbidities were defined using the Elixhauser classification. The definition includes 31 acute and chronic comorbidities: congestive heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation disorders, peripheral vascular disease, uncomplicated hypertension, complicated hypertension, uncomplicated diabetes, complicated diabetes (i.e. coma, ketoacidosis, vascular disease), renal failure, liver disease, coagulopathy, blood loss anemia, deficiency anemia, hypothyroidism, peptic ulcer disease excluding bleeding, chronic pulmonary disease (COPD), obesity (BMI $\geq$ 30 kg/m^2), weight loss, solid tumor without metastasis, metastatic cancer, lymphoma, fluid and electrolyte disorders, rheumatoid arthritis/collagen vascular diseases, paralysis, other neurological disorders, alcohol abuse, drug abuse, psychoses, depression, and AIDS/HIV. Comorbidities were identified using the coding algorithm by Quan et al. based on the ICD-10 coding [22]. AMI, cardiogenic shock, NYHA class (I vs. II, III or IV), left main CAD, multi-vessel disease (2 or 3 vessels), which

are not included in the Elixhauser classification, were also included because they are potential risk factors and differ between the analysed groups ($p < 0.005$). All comorbidities were entered as separate dichotomous variables. Age was used as a continuous variable in the regression analysis. Patients in whom AOK insurance ended before the end of the 1-year follow-up period were censored, resulting in differing case numbers for different follow-up periods. All analyses were performed using STATA 11.2 (StataCorp, College Station, Texas).

Ethics

The present study is based on data provided by hospitals for health insurance accounting. The recommendations for good practice in secondary data analysis developed by the German Working Group on the Collection and Use of Secondary Data [23] were applied in full. This type of analysis requires no formal ethics committee approval.

Results

The analysis included 243,581 cases with PCI, 143,765 (59.02%) in the DES group excluding BVS, 1,440 (0.59%) in the BVS group and 98,376 (40.39%) in the BMS group. In total, 37.0% of all eligible cases (N= 659,067) with PCI were included. Cases were excluded according to the exclusion criteria (AMI at the index hospitalisation, cardiac surgery or PCI in the year before the index hospitalisation or age below 20 years).

Study population

Table 1 shows basic characteristics of our study population. There were significant differences in patient characteristics between groups (patient age: $p< 0.001$, median test; other variables: $p < 0.05$; chi-squared test) in all variables except coronary 2-vessel disease ($p=0.408$; chi-squared test) and obesity ($p=0.054$; chi-squared test). Patients in the DES group excluding BVS were 2 years younger than patients in the BMS-group (median: 70 vs. 72

years). The proportions of patients with prior MI, coronary 3-vessel disease, left main CAD and diabetes were higher in the DES group excluding BVS as was the proportion of patients with multiple stenting (number of PCIs >1; DES: 18.5% vs. BMS: 6.3%). In the BMS group, the proportions of patients with heart failure, NYHA class >1, cardiac arrhythmia, valvular disease, and COPD were higher. The median age of the BVS group was 64 years and the proportion of patients with concomitant diseases was lower than in the other groups.

The age of patients increased in all groups over time, but more prominently in the BMS group (median age in years: DES group excluding BVS 2008: 68; 2014: 71; BMS group 2008: 70; 2014: 75). In 2014, the proportion of patients with an age above 70 years was 53.80% in the DES group excluding BVS, 69.60% in the BMS group, and 35.96 in the BVS group. Likewise, the proportion of comorbidities increased over time. This was also most prominent in patients of the BMS group with heart failure, cardiac arrhythmia, valvular diseases, and chronic kidney disease. The proportion of patients with cardiac arrhythmia, for example, increased by 8.5% (2008: 16.0%; 2014: 24.5%) in the DES group excluding BVS and by 28.2% (2008: 24.3%; 2014: 52. 5%) in the BMS group.

	Total	**DES excluding BVS**	**BMS**	**BVS**
Number [N]	**243,581**	**143,765**	**98,376**	**1,440**
Age [Median (IQR)]	71 (62-77)	70 (61-76)	72 (65-78)	64 (55-73)
Female patients [%]	32.23%	31.52%	33.31%	28.47%
Diagnoses at the index hospital stay [%]*				
Cardiovascular diseases				
Prior MI	9.60%	10.34%	8.55%	7.50%
Stroke	0.48%	0.40%	0.59%	0.28%
TIA	0.27%	0.21%	0.35%	0.14%
Intracerebral bleeding	0.04%	0.03%	0.06%	0.00%
Congestive heart failure	26.69%	25.45%	28.53%	25.21%
NYHA stage > 1	22.07%	21.02%	23.62%	21.67%
Coronary 2-vessel disease	31.54%	31.63%	31.39%	32.15%

Coronary 3-vessel disease	37.63%	40.36%	33.73%	30.49%
Left main CAD	3.77%	4.68%	2.47%	1.46%
Shock	0.55%	0.49%	0.64%	0.14%
Arterial hypertension	78.63%	79.52%	77.34%	77.92%
Cardiac arrhythmia	25.30%	20.48%	32.44%	17.29%
Valvular disease	10.11%	8.75%	12.14%	7.43%
Peripheral vascular disorders	11.56%	11.25%	12.06%	8.06%
Other concomitant diseases				
Diabetes mellitus	33.51%	35.22%	31.07%	28.75%
COPD	9.55%	8.76%	10.71%	9.31%
CKD	19.48%	18.70%	20.73%	12.15%
ESRD	3.92%	3.91%	3.97%	2.26%
Hypothyroidism	7.22%	7.54%	6.71%	9.44%
Obesity (BMI ≥ 30 kg/m²)	12.00%	12.03%	11.93%	13.96%
Interventions at index hospital stay [%]				
PCI > 1 coronary artery**	13.52%	18.45%	6.32%	12.57%
Pacemaker	1.20%	1.04%	1.45%	0.63%
ICD-implantation	0.79%	0.70%	0.93%	0.28%
Dialysis	1.75%	1.59%	2.00%	0.69%

Table 1: **Patient characteristics, for all patients and for the subgroups of patients with DES excluding BVS, BMS and BVS**

*other comorbidities according to Elixhauser et al. with a frequency <5% are not shown (pulmonary circulation disorders, liver disease, blood loss anemia, deficiency anemia, peptic ulcer disease excluding bleeding, coagulopathy, weight loss, solid tumor without metastasis, metastatic cancer, lymphoma, rheumatoid arthritis/collagen, paralysis, other neurological disorders, alcohol abuse, drug abuse, psychoses, depression, AIDS/HIV) **At least two stents in one or more coronary arteries during index hospitalisation.

Abbreviations: DES drug eluting stent; BMS bare metal stent; BVS bio-resorbable vascular scaffolds; IQR interquartile range; MI myocardial infarction; TIA transient ischaemic attack; CKD chronic kidney disease; ESRD end stage renal disease; COPD chronic obstructive pulmonary disease; PCI percutaneous coronary intervention; ICD implantable cardioverter defibrillator

Time trends in percutaneous coronary interventions

Figure 1 shows the frequency of PCI treatment in AOK patients over time. The proportion of DES increased from 33.6% in 2008 (n=10,843) to 84.2% in 2014 (n=30,181), including 2.3% BVS in 2014 (n=856). The proportion of BMS decreased accordingly.

Figure 2 shows the development of DES treatment over the pre-defined 7-year period according to pharmaceutical drug and carrier materials used. The proportion of Everolimus-eluding stents with polymer increased markedly (2008: 25.5%; 2014: 46.4%). The same is true for the proportion of Zotarolimus- and Biolimus-eluding stents with polymer (2008: 17.7%; 2014: 25.5% and 2008: 5.8%; 2014: 12.4%, respectively). The use of all other stents decreased over this time period, most prominently Paclitaxel-eluting stents with polymer (2008: 29.7%; 2014: 1.5%). Very rarely used stents with case numbers below 100 over the five-year period are not shown. Drugs used in BVS are not sufficiently coded in the data set.

MACCE und repeat revascularisation within one year

Table 2 shows event rates for the DES group excluding BVS and BMS group over the whole study period and for the respective years of the study period. In total, the proportion of MACCE during the one-year period after the index PCI was 7.4% in the DES group excluding BVS and 11.3% in the BMS group. Repeat coronary procedures occurred more frequently in the DES group excluding BVS. The proportion of repeat coronary angiographies, for example, was 3.4% higher in the DES group excluding BVS (34.5% as compared to 31.1% in the BMS group). In the BVS group (data available only for 2013 and 2014) the proportion of 1-year MACCE was 5.0% and the 1-year mortality was 2.5%. Repeat coronary procedures within one year occurred more frequently in BVS patients (PCI 25.8%; repeat coronary angiographies 39.6%).

In the DES group excluding BVS, there was a small increase with respect to 1-year MACCE over time ($p<0.001$, trend test). One-year mortality increased (2008: 3.6%; 2014: 5.1%; $p<0.001$), whereas the proportion of AMI decreased slightly over time (2008: 2.5%; 2014: 2.2%; $p=0.013$). In the BMS group, the proportion of 1-year MACCE increased by 5.3%

(2008: 9.6%; 2012: 14.9%; p<0.001). This is mostly driven by an increased mortality (2008: 5.3%; 2014: 10.8%; p<0.001).

Looking at repeat coronary procedures over time, data show a decrease, particularly of coronary angiographies, (DES excluding BVS: 2008: 40.81%, 2014: 30.69%; BMS: 2008: 33.66%, 2014: 26.53%; p<0.001 for both) but also of CABG surgery (DES excluding BVS: 2008: 1.94%, 2014: 0.90%; BMS: 2008: 2.15%, 2014: 1.28%, p<0,001 for both).

	Total [%]	2008 [%]	2009 [%]	2010 [%]	2011 [%]	2012 [%]	2013 [%]	2014 [%]
DES excluding BVS (N=143,765)								
Mortality during index hospitalisation	**0.57**	0.41	0.42	0.50	0.44	0.56	0.60	0.83
MACCE (1y)	**7.42**	7.04	7.60	7.21	7.01	7.17	7.53	8.28
Mortality	**4.22**	3.59	3.53	3.94	3.88	4.07	4.43	5.10
AMI	**2.22**	2.52	2.52	2.14	2.16	2.18	2.09	2.19
Stroke	**1.06**	1.05	1.01	1.13	1.10	0.93	1.07	1.13
TIA	**0.55**	0.50	0.44	0.61	0.48	0.60	0.60	0.55
CABG after index hospitalisation (1y)	**1.20**	1.94	1.44	1.52	1.22	1.04	1.02	0.90
- of these: within 30d	**0.09**	0.11	0.08	0.11	0.10	0.11	0.09	0.08
- of these: within 31-365d	**1.10**	1.83	1.36	1.41	1.12	0.93	0.93	0.81
PCI after index hospitalisation (1y)	**21.40**	22.50	22.86	22.46	21.80	21.09	20.65	20.32
- of these: within 90d	**12.59**	11.62	12.18	12.37	12.75	12.91	12.75	12.76
- of these: within 91-365d	**8.52**	10.68	10.44	9.83	8.79	7.90	7.55	7.20
Coronary angiography after index hospitalisation (1y)	**34.49**	40.81	39.13	37.50	35.02	33.19	32.49	30.69
BMS (N=98,376)								
Mortality during index hospitalisation	**0.97**	0.64	0.83	0.95	1.00	1.23	1.51	1.33
MACCE (1y)	**11.29**	9.58	10.33	11.05	11.32	12.68	14.10	14.93
Mortality	**7.08**	5.26	6.15	6.76	7.32	8.60	9.64	10.80
AMI	**3.33**	3.44	3.26	3.38	3.19	3.20	3.47	3.35
Stroke	**1.44**	1.36	1.26	1.42	1.47	1.51	1.75	1.72
TIA	**0.72**	0.61	0.82	0.70	0.62	0.81	0.87	0.74
CABG after index hospitalisation (1y)	**1.70**	2.15	1.97	1.66	1.39	1.28	1.40	1.25

- of these: within 30d	**0.14**	0.13	0.12	0.14	0.15	0.11	0.14	0.23
- of these: within 31-365d	**1.56**	2.01	1.84	1.51	1.24	1.16	1.25	1.00
PCI after index hospitalisation (1y)	**19.90**	21.22	20.00	20.22	19.67	19.50	18.08	17.37
- of these: within 90d	**10.17**	10.55	10.02	10.28	10.42	10.28	9.44	8.99
- of these: within 91-365d	**9.38**	10.43	9.66	9.61	8.85	8.79	8.16	7.84
Coronary angiography after index hospitalisation (1y)	**31.14**	33.66	32.21	31.84	30.26	28.71	28.29	26.53

Table 2: Event rates during the 5-year observation period and during the individual years (claims data of the German local healthcare funds 2008-2014)

Patients in whom AOK insurance ended before the end of the 1-year follow-up period were censored, resulting in differing case numbers for different follow-up periods. Abbreviations: DES drug eluting stent; BVS bio-resorbable vascular scaffolds; MACCE major cerebro- and cardiovascular events; AMI acute myocardial infarction; TIA transient ischaemic attack; CABG coronary artery bypass graft; PCI percutaneous coronary intervention; BMS bare metal stent.

Table 3 shows odds ratios (OR) for DES excluding BVS compared to BMS treatment, risk-adjusted for patient characteristics and year of treatment. After risk-adjustment, the DES group excluding BVS had a lower risk for 1-year MACCE (OR= 0.72; 95% CI: 0.70-0.75), and particularly for 1-year mortality (OR = 0.70; CI: 0.67-0.74), 1-year CABG surgery (OR = 0.69; CI: 0.63-0.75), and repeat PCI within days 91-365 after the index PCI (OR = 0.87; CI: 0.81-0.93). DES group excluding BVS also had a higher risk of PCI within 90 days after the index PCI (OR = 1.14; CI: 1.07-1.21) and of repeat coronary angiography within 1 year (OR = 1.14; CI: 1.06-1.23).

Like DES excluding BVS, the odds ratios for BVS compared to BMS were lower for 1-year MACCE (OR= 0.59; 95% CI: 0.46-0.74) and for 1-year mortality (OR = 0.55; CI: 0.41-0.74). The BVS group also had a higher risk of PCI within 90 days after the index PCI (OR = 1.83; CI: 1.51-2.22) and of repeat coronary angiography within 1 year (OR = 1.64; CI: 1.33-2.02).

	Adjusted OR* (95% CI)	**Crude OR (95% CI)**
Mortality during index hospitalisation	**0.70**	**0.59**

	(0.61-0.80)	**(0.53-0.66)**
MACCE (1y)	**0.72 (0.70-0.75)**	**0.63 (0.61-0.65)**
- of these: mortality (1y)	**0.70 (0.67-0.74)**	**0.58 (0.55-0.61)**
CABG after index hospitalisation (1y)	**0.69 (0.63-0.75)**	**0.70 (0.65-0.76)**
- of these: within 30d	**0.60 (0.47-0.76)**	**0.68 (0.54-0.87)**
- of these: within 31-365d	**0.70 (0.64-0.77)**	**0.70 (0.65-0.77)**
PCI after index hospitalisation (1y)	0.99 (0.94-1.04)	**1.11 (1.04-1.15)**
- of these: within 90d	**1.14 (1.07-1.21)**	**1.27 (1.20-1.35)**
- of these: within 91-365d	**0.87 (0.81-0.93)**	**0,90 (0,84-0.96)**
Coronary angiography after index hospitalisation (1y)	**1.14 (1.06-1.23)**	**1.16 (1.09-1.25)**

Table 3: Uni- and multivariable logistic regression analysis of the effect of PCI treatment - DES excluding BVS vs. BMS (reference) - on event rates (claims data of the German local healthcare funds 2008-2014) *Risk adjustment included age, sex, comorbidities according to the Elixhauser classification, shock, NYHA class (I vs. II, III or IV), left main CAD, multi-vessel disease (2 or 3 vessels), number of PCI (one coronary artery vs. a minimum of two) at index hospitalisation, AMI and dialysis in the year preceding admission and year of treatment. Significant odds ratios are highlighted in bold. Abbreviations: DES drug eluting stent; BMS bare metal stent; BVS bio-resorbable vascular scaffolds; OR odds ratio; CI confidence interval; MACCE major cerebro- and cardiovascular events; CABG coronary artery bypass graft; PCI percutaneous coronary intervention.

Influence of DES stent type

Table 4 shows the comparison of newer versus first generation (Paclitaxel) DES. Bio-resorbable stents were excluded as the respective code was only available for 2013 and 2014.

		Adjusted OR (95%-CI)*				
	OPS	**Mortality in hospital**	**MACCE 1 year**	**Bypass-surgery 1 year**	**PCI 1 year**	**Repeat CA 1 year**

Paclitaxel-eluting stents (PES) with polymer	558b.04 558b.06	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Everolimus-eluting stents (EES) with polymer	883b.02 883b.0b 883b.0c	0.81 (0.61-1.07)	0.97 (0.90-1.04)	**0.81 (0.68-0.95)**	1.01 (0.96-1.05)	0.97 (0.94-1.01)
Zotarolimus-eluting (ZES) stents with polymer	558b.00	1.10 (0.82-1.46)	1.05 (0.97-1.13)	0.90 (0.76-1.07)	1.00 (0.95-1.04)	0.98 (0.94-1.03)
Sirolimus-eluting stents (SES) mit Polymer	558b.08	**0.64 (0.43-0.95)**	0.99 (0.90-1.08)	0.93 (0.75-1.14)	1.02 (0.96-1.08)	**1.07 (1.01-1.12)**
Sirolimus-eluting stents (SES) without polymer	558b.07	1.09 (0.54-1.11)	1.27 (1.06-1.53)	1.17 (0.76-1.80)	**1.36 (1.20-1.54)**	**1.67 (1.50-1.86)**
Biolimus-eluting stents (BES) with polymer	558b.01	0.76 (0.52-1.11)	1.06 (0.96-1.16)	**0.75 (0.60-0.94)**	1.04 (0.98-1.10)	**0.89 (0.85-0.94)**

Table 4: Multivariable logistic regression analyses of the effect of DES type on event rates (claims data of the German local healthcare funds 2008–2014) *risk adjusted for age, sex, co-morbidities according to Elixhauser classification, shock, NYHA class (I vs. II, III or IV), left main disease, multi-vessel disease (2 or 3 vessels), number of PCI (one coronary artery vs. a minimum of two) at index hospitalisation, AMI and dialysis in the year preceding admission. Significant odds ratios are highlighted in bold. BVS were not included. Abbreviations: DES drug eluting stent; BMS bare metal stent; BVS bio-resorbable vascular scaffolds; OR odds ratio; CI confidence interval; MACCE major cerebro- and cardiovascular events; CABG coronary artery bypass graft; PCI percutaneous coronary intervention; CA coronary angiography.

Discussion

This study assesses the safety of DES in clinical routine in Germany within the first year after index PCI, using statutory health insurance claims data from the largest health insurance in Germany, which covers around 30% of the German population. In addition, we analysed the consequences of changes in DES utilization over a 7-year time period. Our data show that the use of DES increased over time. 1-year MACCE are consistently less frequent than with BMS over the whole observation period.

Limitations

Our analyses included AOK patients only. Even though AOK patients form a large population of 24 million insured persons and represent around one third of all inpatient hospital cases in Germany, external validity of our data on PCI utilization and MACCE rates is limited due to the fact that the AOK-insured population differs in age and comorbidity profile when compared to other health insurance providers in Germany [24]. Comparing AOK cases to all German patients with coronary angiography and PCI in 2013, there are slight differences in our study population (female sex 39.8% (AOK) vs. 35.4% (Germany), age ≥ 70 years 52.7% (AOK) vs. 51.8% (Germany)) [25]. However, these patient characteristics were controlled for in risk-adjusted analyses.

Data were generated as routine data for billing of claims. Coding inaccuracies cannot be ruled out and important variables may be missing. For example, we were unable to assess whether a repeat revascularisation was performed in the same vessel as the index PCI. We were also unable to differentiate re-stenoses and stent thromboses, and therefore chose mortality, AMI and repeat coronary procedures as outcomes.

In addition, it has to be noted that due to missing POA (present on admission) indexing of AMI, stroke and TIA in claims data, these diagnoses cannot be included under MACCE during the index hospitalisation. The proportion of these diagnoses after PCI has been reported at around 0.3% [25].

Finally, routine data do not include detailed clinical information e.g. that needed to check whether indications conformed to the guidelines.

Study population

Our data show a distinct change in patient characteristics over the study period from 2008 to 2014. The proportion of patients with an age above 70 years increased, as has been previously reported for PCI patients in Germany (German Heart Report: relative increase by 14.4% in men and 6.1% in women). The proportions of patients with diabetes and chronic kidney

disease in our data were 34% and 19%, respectively (German Heart Report: 27% und 23% in 2014) [1]. Patients in the BMS group were slightly older and had more comorbidities such as valvular diseases, atrial fibrillation and coagulopathies, indicating a need for chronic anticoagulation or an increased tendency to bleed. For these patients, treatment seems to follow the current guideline recommendations [15]. Our data show a significant increase of these comorbidities in the BMS group over time. In the DES group excluding BVS, the proportions of patients with multiple-vessel CAD, left main CAD, previous AMI and diabetes were higher. In addition, multiple stenting occurred more frequently in this group. These observations confirm study results and recommendations of Medical Societies on an advantage of DES in patients with an increased risk for re-stenosis or left main stenosis [26-28]. BMS treatment is currently recommended for patients with an increased risk of stent thrombosis and in patients with expected complications regarding dual anti-platelet therapy, e.g. due to planned elective surgery or anticipated compliance issues [27].

Time trends in percutaneous coronary interventions

Whilst the utilization of PCI has stabilized on a high level over the past years, the proportion of DES doubled during the study period from 33.6% in the year 2008 to 84.2% in 2014, and accordingly the proportion of BMS was quartered during this period. Case numbers for 2014 confirm a published proportion for Germany of 85.9% for DES [1], although these include patients with AMI. For 2013, an increase of DES utilization to 79% was reported [1]. In our analysis, immunosuppressive drugs with polymer cover 83.1% of DES in 2014 (Everolimus: 45.5%, Zotarolimus: 23.9%, Sirolimus: 8.7 and Biolimus: 8.0%). The increase of DES can be explained by recent reports of clinical trials on their efficacy and safety [26 29 30].

Nevertheless, in the Swedish SCAAR registry (DES use data available until 2010) the DES rate was a little bit lower with 32% in the time frame 2009-2010 with same tendency of continuous increase except in 2007-2008 when safety issues were intensively discussed worldwide [31].

MACCE und repeat revascularisation within one year

The one-year MACCE rate in our cohort was 7.4% in the DES group excluding BVS and 11.3% in the BMS group. In the DES excluding BVS group, the MACCE rate remained nearly stable over time, despite the extended utilization in elder patients and despite the increase of complex procedures. Considering this, the slight increase in mortality is hardly surprising, especially as some patients who would have been candidates for CABG surgery in earlier days (e.g. patients with left main CAD) are increasingly treated with PCI. The decreasing proportion of AMI can be explained by the progress of DES development and the use of modern anti-platelet agents like Prasugrel and Ticagrelor [15]. The proportion of coronary angiographies during the one-year follow-up decreased markedly over time. This could be explained by an increasing perception of DES as a safe and routinely used treatment option.

Our finding of a distinctly increased 1-year MACCE rate in the BMS group as compared to the DES group has to be discussed considering the higher proportion of patients with an age over 70 years and with comorbidities in the DES group. One-year mortality in the BMS group was twice as high, and the proportion of AMI higher by a third than in the DES group excluding BVS. In total, the proportion of MACCE in the BMS group increased significantly over the observed time frame.

The adjusted odds ratio for the DES group excluding BVS as compared to the BMS group for 1-year MACCE was 0.72 (95%-CI: 0.70-0.75). Because the practices of German cardiologists have evolved during the study period, we included the year of PCI treatment as a possible confounder in the multivariable regression analysis. But it has to be considered that DES treatment is not suitable for all patients and that the probability of ISR is higher in the „rest of patients" for whom DES treatment is not suitable. Clinical trials recently showed similar risks for DES and BMS in patients with STEMI with respect to mortality and repeat AMI but

advantages of DES with respect to repeat revascularization [32 33]. A Canadian registry study, on the other hand, reported a reduced 3-year mortality of the DES group in 2007 [6]. Finally, DES technology has improved over recent years [25 34]. With new developments and increased safety, further patient groups will benefit from this treatment.

Conclusions

In summary, our analyses show that DES treatment evolved into the current standard of care over a 7-year observation period. Despite the increased utilization of DES, 1-year MACCE are consistently less frequent than with BMS over the whole observation period, with a small increase in the last two years indicating broader use. The frequency of repeat coronary diagnostics and procedures decreased over time as DES are increasingly perceived as safe. BVS are used in clinical routine in selected cases with high safety, but with a high repeat-coronary angiography rate.

Data sharing statement

Raw data and code are accessible at the WIdO under data protection provisions.

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Competing interests:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Authorship / Contributorship

EJ, MM and JS drafted the manuscript, the other authors revised it critically for important intellectual content. All authors contributed to the conception and design of the research. EJ and CG contributed to the acquisition of the data. EJ and MM analyzed the data. All authors contributed to the interpretation of the results. All authors have approved the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration:

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Figure captions

Figure 1

Frequency of drug eluting stents (DES) and bare metal stents (BMS) including bio-resorbable vascular scaffolds (BVS) utilization over time (2008-2014).

Figure 2

Frequency of the different drug eluting stent (DES) used over time (2008-2014) according to active drug component and carrier material (groups > 1% only) * Multiple selections possible due to implantation of different stent types during index procedure. BVS were not included. OPS "Operationen- und Prozedurenschlüssel" (OPS) German version of the International Classification of Procedures in Medicine (ICPM) [19].

References

1. *Deutsche Herzstifung e.V. (Hrsg). 27. Deutscher Herzbericht 2015*. Frankfurt 2015.

2. Medizinische Leistungen in Deutschland gut zugänglich. Dtsch Arztebl 2017;**114**(13): A-606

3. Schuetz P, Batschwaroff M, Dusemund F, et al. Effectiveness of a procalcitonin algorithm to guide antibiotic therapy in respiratory tract infections outside of study conditions: a post-study survey. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 2010;**29**(3):269-77 doi: 10.1007/s10096-009-0851-0.

4. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. The New England journal of medicine 2003;**349**(14):1315-23 doi: 10.1056/NEJMoa035071.

5. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. The New England journal of medicine 2004;**350**(3):221-31 doi: 10.1056/NEJMoa032441[published Online First: Epub Date]|.

6. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in Ontario. The New England journal of medicine 2007;**357**(14):1393-402 doi: 10.1056/NEJMoa071076.

7. Valgimigli M, Sabate M, Kaiser C, et al. Effects of cobalt-chromium everolimus eluting stents or bare metal stent on fatal and non-fatal cardiovascular events: patient level meta-analysis. Bmj 2014;**349**:g6427 doi: 10.1136/bmj.g6427.

8. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;**369**(9562):667-78 doi: 10.1016/S0140-6736(07)60314-6.

9. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. Journal of the American College of Cardiology 2006;**48**(1):193-202 doi: 10.1016/j.jacc.2006.03.042.

10. Lagerqvist B, James SK, Stenestrand U, et al. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. The New England journal of medicine 2007;**356**(10):1009-19 doi: 10.1056/NEJMoa067722.

11. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. Journal of the American College of Cardiology 2006;**48**(12):2584-91 doi: 10.1016/j.jacc.2006.10.026.

12. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004;**109**(6):701-5 doi: 10.1161/01.CIR.0000116202.41966.D4.

13. Bangalore S, Amoroso N, Fusaro M, et al. Outcomes with various drug-eluting or bare metal stents in patients with ST-segment-elevation myocardial infarction: a mixed treatment comparison analysis of trial level data from 34 068 patient-years of follow-up from randomized trials. Circulation Cardiovascular interventions 2013;**6**(4):378-90 doi: 10.1161/CIRCINTERVENTIONS.113.000415.

14. Bønaa KH MJ, Wiseth R, Aaberge L, Myreng Y, Nygård O, Nilsen DW, Kløw NE, Uchto M, Trovik T, Bendz B, Stavnes S, Bjørnerheim R, Larsen AI, Slette M, Steigen T, Jakobsen OJ, Bleie Ø, Fossum E, Hanssen TA, Dahl-Eriksen Ø, Njølstad I, Rasmussen K, Wilsgaard T, Nordrehaug JE; NORSTENT Investigators. Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease. N Engl J Med 2016;**375(13)**:1242-52

15. Authors/Task Force m, Windecker S, Kolh P, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). European heart journal 2014;**35**(37):2541-619 doi: 10.1093/eurheartj/ehu278.

16. Lipinski MJ, Escarcega RO, Baker NC, et al. Scaffold Thrombosis After Percutaneous Coronary Intervention With ABSORB Bioresorbable Vascular Scaffold: A Systematic Review and Meta-Analysis. JACC Cardiovascular interventions 2016;**9**(1):12-24 doi: 10.1016/j.jcin.2015.09.024.

17. Akin I, Nienaber CA, Richardt G, et al. Risk factors for clinical events at 1-year follow-up after drug-eluting stent implantation: results from the prospective multicenter German DES.DE registry. Clinical research in cardiology : official journal of the German Cardiac Society 2014;**103**(5):363-72 doi: 10.1007/s00392-014-0662-x.

18. International Statistical Classification of Diseases and Related Health Problems 10th Revision. German Modification. Version 2012: Köln: DIMDI, 2012.

19. International Classification of Procedures in Medicine (ICPM). German Modification. Version 2012: Köln: DIMDI, 2012.

20. German Coding Rules (Deutsche Kodierrichtlinien): InEK GmbH 2015.

21. Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. Medical care 1998;**36**(1):8-27

22. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical care 2005;**43**(11):1130-9

23. Arbeitsgruppe Erhebung und Nutzung von Sekundardaten der Deutschen Gesellschaft fur Sozialmedizin und P, Arbeitsgruppe Epidemiologische Methoden der Deutschen Gesellschaft fur Epid e m, Deutschen Gesellschaft fur Medizinische Informatik BuE, et al. [Good practice of secondary data analysis, first revision]. Gesundheitswesen 2008;**70**(1):54-60 doi: 10.1055/s-2007-1022529.

24. Hoffmann F, Icks A. [Structural differences between health insurance funds and their impact on health services research: results from the Bertelsmann Health-Care Monitor]. Gesundheitswesen 2012;**74**(5):291-7 doi: 10.1055/s-0031-1275711.

25. Byrne RA, Serruys PW, Baumbach A, et al. Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary. European heart journal 2015;**36**(38):2608-20 doi: 10.1093/eurheartj/ehv203.

26. Kedhi E, Gomes ME, Lagerqvist B, et al. Clinical impact of second-generation everolimus-eluting stent compared with first-generation drug-eluting stents in diabetes mellitus patients: insights from a nationwide coronary intervention register. JACC Cardiovascular interventions 2012;**5**(11):1141-9 doi: 10.1016/j.jcin.2012.06.020.

27. Scheller B, Levenson B, Joner M, et al. Arbeitsgruppe Interventionelle Kardiologie (AGIK) der Deutschen Gesellschaft für Kardiologie (DGK). [Medikamente freisetzende Koronarstents und mit Medikamenten beschichtete Ballonkatheter. Positionspapier der DGK 2011]. Kardiologe 2011(5):411-35

28. Wang XZ, Xu K, Li Y, et al. Comparison of the efficacy of drug-eluting stents versus bare-metal stents for the treatment of left main coronary artery disease. Chinese medical journal 2015;**128**(6):721-6 doi: 10.4103/0366-6999.152460.

29. *Deutsche Herzstifung e.V. (Hrsg). 25. Deutscher Herzbericht 2013*. Frankfurt 2013

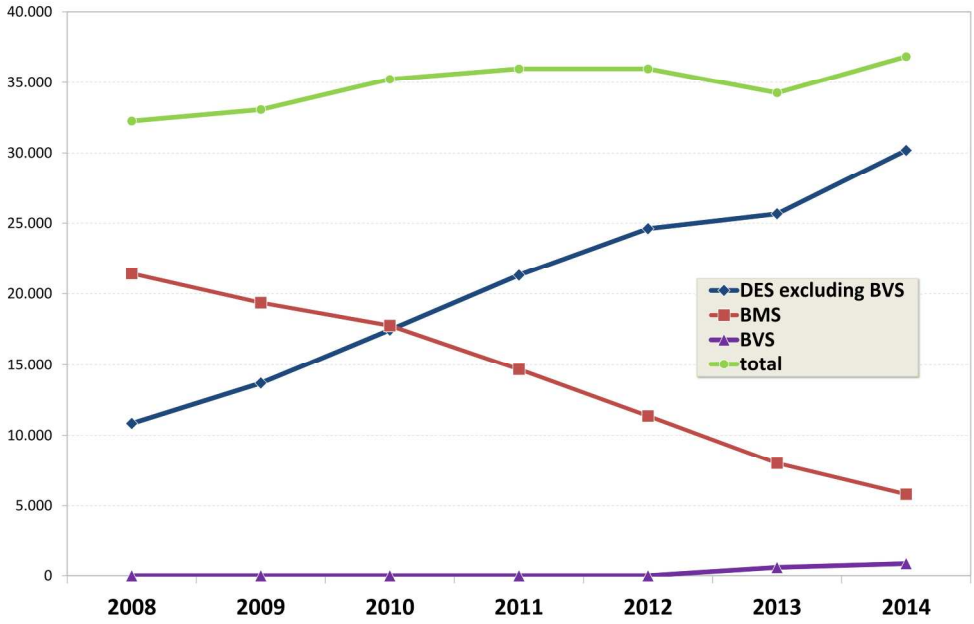
30. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. The New England journal of medicine 2010;**363**(2):136-46 doi: 10.1056/NEJMoa1004130.

31. Fokkema ML, James SK, Albertsson P, et al. Population trends in percutaneous coronary intervention: 20-year results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). Journal of the American College of Cardiology 2013;**61**(12):1222-30 doi: 10.1016/j.jacc.2013.01.007.

32. Cho YK, Hur SH, Park NH, et al. Long-term outcomes of intravascular ultrasound-guided implantation of bare metal stents versus drug-eluting stents in primary percutaneous coronary intervention. The Korean journal of internal medicine 2014;**29**(1):66-75 doi: 10.3904/kjim.2014.29.1.66.

33. Sethi A, Bahekar A, Bhuriya R, et al. Drug-eluting stents versus bare metal stents in ST elevation myocardial infarction at a follow-up of three years or longer: A meta-analysis of randomized trials. Experimental and clinical cardiology 2012;**17**(4):169-74

34. Tada T, Byrne RA, Simunovic I, et al. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. JACC Cardiovascular interventions 2013;**6**(12):1267-74 doi: 10.1016/j.jcin.2013.06.015[published Online First: Epub Date].



Frequency of drug eluting stents (DES) and bare metal stents (BMS) including bio-resorbable vascular scaffolds (BVS) utilization over time (2008-2014).

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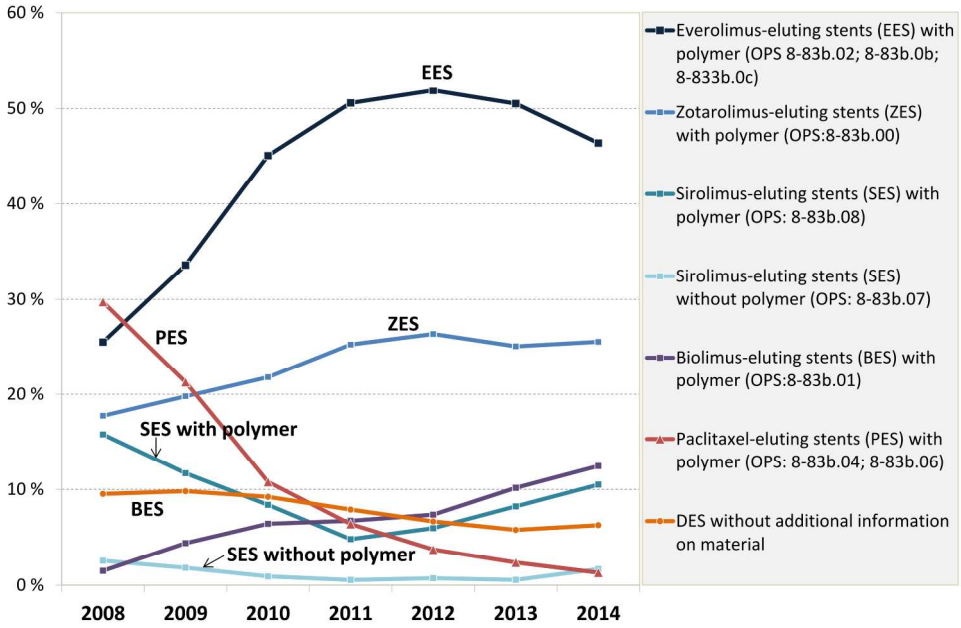

Frequency of the different drug eluting stent (DES) used over time (2008-2014) according to active drug component and carrier material (groups > 1% only) * Multiple selections possible due to implantation of different stent types during index procedure. BVS were not included. OPS "Operationen- und Prozedurenschlüssel" (OPS) German version of the International Classification of Procedures in Medicine (ICPM) [19].

292x191mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract → *page 1,2*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found → *page 2*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported → *page 4*
Objectives	3	State specific objectives, including any prespecified hypotheses → *page 5*
Methods		
Study design	4	Present key elements of study design early in the paper → *page 5*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection → *page 5, 6*
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up → *page 6* *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls → *N/A* *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants → *N/A*
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed → *N/A* *Case-control study*—For matched studies, give matching criteria and the number of controls per case → *N/A*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable → *page 6, 7*
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group → *page 5,6*
Bias	9	Describe any efforts to address potential sources of bias → *page 6*
Study size	10	Explain how the study size was arrived at → *page 6*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why → *page 7*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding → *page 8*
		(*b*) Describe any methods used to examine subgroups and interactions → *page 7*
		(*c*) Explain how missing data were addressed → *page 7*
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed → *page 7* *Case-control study*—If applicable, explain how matching of cases and controls was addressed → *N/A* *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy → *N/A*
		(*e*) Describe any sensitivity analyses → *N/A*

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed → *page 8*
		(b) Give reasons for non-participation at each stage → *page 8*
		(c) Consider use of a flow diagram --
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders → *page 8,9, table 1*
		(b) Indicate number of participants with missing data for each variable of interest → *N/A*
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) → *N/A*
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time → *page 13, table 2*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure → *N/A*
		Cross-sectional study—Report numbers of outcome events or summary measures → *N/A*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included → *page15, table 3*
		(*b*) Report category boundaries when continuous variables were categorized → *N/A*
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period → *N/A*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses → *page16, table 4*
Discussion		
Key results	18	Summarise key results with reference to study objectives → *page 16*
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias → *page 17*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence → *page 18, 19*
Generalisability	21	Discuss the generalisability (external validity) of the study results → *page 17*
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based → *page 20*

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.