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ORIGINAL PAPER

Use of drug-eluting stents in acute myocardial infarction with persistent ST-segment elevation: results of the ALKK PCI-registry

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Abstract
Background Drug-eluting stents (DES) reduce the rate of in-stent restenosis (ISR) and target vessel revascularization significantly when compared with bare metal stents (BMS). Their beneficial effects have been demonstrated in patients with acute myocardial infarction also, but the use of DES in the latter population seems to be still limited in clinical practice.
Methods and results From January 2006 to December 2011, 25,424 patients with ST-elevation myocardial infarction were enrolled in the German ALKK PCI-registry. In 5,467 patients (21.5 %), a DES was implanted in the culprit segment, in 16,911 patients (66.5 %) a BMS, and 2,959 patients (11.6 %) received neither DES nor BMS. The rates of DES for typical subgroups were 31.7 % in patients with diabetes, 36.6 % in unprotected left main stenosis, 32.4 % in ostial lesions, 32.0 % for a stent length >15 mm, 26.2 % for a stent diameter ≤3 mm, and 58.5 % for ISR. There was a wide range in the use of DES between the different ALKK hospitals with a minimum of 2.3 % and a maximum of 58.3 % for the total study period (median 22.0 %, quartiles 14.6 and 37.5 %).
Conclusions Despite convincing data for the use of DES in patients with STEMI, there is still an underuse of DES in this clinical setting in Germany. This is particularly worrying for the subgroups of patients and lesions with a high risk of restenosis. Further efforts are needed to reduce the skepticism about DES and to improve guideline adherent treatment.

Keywords Drug-eluting stent · Myocardial infarction · STEMI · Germany

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Introduction

The introduction of drug-eluting stents (DES) in 2002 [1] was a mile stone in interventional cardiology. Their major positive effect, as documented in many large randomized clinical trials, was a significant reduction of in-stent restenosis (ISR) and target vessel revascularization (TVR) when compared with bare metal stents (BMS) [2–5]. These beneficial effects were most pronounced in small vessels (≤3.0 mm diameter), long lesions (>15 mm stent length), patients with diabetes, and specific lesions highly susceptible to restenosis such as left main stenosis, ostial lesions, and chronical total occlusions. According to current

guidelines, DES are recommended for all these subgroups in the absence of contraindications [6]. Furthermore, implantation of DES is highly effective for BMS–ISR [7].

Concerns about an increased rate of stent thrombosis after DES implantation emerged in 2006. These led to a sustained uncertainty about the safety of DES, despite newer data showing an even greater safety and effectiveness than BMS [8]. In particular, the use of DES in patients with ST-segment elevation myocardial infarction (STEMI) was discussed controversial. But several randomized clinical trials with medium-term follow-up have shown that DES reduce the risk of reintervention compared with BMS in this subgroup of patients also, without having a significant impact on the risk of stent thrombosis, recurrent myocardial infarction, or death [6, 9–13].

Despite growing evidence of their beneficial effects, the use of DES in patients with STEMI seems to be still limited in clinical practice. The aim of this study was an evaluation of the use of DES in patients with STEMI in a real world scenario analyzing data of the ALKK PCI-registry.

Methods

The ALKK PCI-registry

The Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK) PCI-Registry is a prospective registry that was initiated in 1992 to monitor quality control [14]. It contains all consecutive procedures of the participating hospitals on an intention-to-treat basis [14–17]. Data were obtained using the standardized questionnaires in the 42 participating hospitals, including information about the medical history (prior coronary interventions, congestive heart failure, diabetes, renal insufficiency), indication for the procedure, adjunctive antithrombotic therapy, the procedure itself (target vessel, success rate, stent used, etc.), and complications until hospital discharge. All data were analyzed centrally at the Karl Ludwig Neuhaus Datenzentrum, Ludwigshafen, Germany.

Patient selection

There were 42 hospitals identified which had participated in the ALKK PCI-registry for at least three full years during the period from 2006 to 2011. For the unselected patients presenting with STEMI enrolled by these centers, the first PCI performed during hospital stay was evaluated. The analysis was focused on the first treated lesion documented in the data base, which was regarded as the culprit lesion. Patients without stent implantation and a very small group of patients ($n = 87$; 0.4 %) who received BMS as well as DES were excluded from the analysis.

Definitions

STEMI was diagnosed according to one of the two following criteria: persistent angina pectoris >20 min with ST-segment elevation of 1 mm in ≥2 standard leads or ≥2 mm in ≥2 contiguous precordial leads, or the presence of a left bundle branch block. It was later confirmed by elevation of enzymes (creatinine kinase and its MB isoenzyme, aspartate aminotransferase, lactic dehydrogenase) to at least twice the normal value.

Statistical methods

Categorical data are presented as percentages and absolute numbers, metrical variables as mean and standard deviation. The subgroups of patients receiving DES or BMS were compared by Chi-square test with respect to dichotomous variables, and by Mann–Whitney test with respect to continuous variables. The use of DES across centers is demonstrated in a bar chart, with error bars indicating the upper Clopper–Pearson 95 % confidence limits. Determinants for the use of DES were analyzed in multivariable logistic regression models. The patient characteristics significant in univariate comparisons and the relevant lesion characteristics that were documented throughout the observation period were included in the model, together with year of enrollment and center. For the patient and lesion characteristics adjusted odds ratios (OR) with 95 % confidence intervals were calculated, and the values of the log-likelihood ratio statistic (log-LR) are shown as a measure of the information added by each factor when comparing the full model to that without the respective factor.

The statistics were calculated from the available cases. A significance level of 0.05 was assumed and all p values are the results of two-tailed tests. The statistical computations were performed using SAS, version 9.3 (Cary, NC, USA).

Results

From January 2006 to December 2011, 25,424 patients with STEMI were enrolled in the German ALKK PCI-registry. In 5,467 patients (21.5 %) a DES was implanted in the culprit segment, in 16,911 patients (66.5 %) a BMS was implanted. 2,959 patients (11.6 %) received neither DES nor BMS, and in 87 patients (0.4 %) DES as well as BMS were implanted in the culprit segment for unknown reason. The latter were excluded from analysis. The rate of DES improve from 17.5 % in the year 2006 to 53.3 % in the year 2011 (Fig. 1).

There was a wide range in the use of DES in patients with STEMI between the different ALKK hospitals with a

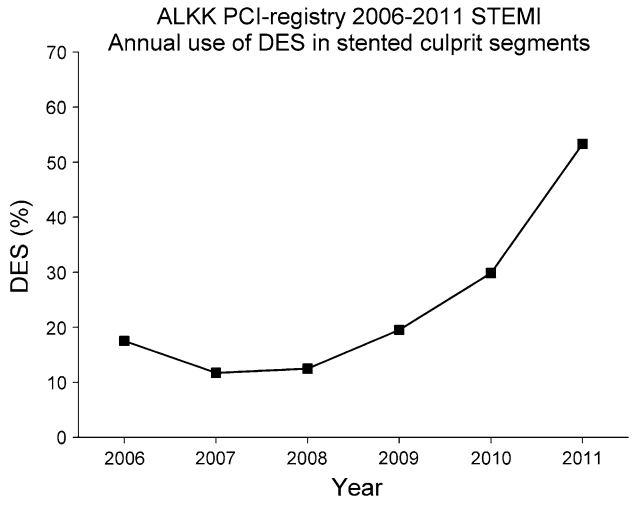

Fig. 1 Annual use of DES in stented culprit segments. Percentage use of DES in the stented culprit segments of patients with ST-elevation myocardial infarction is shown for the years 2006–2011. *DES* drug-eluting stent, *ALKK* Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte

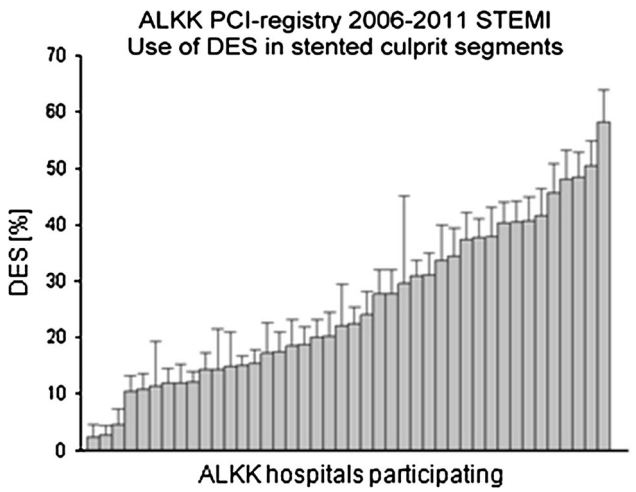

Fig. 2 Use of DES in stented culprit segments. Percentage use of DES in the stented culprit segments of patients with ST-elevation myocardial infarction is shown for all participating ALKK hospitals. *DES* drug-eluting stent, *ALKK* Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte

minimum of 2.3 % and a maximum of 58.3 % for the study period. The median was 22.0 % (quartiles 14.6 and 37.5 %) (Fig. 2). A wide range was demonstrable for the whole study period, but it was even more pronounced in the last years. Using a Cochran–Armitage test, a significant positive trend for the rate of DES implantation could be found for 30 participating hospitals during the study period, while 11 hospitals showed no significant changes in implantation policy and one hospital even showed a significant negative development (data not shown).

Table 1 Patient characteristics

	BMS	DES	*p* value
Number of patients	16,911 (75.6 %)	5,467 (24.4 %)	
Age	64.5 ± 13.0	62.1 ± 12.4	<0.0001
Male/female	72.7/27.3 %	74.3/25.7 %	<0.05
Diabetes	18.0 %	24.3 %	<0.0001
Arterial hypertension	71.7 %	72.4 %	n.s.
Smoking[a]	43.8 %	45.9 %	<0.05
Hyperlipidemia[a]	58.6 %	60.1 %	n.s.
Prior PCI/CABG	11.9 %	20.1 %	<0.0001
Peripheral artery disease[a]	6.8 %	6.5 %	n.s.
Renal insufficiency	12.7 %	10.2 %	<0.0001
Heart failure	13.1 %	10.2 %	<0.0001
Cardiogenic shock	6.9 %	4.4 %	<0.0001
1 Vessel disease[a]	39.5 %	37.0 %	<0.01
2 Vessel disease	29.7 %	32.0 %	<0.01
3 Vessel disease	30.7 %	31.0 %	n.s.
Left main disease[a]	5.5 %	6.0 %	n.s.

BMS bare metal stent, *DES* drug-eluting stent, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting

[a] Available only in a subset of patients

Clinical characteristics of included patients are summarized in Table 1. Patients receiving a DES were significantly younger, suffered significantly more often from diabetes, were significantly more often smokers, had significantly more often a history of PCI or CABG, but had significantly less renal insufficiency. Critically ill patients with acute heart failure or cardiogenic shock received significantly less DES.

Further analysis focused on subgroups with typical indications for the use of DES. The angiographic characteristics of treated culprit lesions are summarized in Tables 2, 3. The culprit lesion of STEMI was treated by implantation of a DES in 1,255 of 3,965 patients (31.7 %) with diabetes, in 74 of 202 patients (36.6 %) with unprotected left main stenosis, in 236 of 728 patients (32.4 %) with ostial lesions, in 3,506 of 10,957 patients (32.0 %) with a stent length >15 mm, in 3,663 of 14,001 patients (26.2 %) with a stent diameter ≤3 mm, and in 418 of 715 patients (58.5 %) with ISR. Altogether, nearly half of the patients with ISR and about two-thirds of patients with another distinct indication for the use DES were treated with a BMS at their culprit lesion, considering the total study period.

In the last surveyed years, an increased use of DES was recognizable. In 2011, the rates of DES implantation had increased to 56.2 % for patients with diabetes, 53.8 % for unprotected left main stenosis, 63.9 % for ostial lesions,

Table 2 Culprit lesion characteristics

Culprit lesion	No. of patients	BMS	DES
Unprotected left main	202	63.4 % ($n = 128$)	36.6 % ($n = 74$)
LAD	9,414	71.8 % ($n = 6,761$)	28.2 % ($n = 2,653$)
CX	3,120	77.5 % ($n = 2,418$)	22.7 % ($n = 702$)
RCA	9,130	79.3 % ($n = 7,239$)	20.7 % ($n = 1,891$)
Ostial lesion	728	67.6 % ($n = 492$)	32.4 % ($n = 236$)
Bypass graft	331	69.5 % ($n = 230$)	30.5 % ($n = 101$)
Last vessel	96	87.5 % ($n = 84$)	12.5 % ($n = 12$)
In 3 vessel disease	5,140	72.0 % ($n = 3,700$)	28.0 % ($n = 1,440$)
In-stent restenosis	715	41.5 % ($n = 297$)	58.5 % ($n = 418$)

BMS bare metal stent, *DES* drug-eluting stent, *LAD* left anterior descending coronary artery, *CX* circumflex coronary artery, *RCA* right coronary artery

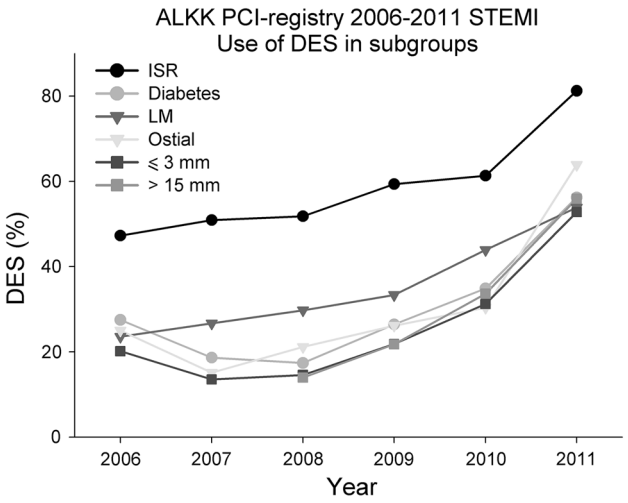

Fig. 3 Use of DES in subgroups. Percentage use of DES in the stented culprit segments of patients with ST-elevation myocardial infarction with is shown for distinct subgroups for the years 2006–2011. *DES* drug-eluting stent, *STEMI* st-elevation myocardial infarction, *ALKK* Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte, *LM* left main stenosis, *ISR* in-stent restenosis

Table 3 In-hospital complications

Complication	BMS (%)	DES (%)	*p* value
Death	6.2	4.2	<0.0001
Non-fatal myocardial infarction	0.4	0.2	n.s.
Non-fatal stroke	0.1	0.1	n.s.
Cardiopulmonary resuscitation	0.9	1.0	n.s.
Bleeding events	0.6	0.7	n.s.
Puncture site complication	1.5	1.3	n.s.
Acute renal failure	1.3	0.7	<0.01
Pulmonary embolism	0.0	0.0	n.s.
Total in-hospital complications	10.7	9.1	<0.001

55.9 % for a stent length >15 mm, 52.8 % for a stent diameter ≤3 mm, and 81.3 % for treatment of ISR (Fig. 3).

The rates of in-hospital complications were comparable for both groups except for death and acute renal failure which occurred significantly more often in the group of patients receiving a BMS (Table 3). There were no statistically significant differences in the rate of complications between hospitals with a rate of DES use above the median compared to hospitals with a rate below the median.

Predictors for the use of DES in patients with STEMI determined by a logistic regression model are shown in Table 4. The most informative predictors were the year of stent implantation (log-LR 2,542.73) and the implanting center (log-LR 2,404.42). Age and diabetes at baseline, and ISR and small vessel diameter as angiographic characteristics turned out to be highly significant determinants for the choice of stent types. Out of the partially documented variables, smoker [OR 0.79 (0.71–0.88)] and a stent length >15 mm [OR 1.85 (1.66–2.07)] also remained significant determinants after adjusting for the variables in the final model (not shown in Table 4).

Table 4 Predictors for the use of DES in the culprit lesion

Variables	log-LR[a]	Adjusted odds ratio	95 % CI
Age (per decades)	341.84	0.75	0.72–0.77
Female	0.16	0.98	0.90–1.07
Diabetes	136.45	1.76	1.60–1.94
Prior PCI/CABG	79.42	1.70	1.51–1.91
Cardiogenic shock	50.76	0.51	0.43–0.62
Moderate heart failure	18.11	0.70	0.59–0.83
In-stent restenosis	257.06	5.32	4.33–6.54
Unprotected left main	43.57	3.99	2.68–5.93
Ostial lesion	29.35	1.77	1.44–2.16
LAD	109.06	1.51	1.40–1.63
Vessel diameter ≤3 mm	192.62	1.82	1.67–1.98
Year	2,542.73	–	–
Center	2,404.42	–	–

ALKK PCI-registry 2006–2011: first PCI in patients with STEMI; logistic regression, adjusted for center and year; $n = 4,713/18,093$

LAD left anterior descending coronary artery, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting

[a] Two times logarithm of the likelihood ratio

Discussion

The aim of this study was to determine the use of DES in patients with STEMI in a real world scenario analyzing data of the ALKK PCI-registry. Over the whole study period, 75.6 % of all patients with STEMI who received a stent, 41.5 % of the patients with ISR as culprit lesion, and about two-thirds of patients with another typical indication for the use of DES were treated with a BMS. A rate of 24.4 % DES in patients with STEMI is even slightly lower when compared with the available data about the use of DES in patients with STEMI in the period 2004–2007 [18, 19]. There are no reliable data about the use of DES in patients with STEMI in real world scenarios outside clinical trials or single-center experience for the past years, either for Germany or for other European countries.

Most interestingly, a main indicator for the use of DES in patients with STEMI was the policy of the implanting hospital. There was a wide range in the use of DES between the different ALKK hospitals, and no explaining differences between the hospitals could be determined. In consideration of an identical scientific database, these findings demonstrate the subjectivity of decision-making process reflecting a more eminence-based instead of evidence-based medicine.

Another main indicator for the use of DES in our registry was the year of implantation. Since the introduction of DES, their use in patients with STEMI was a matter of debate. Concerns over the safety of DES emerged in 2006, in particular over a possibly increased rate of late and very late stent thrombosis [20, 21]. We found a corresponding decrease in the use of DES in the year 2007. In fact, the Swedish Stent Registry (SCAAR), which reported these concerns for the first time, has shown the opposite in a later analysis with DES showing even greater safety and effectiveness than BMS [8]. However, for patients with acute myocardial infarction concerns remained. A recently published meta-analysis showed an early benefit of early generation DES in primary PCI for STEMI with a reduction of TVR and a trend to less definite stent thrombosis, but an increased risk of very late stent thrombosis [22]. Main mechanisms of stent thrombosis are impaired endothelialization due to antiproliferative effects of the eluted drug, chronic local inflammation potentially related to the persistence of durable polymers as well as incomplete stent apposition. A differential healing response of DES implanted into plaques of patients with STEMI when compared with stable coronary artery disease has been shown with evidence of persistent inflammation and a higher proportion of uncovered stent struts among coronary segments treated with DES than BMS [22, 23]. Furthermore, incomplete stent apposition has been recognized as an important morphological substrate associated with the occurrence of very late stent thrombosis [24]. This phenomenon seems to be more frequent in patients with STEMI [25] and may be related to incomplete stent apposition at the time of implantation due to vasoconstriction of the vessels, presence of a jailed thrombus with subsequent resolution, or vessel remodeling in response to the drug or polymer [22].

However, several randomized clinical trials, registries and meta-analysis have shown a significant reduction of TVR for the use of first-generation DES in patients with STEMI when compared with BMS, without having a significant impact on the risk of stent thrombosis, recurrent myocardial infarction, or death [9–13, 22, 26–30]. Moreover, new generations of DES have been developed in the recent years with thinner, more flexible struts as well as new drugs and more biocompatible polymers that elute the drug. In most randomized clinical trials and observational studies, they showed an increased efficacy and safety: both the risks of stent thrombosis and the rate of restenosis have been reduced further from first-generation devices [31–34]. A recently published meta-analysis demonstrated substantial decrease of stent thrombosis with no increase in very late stent thrombosis for patients with STEMI treated with everolimus-eluting stents when compared with first-generation DES and BMS [35]. Furthermore, another recently published meta-analysis found significantly lower rates of stent thrombosis, myocardial infarction and death for everolimus-eluting stents when compared with BMS [36]. Fortunately, with growing evidence of the safety and efficacy of DES in the setting of STEMI, a positive trend was recognizable in the last two surveyed years of our registry. However, this increase was found in about three quarters of the hospitals only, demonstrating subjectivity of clinical decision-making process again.

In respect of the literature, the latest guideline of the European Society of Cardiology, published after our study period in 2012, recommends the use of DES for all patients with STEMI in the absence of contraindications to prolonged dual antiplatelet therapy (DAPT) [37]. Actually, the latter aspect remains a major problem in patients with STEMI due to difficulties in determining reliably contraindications for DAPT, drug compliance, necessity of oral anticoagulation, or planned surgery. Furthermore, a restricted use of DES in patients with acute heart failure and cardiogenic shock, as shown in our registry, might reflect economic aspects in respect of an anticipated poor prognosis. The higher rates of cardiogenic shock and chronic kidney disease in the BMS group might explain the higher rates of in-hospital death and acute renal failure of this patient group in our registry. Altogether, there are some reasons for the use of BMS in patients with STEMI, but DES can reduce the need of TVR significantly without a significant impact on MACE. Therefore, in patients with

a high risk of restenosis DES should be used in the absence of contraindications. Well-established risk factors for development of restenosis comprise lesions in small vessels (≤3.0 mm diameter) as well as long lesions (>15 mm stent length) [38], patients with diabetes [39], and specific lesions such as left main stenosis [40], ostial lesions, chronical total occlusions, and treatment of ISR of BMS. For these subgroups with an increased risk of restenosis, the use of DES is strictly recommended [6, 41, 42].

Limitations

The data presented reflect the use of DES in patients with STEMI in a real world scenario. Due to the concept of the registry, no follow-up information about major adverse events or rates of TVR can be given. Also, the registry contained no reliable data about the need of anticoagulation or other contraindications for DAPT. In the absence of a structured monitoring of data acquisition, input data errors cannot be excluded.

A very small group of patients received BMS as well as DES in their index procedure, and 2,959 patients received neither BMS nor DES. These patients were neglected for this analysis due to difficulties in causal interpretation.

Conclusion

Despite convincing data for the use of DES in patients with STEMI, there is still an underuse of DES in this clinical setting in Germany. This is particularly worrying for the subgroups of unprotected left main stenosis, ostial lesions, ISR, and diabetic patients. In the last years, a positive trend for the use of DES was recognizable, but further efforts are needed to reduce the skepticism about DES and to improved guideline adherent treatment.

Conflict of interest None.

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