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Long-term follow-up of drug-eluting stents in patients with or without acute coronary syndrome

Abstract

Objectives: Drug eluting stents (DES) reduce neointimal hyperplasia after stenting, leading to decreased late luminal loss and decreased angiographic restenosis, as compared with bare-metal stents (BMS) and therefore reducing the need for subsequent revascularisation procedures. Excitement of DES and their promise of reduced restenosis rates have been tempered by recent concerns about safety of these devices. We documented the two years follow-up in a cohort of patients with acute coronary syndromes or stable coronary disease in a single academic medical center.
Methods: Between April 2002 and December 2004 543 patients requiring percutaneous coronary intervention (PCI) and receiving a DES were included into the study. Clinical and procedural data were collected. Primary outcome was the occurrence of major adverse cardiac events (MACE), defined as death of all cause, non-fatal myocardial infarction (MI), target lesion revascularisation (TLR) and target vessel revascularisation (TVR). Secondary endpoints included stent thrombosis, stroke and major bleeding.
Results: 7.6% of patients had a MACE, 2.0% due to a non-fatal MI, 1.7% TLR, and 1.5% TVR. Death occurred in 2.4% of patients but only in patients with severe comorbidities and was not related to DES implantation. Stent thrombosis occurred in 1.3% of patients, 6 out of 7 cases occurred in patients initially treated for ST-elevation MI. No cases of stroke or major bleeding could be identified. In univariate analysis the use of abciximab for 12 h after intervention and no shock on admission improved outcome. Left ventricular ejection fraction <50% on admission, ventricular fibrillation on admission, the use of >1 stent and elevated CK, CK-MB and troponin levels worsened outcome. In multivariate analysis only elevated troponin was related with worsened outcome.
Conclusion: In this cohort study, the results confirm the safety and efficacy of DES implantation in daily routine practice in a two years follow-up.

Key words: bare-metal stent; drug-eluting stent; major adverse cardiac event; myocardial infarction; percutaneous coronary intervention; thrombolysis in myocardial infarction; target lesion; target vessel revascularisation

Zusammenfassung

Hintergrund: Die Verwendung von medikamentös-beschichteten Stents (drug eluting stents [DES]) reduziert die neointimale Hyperplasie nach einer Stent-Implantation und führt zu verminderter Restenose, verglichen mit nicht medikamentös-beschichteten Stents (bare metal stents [BMS]). Durch DES wird der Bedarf für eine erneute Intervention an einem bereits mit einem Stent behandelten Gefässabschnitt reduziert. Seit der Einführung der DES sind jedoch Bedenken bezüglich der Sicherheit dieser Stents laut geworden. Wir haben daher den 2-Jahres-Verlauf in einer Kohorte von Patienten mit akutem Koronarsyndrom oder stabiler koronarer Herzerkrankung untersucht.
Methoden: Zwischen April 2002 und Dezember 2004 wurden 543 Patienten, die im Rahmen einer perkutanen koronaren Intervention einen medikamentös-beschichteten Stent erhielten, in die Studie eingeschlossen. Der primäre Endpunkt war das Auftreten von Tod, nichttödlichem Myokardinfarkt, erneuter perkutaner Revaskularisation eines vorher behandelten Gefässabschnittes oder eines bereits vorher behandelten Gefässes. Sekundäre Endpunkte waren Stent-Thrombosen, Schlaganfälle oder ernsthafte Blutungen.

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Resultate: 7,6% der eingeschlossenen Patienten erreichten den primären Endpunkt, 2,0% durch nicht-tödlichen Myokardinfarkt, 1,7% durch erneute perkutane Revaskularisation eines vorher behandelten Gefässabschnittes und 1,5% durch erneute perkutane Revaskularisation eines bereits vorher behandelten Gefässes. 2,4% der Patienten verstarben, wobei der Tod jeweils nicht in Zusammenhang mit der Implantation eines medikamentös-beschichteten Stents eintrat. Eine Stent-Thrombose trat bei 1,3% der Patienten auf, 6 von 7 Patienten mit Stent-Thrombose wurde initial wegen eines ST-Hebungsmyokardinfarkts therapiert. In der univariaten Analyse korrelierte der Gebrauch von Abciximab, für 12 h nach Intervention, und ein fehlender Schock bei Spitaleintritt mit einer verbesserten Prognose. Eine initiale linksventrikuläre Auswurffraktion <50%, Kammerflimmern bei Eintritt, der Gebrauch von mehr als einem Stent sowie erhöhte kardiale Enzyme (CK, CK-MB und Troponin) verschlechterten die Prognose. In der multivariaten Analyse war lediglich ein erhöhtes Troponin mit einer schlechteren Prognose verbunden.
Schlussfolgerung: In dieser Kohortenstudie bestätigen die Resultate die Sicherheit und Effizienz der Implantation von medikamentösbeschichteten Stents in der täglichen Routine in einem 2-Jahres-Verlauf.

Schlüsselwörter: unbeschichteter Metall-Stent; medikamentös-beschichteter Stent; schwerwiegende kardiale Nebenwirkungen; Myokardinfarkt; perkutane koronare Intervention; Thrombolyse Myokardinfarkt; Revaskularisation initial behandelte Läsion; Revaskularisation initial behandeltes Gefäss

Background

Since the approval of the first drug-eluting stents (DES), randomised trials and registries have shown, that DES reduce neointimal hyperplasia after vascular injury, leading to decreased late luminal loss and decreased angiographic restenosis, as compared with bare-metal stents (BMS) and therefore reducing the need for subsequent revascularisation procedures [1–5]. As a result, the use of drug-eluting stents has increased rapidly, with current rates up to 70% of all stenting procedures in Switzerland [6]. Excitement of DES and their promise of reduced restenosis rates have been tempered by recent concerns about safety of these devices. Recently, patho-anatomical studies [7–10] and meta-analyses of randomised trials [11, 12] and registries [13] have raised concern about incomplete neointimal coverage with a subsequent increase in late stent thromboses, myocardial infarction, and death in patients with drug-eluting stents [14, 15]. The BASKET-LATE study indicated that the implantation of drug-eluting stents was associated with an early reduction in death and myocardial infarction – an improvement that was lost during the subsequent 6 to 18 months by a late increase in the same events [16]. Since there have been no prospective, randomised clinical trials involving long-term follow-up of the "off-label" use of drug-eluting stents, we sought to determine the follow-up in a cohort of patients with either acute coronary syndromes or stable coronary disease treated with DES in routine clinically care with a specific focus on occurrence of major adverse cardiac events (MACE) over time.

Registers have the advantage that they may represent the "real world" population, as reflected by higher numbers of patients with diabetes mellitus or hypertension or high-risk patients including those presenting with acute coronary syndromes or total coronary occlusion as compared to randomised clinical trials [17].

Methods

Patient population and data collection

The objective of this study was to determine the incidence of major adverse events in patients receiving DES in routine clinical practice in an academic medical center. To address this question, a retrospective analysis of the Andreas-Grüntzig catheterization laboratory (University Hospital Zürich, Switzerland) percutaneous coronary intervention (PCI) data was performed. All patients receiving a sirolimus (Cypher™, Johnson and Johnson-Cordis Unit; Miami Lakes, FL) or paclitaxel (Taxus™ Boston Scientific Corporation, Natick, MA, USA) covered stent within a 2-year period were studied with 1-year-follow-up. Importantly, all patients receiving a DES, were included regardless of length, size or number of stenoses and this cohort included high-risk subsets, such as acute coronary syndromes, total coronary occlusion, bifurcational and ostial diseases,

thrombus-containing lesions, overlap stenting, and vein graft interventions that were excluded from clinical trials of these devices. The local institutional Ethics Committee approved the study. Acute coronary syndrome was defined according to ESC guidelines [18].

During the study time, 85% of the population undergoing PCI received at least one DES during the intervention. Periprocedural glycoprotein IIb/IIIa inhibitors and antithrombotic medication were used according to the operator's decision. Patients were treated at discharge with lifelong aspirin 100 mg/d and clopidogrel (loading dose 300 mg, thereafter 75 mg/d) for 12 months, a high dose statin and other drugs as necessary. Information about in-hospital clinical course was obtained using electronic hospital charts and if necessary by individual chart review. Baseline clinical and procedural data were collected retrospectively. Data on vital status and adverse events were accessible for all patients included.

Study end points

The primary endpoint was the occurrence of MACE, defined as death of all cause, non-fatal myocardial infarction (MI), target lesion revascularisation (TLR) and target vessel revascularisation (TVR). Secondary endpoints included stent thrombosis, stroke (verified by imaging techniques) and major bleeding (requiring therapeutically intervention). MI was diagnosed by a rise in the creatine kinase (CK) level to equal or more than twice the upper normal limit after the initial fall of CK after the first PCI. TLR was defined as a repeated PCI to treat a luminal stenosis within the stent or within 5 mm distal or proximal to the stent. TVR was defined as any PCI on a lesion different from that treated during the first intervention in the same epicardial vessel. Stent thrombosis was considered if TIMI flow grade 0, TIMI 1 grade flow or a flow-limiting thrombus was documented. Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of TIMI 3 grade flow.

Statistical analysis

Continuous variables were presented as mean ± SD and were compared by means of the Student unpaired t-test in case of normal distribution. Data with a skewed distribution were compared using Wilcoxon rank sum test. Categorical variables were presented as counts and percentages and compared by means of Pearsons χ-square test. The cumulative incidence of MACE was estimated by the method of Kaplan-Meier, and Cox proportional hazards models were used to identify independent predictors of adverse events.

Results

Baseline and procedural characteristics

Clinical baseline and procedural characteristics are given in table 1 and 2. A total of 543 patients received 974 DES. Forty-seven percent received one stent, 34% received 2 stents, 12% received 3 stents and 7% received more than 4 stents during the initial hospitalisation. Cardiovascular risk factors were distributed as described for population-based samples [19].

Clinical outcome

Total patient population

Complete follow-up information was available for all patients with mean follow-up of 11.3 ± 5.8 months. Maximal follow-up was 23.4 months and 25% of patients (136/543 pts.) were followed-up >16 months. Two thirds were admitted with acute coronary syndrome (ACS), and one third had a history of prior PCI. Periprocedural administration of glycoprotein IIb/IIIa inhibitors of at least 12 hours in all patients with acute coronary syndromes was 28%. Details of patients with and without ACS are given in table 3.

Overall, 41 (7.6%) out of 543 patients reached the primary endpoint. Death (13 pts., 2.4%) occurred only in patients with severe comorbidities and was not related to DES implantation. However, there were 11 pts. (2.0%) with non-fatal MI, 9 pts. (1.7%) with TLR and 8 pts. (1.5%) with TVR.

The secondary endpoint was reached by 7 pts. (1.3%) who had stent thrombosis. Six out of these cases occurred in patients initially treated for ST-elevation MI. No cases of stroke or major bleeding could be identified.

Figure 1A shows the Kaplan-Meier curve for the overall MACE. Twenty-one events occurred within the first 30 days, 11 events after 1 to 6 months, 6 events after 6–12 months and 3 events occurred after more than 12 months. In particular, MACE-rates in patients with or without acute coronary syndromes were comparable over time as shown in the Kaplan-Meier curve (log-rank p = 0.0885; fig. 1B).

Subgroup analysis

Several subgroups of the patient population were analysed. In univariate analysis the use of abciximab (Reopro™) for 12 h after intervention (HR 0.64, 95%-CI 0.46–0.92) and no shock on admission (HR 0.34, 95%-CI 0.21–0.58) improved outcome. Left ventricular ejection fraction (LVEF) <50% on admission

(HR 1.57, 95%-CI 1.01–2.34), ventricular fibrillation on admission (HR 2.65, 95%-CI 1.04–6.74), the use of >1 stent (HR 1.38, 95%-CI 1.03–1.80) and elevated CK, CK-MB and troponin levels worsened outcome (table 4). In multivariate analysis only elevated troponin was related with worsened outcome (HR 1.149, 95%-CI 1.018–1.296) (table 5). Neither diabetes mellitus (log-rank p = 0.1368) nor gender (log-rank p = 0.0713) was related to outcome after 2 years (fig. 2).

Table 1
Clinical baseline characteristics.

Number of patients	543	
Age [years]	62.4 ± 10.8	
Sex, male	419	(77.2%)
Mean Follow-up time (range)	11.3 ± 5.8 months (0–23.4)	
Risk factors		
Diabetes mellitus	114	(21%)
Current smoking	307	(57%)
Hypertension	326	(60%)
Hypercholesterolaemia	392	(72%)
Obesity	139	(26%)
Family history	200	(37%)
History of		
MI	166	(31%)
CABG	64	(12%)
PCI	170	(31%)
Clinical presentation		
Asymptomatic	71	(13%)
Stable angina	131	(24%)
Unstable angina	162	(30%)
NSTEMI	72	(13%)
STEMI	107	(20%)
Number of vessels		
Singel	155	(29%)
Two	175	(32%)
Three	211	(39%)
Treated vessels		
LM	3	(1%)
LAD	307	(56%)
LCX	114	(21%)
RCA	119	(22%)
Glycoprotein IIb/IIIa inhibitor in ACS patients	94	(28%)
Clopidogrel	472	(87%)
Aspirin	526	(97%)
Statin	510	(94%)
ACE-inhibitor / AT-2 antagonist	424	(78%)
Betablocker	213	(39%)

Table 2
Procedural characteristics.

Number of patients	543	
Number of implanted stents	974	
Type of stent in target lesion		
Cypher only	423	(77.9%)
Taxus only	103	(19%)
Mixed	17	(3.1%)
Stenosis		
Number of stents per patient by end of follow-up	1.8 ± 1	
Length of stents (mm)	18.6 ± 6.3	
Diameter of stent (mm)	2.8 ± 0.3	
Success	967	(99%)

Table 3
Patients with and without acute coronary syndrome (ACS).

	ACS	non-ACS	p-value
Number	341 (63%)	202 (37%)	
Age	61.3 ± 12	64.1 ± 11	0.0038
Sex, male	256 (75%)	163 (81%)	0.1316
Risk factors			
Diabetes mellitus	63 (18%)	51 (25%)	0.0611
Current smoking	205 (60%)	102 (51%)	0.0288
Hypertension	192 (56%)	134 (66%)	0.0211
Hypercholesterolaemia	244 (72%)	148 (73%)	0.6667
Obesity	92 (27%)	47 (23%)	0.3880
Family history	124 (36%)	76 (38%)	0.7686
History of			
MI	87 (26%)	79 (39%)	0.0009
CABG	32 (9%)	32 (16%)	0.0241
PCI	83 (24%)	87 (43%)	<0.0001

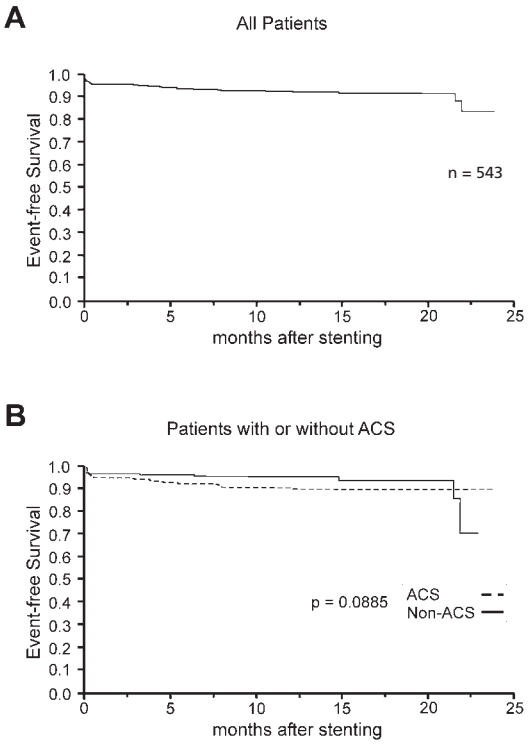

Figure 1
A Kaplan-Meier event-free survival curve for MACE for all patients (n = 543).
B Kaplan-Meier event-free survival curve for MACE by patients with acute coronary syndrome or elective intervention. No statistical difference was detected between the groups (log-rank p = 0.0885).

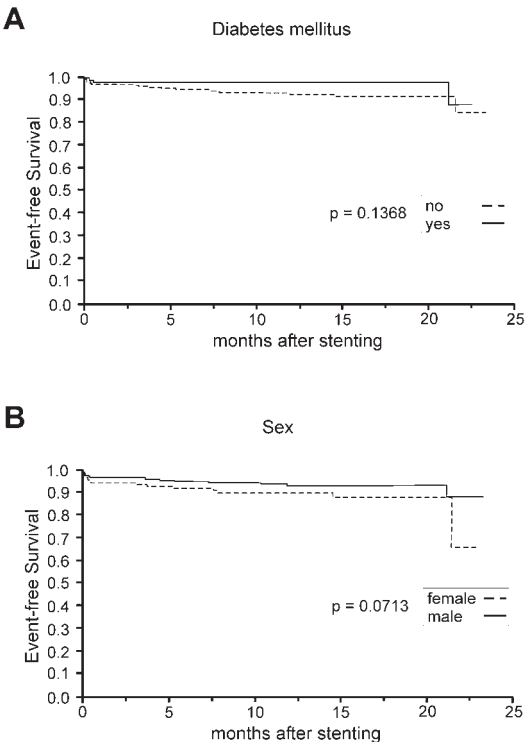

Figure 2
A Kaplan-Meier event-free survival curve for MACE by diabetic status.
B Kaplan-Meier event-free survival curve for MACE by sex.

Discussion

This study demonstrates in a consecutive serie of over 500 patients in a single academic center that DES implantation is associated with good results in males and females, acute and stable patients, as well as those with or without diabetes.

The baseline clinical characteristics of the cohort studied were consistent with those found in other interventional studies of angioplasty with or without stent implantation for single or multivessel coronary artery disease, but the number of patients with diabetes was lower (21%) and the number of current smokers was higher [20]. However, the mean reference vessel diameter in this study (2.8 mm) was equal to that in the SIRIUS trial [2] (2.8

Table 4
Univariate Cox proportional hazards analyses.

Variable	HR	95%-CI	p-value
Age	1.01	0.98, 1.04	0.4795
Age <70y/o	0.91	0.66, 1.29	0.5887
Sex (female)	1.34	0.96, 1.84	0.0862
H/O MI	1.24	0.87, 1.85	0.2397
H/O PCI	1.16	0.82, 1.70	0.4073
H/O CABG	1.32	0.72, 2.42	0.3619
Smoking	1.19	0.86, 1.65	0.2911
Hypertension	1.15	0.96, 1.37	0.1375
Dyslipidaemia	1.13	0.93, 1.37	0.2231
Diabetes	1.22	0.96, 1.51	0.0683
Obesity	1.06	0.75, 1.57	0.7341
Family h/o CAD	0.82	0.60, 1.13	0.2275
Abciximab for 12h	0.64	0.46, 0.92	0.0169
No shock on admission	0.34	0.21, 0.58	0.0003
Ventricular fibrillation	2.65	1.04, 6.74	0.0406
LVEF <50% on admission	1.57	1.01, 2.34	0.0460
Cypher *vs* taxus	0.64	0.39, 1.13	0.2536
ACS *vs* elective	1.26	0.90, 1.82	0.1839
Total length	1.01	0.99, 1.03	0.0650
Number DES	1.38	1.03, 1.80	0.0331
CK max.	1.00	1.00, 1.01	0.0147
CK MB max.	1.00	1.00, 1.01	0.0247
Troponin max.	1.16	1.08, 1.24	0.0002

Table 5
Final multivariate Cox proportional hazards model.

Variable	HR	95%-CI	p-value
Sex (female)	1.421	0.588, 3.432	0.4351
Smoking	0.615	0.245, 1.543	0.3002
Hypertension	0.611	0.251, 1.488	0.2780
Diabetes mellitus	2.098	0.676, 6.5	0.1997
Obesity	0.585	0.246, 13.91	0.2251
LVEF <50%	0.971	0.938, 1.005	0.0892
Troponin max.	1.149	1.018, 1.296	0.0243
Number DES	1.324	0.898, 1.952	0.1562
No shock on admission	0.207	0.039, 1.088	0.0629

mm) and comparable to that of the TAXUS-IV study [21] (2.75 mm). In our cohort both DES showed a high deliverability and similar immediate procedural outcomes (success 99%). In contrast to randomised trials where patients with complex coronary lesions and at higher periprocedural risks are generally less likely to be enrolled, patients in our cohort presented with moderately complex lesions. 39% had three-vessel disease and 32% had two-vessel disease compared to the REALITY trial, were nearly 50% of the patients had single-vessel disease [20]. Lesion localisation and treated vessels in our cohort was comparable to that of other studies, most lesions where treated in the LAD, followed by lesions in the RCA and LCX, while only 1% of patients received a DES in the left main coronary artery.

The 24-month rates of major adverse events were low in all patients, as well as in the subgroups, confirming the good clinical performance of both DES. In particular, there was no statistically significant difference in any of the major clinical events including death, myocardial infarction, target vessel revascularisation, target lesion revascularisation and stent thrombosis between patients with or without ACS (p = 0.0885). As expected in the univariate hazards analysis initial presentation at the catheterisation laboratory with clinical symptoms of shock or ventricular fibrillation, a reduced left ventricular systolic function (LV-EF <50%), elevated cardiac enzymes (CK, CK-MB and troponin) and a higher number of DES used elevated the risk for MACE. In the multivariate analysis only an elevated troponin was a risk factor for MACE. Since our study was not designed to compare

DES *vs* BMS it is difficult to tell from our data if the DES alone accounts for the higher risk in our study or if the results reflect a high-risk patient cohort, in which the use of multiple stents was associated with a higher risk. The investigators of the BASKET study comparing DES and BMS in 826 patients found a rate for MACE of 7.2% which is comparable to our rate of 7.6%]22]. In the BASKET study the use of DES reduced the rate of MACE significantly by 44% as compared to third generation BMS. However, our study was not designed to compare the two DES used head to head in a prospective, randomised fashion. In contrast to the randomised SIRTAX trial [23] we could not show any difference between both DES in regard of MACE. As in our study, the investigators of the BASKET study found no significant difference between the Cypher and the Taxus stents.

In our study, the rate of death (2.2%) was low but somewhat higher than that reported in the REALITY trial (1%) [20]. However, possibly due to the higher number of patients with multivessel disease and interventions. In the REALITY trial the number of TLR (6.1%) and TVR (1.9%) were higher compared to our study (1.7% and 1.5%, respectively). Since the vessel diameter in both studies was the same, this difference might be due to the higher rate of diabetics in the REALITY trial. In both the REALITY trial and our study, a very low rate of stent thrombosis (1.3% *vs* 1.2%, respectively was observed [20]. This is remarkable as the follow-up of this study was longer and case-reports suggest the occurrence of late stent thrombosis with DES [24, 25]. However, in a recent pooled analysis of data from four double-blind trials in which 1748 patients were randomly assigned to receive either sirolimus-eluting stents or bare-metal stents and five double-blind trials in which 3513 patients were randomly assigned to receive either paclitaxel-eluting stents or bare-metal stents, MACE were analysed [26]. The investigators found a 4 year rate of stent thrombosis of 1.2% for the sirolimus-stent group and 1.3% in the paclitaxel-stent group. The stent thrombosis rates did not significantly differ between DES and BMS. However, after 1 year of implantation, the investigator found 5 episodes of stent thrombosis in the sirolimus-stent group *vs* none in the BMS group (p = 0.025) and nine episodes in the paclitaxel-stent group *vs* 2 in the BMS group (p = 0.028) [26]. In another analysis of the randomised controlled trials with DES, the investigators found an incidence of definite or probable events occurring 1 to 4 years after implantation of 0.9% in the sirolimus-stent group versus 0.4% in the bare-metal-stent group and 0.9% in the paclitaxel-stent group versus 0.6% in the bare-metal-stent group [27].

Interestingly, in our study 6 out of 7 patients with stent thrombosis presented as ACS at the time of intervention, suggesting that inflammation and/or a prothrombotic state may be crucial for this MACE with DES. Indeed, in endothelial cells in culture rapamycin and paclitaxel potentiate tissue factor expression in the presence of thrombin and tumor necrosis factor-alpha, conditions that may be relevant in ACS [28].

Conclusion

In conclusion this cohort study confirms the long-term safety and efficacy of DES implantation in daily routine practice in all comers as well as in several subgroups including patients with ACS and/or diabetes.

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