Original Research

Clinical Outcomes of Drug-Eluting Stents Compared with Bare Metal Stents in Our Routine Clinical Practice

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Introduction: This study was designed to characterize patients treated with drug-eluting stents (DES) versus those treated with bare metal stents (BMS) and to investigate their clinical outcomes in our routine clinical practice.

Methods: We studied a consecutive series of 1796 patients, selected from a computerized registry, who underwent stenting for coronary artery lesions either with BMS (1568 patients, 87.3%) or DES (228 patients, 12.7%) between April 2003 and March 2005. In this study, those with myocardial infarction (MI) within 48 hours preceding the procedure were excluded. Patients with more than one lesion were included only if the lesions were entirely treated either with BMS or DES.

Results: Type B2/C, left anterior descending artery, and diffuse lesions were more frequent in the group treated with DES ($p<0.001$). There was no difference between these groups in terms of acute success rates, although periprocedural non-Q wave MI occurred more frequently in the DES group (2.7% vs. 0.9%, $p=0.03$). At 18-month follow up, a univariate analysis showed no difference in the rate of major adverse cardiac events (MACE) with DES (2.2%) vs. BMS (4.2%). However, a multivariate analysis showed DES to independently decrease the risk of this cumulative outcome (hazard ratio=0.36, 95% CI=0.13-0.95) and the single endpoint of target vessel revascularization (hazard ratio=0.25, 95% CI=0.07-0.89). At 12 months, the survival rate in the DES group was higher than that in the BMS group as a trend ($p=0.06$). At 18 months, the occurrence of late thrombotic events in the DES group reduced this gap (95.7% vs. 94.7%, $p=0.1$).

Conclusions: Use of drug-eluting stents in our routine practice was effective in reducing the rate of major adverse cardiac events, when compared with patients treated with bare metal stents at mid-term follow up. For the evaluation of effects of drug-eluting stents in long-term follow up, further studies of larger populations are required.

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Stent implantation has significantly reduced the short- and long-term complications in patients undergoing percutaneous coronary intervention (PCI) compared with angioplasty alone.[1] However, in-stent restenosis remains a major limitation of coronary artery stenting, especially in high-risk groups, including those with diabetes mellitus, small vessel size, and longer lesions.[2-5] Newer randomized controlled trials have shown that drug-eluting stents (DES) have resulted in a substantial decrease in restenosis across a wide range of coronary lesions and patient subsets.[6-10] However, there is growing evidence that late thrombosis, as a complication of drug-eluting stents, may obscure their brilliant characteristics.[11-14] Since there is a paucity of real-world experience of clinical restenosis in patients treated with PCI including DES implantation in the developing countries and the Middle East region,

we conducted this study to investigate the clinical outcomes of DES and compare the results with bare metal stents (BMS) in our routine clinical practice.

Methods

Between April 2003 and March 2005, a total of 2918 stenting procedures were performed for the treatment of coronary lesions in 2353 patients at our center. Patients with more than one lesion treated were included only if the lesions were entirely treated with either BMS or DES. Moreover, patients with myocardial infarction (MI) within 48 hours prior to the procedure were excluded. In this study, 1568 patients (87.3%) were treated with BMS and the remaining 228 (12.7%) with DES. The choice between the two stent types was left to the discretion of the interventionists, which was influenced by the patients' financial situation. The indications for use of DES were length >18 mm, diameter <3 mm (<3.5 mm for proximal left anterior descending artery lesions), diabetes mellitus, bifurcation, ostial lesions, in-stent restenosis, chronic total occlusions, and saphenous vein grafts. Baseline clinical, angiographic, and procedural characteristics and in-hospital outcomes were obtained by research physicians and entered into a computerized database by computer operators. Finally, clinical outcomes, most importantly major adverse cardiac events (MACE), were obtained by cardiologists in clinics, or by formal telephone interviews, at 6 months and once yearly thereafter and recorded in datasheets, which were later entered into our computerized database. This study was approved by the Ethics Committee in our center, according to the Declaration of Helsinki, as revised in 2000. Informed consent was obtained from all patients before enrolment into this study.

Coronary procedures

All angioplasty procedures were done with a 6 or 7 French guiding catheter and a femoral approach. Patients received 600 mg of clopidogrel and 325 mg of aspirin before and 7500-10000 IU of heparin at the start of the procedure. The femoral sheath was removed after normalization (<40 seconds) of the partial thromboplastin time. After stent placement, ticlopidine (250 mg twice daily) or clopidogrel (75 mg once daily) was given routinely for 4 weeks for bare metal stents and for 6 to 12 months for drug-eluting stents. Aspirin was given indefinitely to all patients. Angiographic findings, such as vessel dimensions, pre-and post-procedural stenoses, lesion length, and Thrombolysis In Myocardial Infarction (TIMI) flow grade, were determined by visual estimation using the guiding catheter as a reference object for calibration. The angiographic characteristics were also further analyzed by an independent interventional cardiologist not involved in the procedure and checked for inter-observer agreement.

Definitions

Angina symptoms were defined according to the classification of the Canadian Cardiovascular Society.[15] Lesion types were noted according to the American College of Cardiology/American Heart Association (ACC/AHA) lesion characteristics classification.[16] Q-wave MI was defined as the presence of new Q-waves in the post-procedure electrocardiogram, with a 3-fold increase in MB fraction of creatinine kinase. Non-Q-wave MI was defined as a 3-fold increase in MB fraction of creatinine kinase without the development of new Q waves.[17] Angiographic success was defined as residual stenosis <20% plus normal TIMI flow grade 3. Procedural success was defined as angiographic success without major complications (death, MI, emergency bypass surgery, or PCI) during hospitalization. MACE was defined as the presence of cardiac death, non-fatal MI, or target vessel revascularization (TVR) during the follow-up period. TVR was defined as ischemia-driven repeat percutaneous intervention or bypass surgery of the target vessel. Target lesion revascularization was defined as ischemia-driven repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel.[9]

Statistical analysis

Statistical testing was performed using the chi-square or Fisher's exact test (2-tailed) for categorical variables. Student's t-test was used for comparison of continuous variables. Univariate and multivariate analyses of hazard ratios, including 95% confidence intervals, were calculated using the Cox proportional hazard method. Factors with p values <0.15 in the univariate analysis were entered into the multivariate model. MACE-free survival curves were drawn using the Kaplan-Meier method. The log-rank was used to test for differences between survivals. Univariate analyses were performed with SPSS software version 13. Multivariate analyses were conducted with SAS software version 9.1.

Results

Baseline characteristics

Selected baseline characteristics are shown in Table 1. Patients receiving DES more often had diabetes mellitus and a history of PCI (26.1% and 12.4% vs. 20.4% and 4.7%, p=0.06 and p<0.001, respectively). However, history of MI was less frequent in these patients (26.2% vs. 36.8%, p=0.002). Other demographic characteristics did not differ between the groups. Type B2/C, diffuse, and left anterior descending artery lesions were more frequent in the DES group (76.4% vs. 53.1%; 60.2% vs. 18.2%; and 81.4% vs. 59.8%, p<0.001). Nonetheless, eccentric lesions were less frequent (p=0.001), and the pre-procedural stenosis percentage was smaller in this group. These patients had smaller vessels and longer lesions. Therefore, longer stents with smaller dimensions were implanted for this group (p<0.001).

Clinical outcomes (Table 2)

Although non-Q-wave MI during hospitalization occurred more frequently in patients treated with DES (2.7% vs. 0.9%, p=0.03), there was no statistically significant difference between these groups in terms of angiographic and clinical success rates (p=0.72 and p=0.097, respectively).

The mean follow-up duration was 11.6 ± 3.4 in the DES vs. 10.2 ± 3.9 months in the BMS group. In the univariate analysis, the rate of MACE during follow up was not significantly different between DES (2.2%) and BMS (4.2%) (Table 2). The difference between these 2 groups over time is illustrated in Figure 1. The hazard ratio for predictors of MACE at long-term follow up was calculated by multivariate analysis (Table 3). The risk of MACE was about one-third when DES was compared with BMS (hazard ratio=0.36, 95% CI 0.13-0.95). Left anterior descending artery (hazard ratio=1.78, 95% CI=1.01-3.16) and ostial lesions (hazard ratio=2.77, 95% CI=1.07-7.15) were also predictors of an increased risk of clinical restenosis in the multivariate analysis. We also found DES to be the independent predictor for TVR (hazard ratio=0.25, 95% CI=0.07-0.89). The other independent predictors for TVR were restenotic lesions (hazard ratio=2.74, 95% CI=1.05-7.14) and left anterior descending artery lesion (hazard ratio= 2.16, 95% CI=1.4-4.48).

Discussion

Recently, drug-eluting stents have resulted in a substantial decrease in restenosis across a wide range of coronary lesions and patient subsets in randomized clinical trials.[6-10] Moreover, DES implantation has been proved to markedly reduce the incidence of restenosis and repeat revascularization in an unselected daily practice population.[18,19]

The present study enrolled a consecutive cohort of unselected PCI patients with stenting procedures. As was expected, patients treated with DES had a higher risk profile for MACE than the BMS-treated group. Although in the univariate analysis the rates of MACE and TVR were only numerically lower in pa-

Table 1. Selected baseline clinical and angiographic characteristics in patients treated with drug-eluting stents versus bare metal stents.

	Drug-eluting stent (n=228)	Bare metal stent (n=1568)	p
Female gender, no. (%)	68 (30.1)	435 (28)	0.53
Age (years), mean ± SD	55 ± 10.9	56.3 ± 10.46	0.1
Diabetes mellitus, no. (%)	58 (26.1)	314 (20.4)	0.06
MI history, no. (%)	59 (26.2)	570 (36.8)	0.002
Prior PCI, no. (%)	28 (12.4)	73 (4.7)	<0.001
Type B2/C lesions, no. (%)	168 (76.4)	770 (53.1)	<0.001
Pre-procedural stenosis, mean ± SD	87.65 ± 9.56	90 ± 8.80	<0.001
Ostial lesion, no. (%)	14 (6.1)	46 (2.9)	0.014
LAD territory, no. (%)	184 (81.4)	929 (59.8)	<0.001
Eccentric, no. (%)	30 (13.3)	359 (23.1)	0.001
Thrombus, no. (%)	2 (0.9)	57 (3.7)	0.027
Stent length (mm), mean ± SD	27.15 ± 5.63	16.96 ± 5.257	<0.001
Stent diameter (mm), mean ± SD	2.90 ± 0.242	3.05 ± 0.357	<0.001

LAD – left anterior descending artery; MI – myocardial infarction; PCI – percutaneous coronary intervention.

Table 2. In-hospital and late clinical outcomes in patients treated with drug-eluting stents versus bare metal stents: no (%).

	Drug-eluting stents	Bare metal stents	p
In-hospital outcomes:	n=228	n=1568	
Peri-procedural non-Q-wave MI	6 (2.7)	13 (0.9)	0.028
Angiographic success	223 (99.1)	1535 (98.8)	0.72
Procedural success	216 (96)	1520 (97.9)	0.097
Long-term outcomes:	n=203	n=1399	p*
MACE	5 (2.2)	65 (4.2)	0.11
Cardiac death	1 (0.4)	11 (0.7)	0.61
Non-fatal MI	1 (0.4)	11 (0.7)	0.63
TVR	3 (1.3)	45 (2.9)	0.13
TLR	2 (0.9)	19 (1.2)	0.54
CABG	1 (0.4)	26 (1.9)	0.09

*Kaplan-Meier estimates.
CABG – coronary artery bypass grafting; MACE – major adverse cardiac events; MI – myocardial infarction; TLR – target lesion revascularization; TVR – target vessel revascularization.

tients treated with DES, a multivariate Cox proportional hazard model demonstrated that the 18-month cumulative risk of clinically driven MACE was about one-third for DES compared with BMS. This result is consistent with the results of Jensen et al,[20] who showed a similar decrease in the risk of restenosis after DES implantation. In the RESEARCH registry, the hazard ratio for the occurrence of MACE in the DES group was 0.62 (95% CI=0.44 to 0.89) compared to the BMS group.[18]

In our study, the predictors for increased MACE in follow up were LAD and ostial lesions. Moreover, DES usage was found to independently decrease the rate of MACE. In a previous study conducted on a population treated with coronary angioplasty, we demonstrated that the location of stenosis in LAD was not an independent predictor for MACE.[21] According to the results of a recent study by Lee et al,[22] post-intervention minimal lumen diameter and lesion length were among the predictors of restenosis after the placement of drug-eluting stents in coronary arteries. This study also showed that the rate of restenosis after DES implantation in routine clinical practice was similar to the rate reported in clinical trials,[22] confirming the efficacy of DES in routine clinical practice.

Figure 1 shows that the 18-month survival rate was lower in the DES group only as a statistically non-significant trend (p=0.1). For more clarification, we also conducted a Kaplan-Meier analysis of survival rates up to 12 months, when the anti-platelet drugs were discontinued. In this interval, the difference between survival rates was more significant (p=0.06). As is

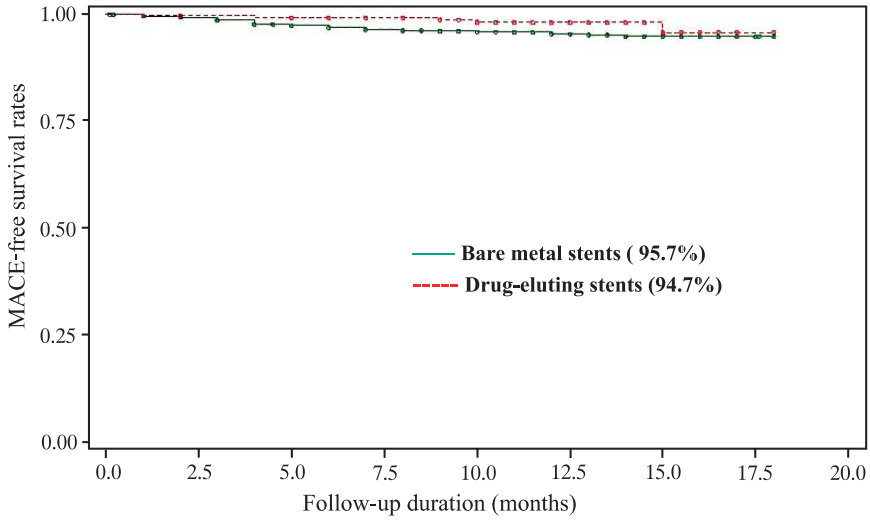

Figure 1. Event-free survival (free of major adverse cardiac events, MACE) in patients treated with drug-eluting versus bare metal stents.

Table 3. Predictors of major adverse cardiac events at follow-up.

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
Diabetes mellitus	1.54	0.92-2.58	0.10	1.37	0.78-2.40	0.27
Prior MI	0.62	0.36-1.06	0.08	0.67	0.38-1.17	0.16
Prior PCI	2.12	1.02-4.43	0.05	2.13	0.9-5.04	0.09
B2/C	0.85	0.52-1.38	0.50			
Diffuse	1.10	0.64-1.89	0.72			
RVD	0.91	0.47-1.76	0.78			
Stenosis (pre)	1.00	0.97-1.03	0.98			
LAD	1.52	0.90-2.55	0.11	1.78	1.01-3.16	0.01
Ostial	2.35	0.95-5.85	0.06	2.77	1.07-7.15	0.04
Eccentric	1.18	0.68-2.03	0.56			
Thrombus	0.41	0.06-2.97	0.38			
Total occlusion	0.98	0.45-2.14	0.96			
DES	0.48	0.19-1.20	0.11	0.36	0.13-0.95	0.03

DES – drug-eluting stent; LAD – left anterior descending artery; MI – myocardial infarction; PCI – percutaneous coronary intervention; RVD – reference vessel diameter.

stated in the results section, only TVR, but not MI or cardiac death rates, as other components of cumulative MACE, were lower after use of DES. This suggested that the occurrence of late stent thrombosis (angiographic documentation of stent thrombosis, and/or unexpected sudden cardiac death or ST-elevation MI correlating with the site of stent placement) after discontinuation of anti-platelet drugs in the DES group may have contributed to the narrowing of the gap in MACE-free survival rates between these groups in the long term, despite the more significant difference between the groups in the mid term. Although most long-term randomized trials have shown no higher risk of thrombosis after treatment with DES compared with BMS,[23-26] in real-world situations DES has been associated with higher rates of late thrombosis in the long term, particularly after the discontinuation of antiplatelet therapy.[11-14] During follow up of patients treated with stenting in the BASKET study, the rate of cardiac death and myocardial infarction in the long term was almost four times greater in the DES than in the BMS group (4.9% vs. 1.3%, p=0.01),[27] which was strongly suggestive of late thromboses in patients with DES. In a large, non-randomized database study in Sweden, the DES group had a lower adjusted risk of undergoing any new revascularization (relative risk= 0.84; 95% CI= 0.77-0.92). In contrast, there was a higher unadjusted event rate in the group with drug-eluting stents, again corresponding to "possible stent thrombosis".[28]

To avoid stent thrombosis, dual antiplatelet therapy with clopidogrel and aspirin should be continued for at least twelve months and in certain cases, indefinitely.[29] Currently, local delivery of bevacizumab (an antibody specific for vascular endothelial growth factor [VEGF]) has been feasible and safe in experimental models with no increased thrombogenicity and neovascularisation.[30,31] This may have implication for future clinical practice with drug-eluting stents, especially in the case of unstable atheromatous plaques.

In our study, stent selection was based on risk criteria for restenosis, as was reflected by the higher percentage of clinical and angiographic high-risk features in patients with drug-eluting stents. As a result of this tailored therapy, patients in the BMS group showed a relatively low rate of clinical restenosis at long-term follow up. Thus, these data do not support the use of DES for patients who have low or intermediate risk profile for restenosis.

Limitations

Firstly, the choice between the two stent types was partly subject to the patients' financial situation, leading to possible selection bias. Nevertheless, the inevitable imbalance was corrected with statistical methods. Secondly, to achieve a reliable follow up, we selected patients with one-vessel/one-lesion PCI samples or those who were treated entirely with BMS or DES, which probably yielded a lower risk of MACE than a totally unselected PCI population.

Conclusions

This study demonstrates that the use of drug-eluting stents in our "real world" is effective in reducing the rate of major adverse cardiac events, when compared with patients treated with bare metal stents, especially at mid-term follow up. For the evaluation of effects of drug-eluting stents use during long-term follow up, further studies on larger populations are required.

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