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International Journal of Cardiology 125 (2008) 36–40

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Impact of significant chronic kidney disease on long-term clinical outcomes after drug-eluting stent versus bare metal stent implantation ☆

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Received 21 August 2006; received in revised form 22 November 2006; accepted 17 February 2007
Available online 22 May 2007

Abstract

Background: Higher rates of clinical and angiographic restenosis have been reported after coronary stenting in patients with significant chronic kidney disease (CKD). Whether drug-eluting stents (DES) can reduce long-term clinical events in CKD patients compared with bare metal stents (BMS) has not been established.
Methods: The study enrolled 104 consecutive significant CKD patients (estimated creatinine clearance <60 ml/min) treated with DES for 142 *de novo* coronary lesions, comprising 76 patients treated with sirolimus-eluting stents (SES) for 106 lesions and 28 patients treated with paclitaxel-eluting stents (PES) for 36 lesions. Data from these patients were compared to those from a control group comprising 50 patients treated with BMS during the preceding 1 year.
Results: There were no differences in terms of baseline clinical characteristics except that the patients of the DES group were older, had a higher ratio of insulin treatment for diabetes mellitus, and had a more frequent history of previous percutaneous coronary intervention. The patients in the DES group had more unfavorable lesion characteristics with smaller reference vessel diameter (2.8 mm versus 3.3 mm; $P<0.001$) and longer lesion length (28.8 mm versus 20.5 mm; $P<0.001$) than those in the BMS group. Compared to BMS, DES implantation had a lower 1-year major adverse cardiac events rate (cardiac death, non-fatal myocardial infarction or target vessel revascularization) (12% versus 26%; $P=0.042$). There were no significant differences between the SES and PES groups in terms of clinical outcomes.
Conclusions: DES implantation for *de novo* coronary lesions in significant CKD patients reduces 1-year clinical events compared with BMS implantation.

Keywords: Chronic kidney disease; Stents

1. Introduction

The global incidence of chronic kidney disease (CKD) is increasing. The major cause of morbidity and mortality in these patients is cardiovascular disease. Nearly half of the deaths are related to cardiovascular disease with about 20% of those deaths caused by acute myocardial infarction (MI) [1,2]. Percutaneous coronary intervention (PCI), especially with the use of a stent, provides good angiographic success. However, there were some reports showing the higher risk of restenosis and the need for repeat revascularization in patients with CKD [3,4]. Furthermore, PCI in patients with significant CKD (defined as a serial estimated creatinine clearance (CrCl) of <60 ml/min) has been associated with a increased incidence of

☆ This study was supported by grants from the Cardiovascular Research Foundation, Seoul, Korea and the Korea Health 21 R and D Project, Ministry of Health and Welfare, Korea (0412-CR02-0704-0001).
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doi:10.1016/j.ijcard.2007.02.026

in-hospital and long-term clinical events [5,6]. Although drug-eluting stents (DES) have been found to be highly effective compared with bare metal stents (BMS) in reducing the rate of clinical and angiographic restenosis for a range of clinical conditions, the superiority of DES has yet to be established in patients with significant CKD [7–11].

We sought to compare the impact of significant CKD on long-term clinical events after DES versus BMS implantation. Furthermore, we analyzed differences in the effectiveness of sirolimus-eluting stent (SES) versus paclitaxel-eluting stent (PES) implantation in these patients.

2. Methods

2.1. Study population

From the Asan Medical Center clinical core laboratory database between April 2003 and May 2005, we identified 104 consecutive significant CKD patients treated with DES for 142 *de novo* coronary lesions: 76 patients treated with SES (Cypher stent, Cordis/Johnson and Johnson, Warren, NJ) for 106 lesions and 28 patients treated with PES (TAXUS stent, Boston Scientific Corp., Natick, MA) for 36 lesions. The control group comprised 50 patients treated with BMS for 70 *de novo* lesions during the preceding 1 year. Significant renal dysfunction was defined according to the National Kidney Foundation in the Kidney Disease Outcomes Quality Initiative classification of kidney function as an estimated CrCl of <60 ml/min. Patients were excluded if they showed an acute rise in serum creatinine above the baseline value following pre-procedural events, or side-effects of medication. All patients received a 300 mg loading dose of clopidogrel followed by 75 mg/day clopidogrel for at least 6 months, and 200 mg/day aspirin indefinitely.

2.2. Assessment of renal function

Creatinine levels were measured closest before the time of the angiogram, and renal function was assessed based on the CrCl using the Cockcroft–Gault formula: CrCl (ml/min)= {([140-age]×weight [kg])/72×serum creatinine (ml/min)} (×0.85 for women) [12]. This equation had a close correlation with measured creatinine clearance (correlation coefficient 0.83) and represented a more accurate assessment of renal function than serum creatinine alone.

2.3. Quantitative coronary angiographic (QCA) analysis

Using the guiding catheter for magnification calibration and an on-line quantitative coronary angiographic system (ANCOR V2.0, Siemens, Germany), minimal luminal diameter, percent diameter stenosis and reference vessel diameter were measured before and after the intervention from a single matched view showing the smallest luminal diameter. The acute gain was calculated as the difference between minimal luminal diameter before and after the procedure.

2.4. Definitions and clinical follow-up

The number of diseased coronary arteries was defined as the number of major coronary arteries with a luminal diameter stenosis ≥70%. Angiographic success was defined as a Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 and <30% residual diameter stenosis without major procedural complications. MI was defined as an elevation of the MB fraction of creatinine kinase to a value three times the upper limit of the normal range. Target vessel revascularization (TVR) was defined as repeated percutaneous or surgical intervention of the stented vessel. Major adverse cardiac event (MACE) was defined as cardiac death, non-fatal MI or TVR. One-year clinical follow-up data were obtained from out-patient record reviews or telephone interviews in all patients. One-year MACE, including cardiac death, non-fatal MI and TVR, was obtained during same period.

2.5. Statistical analysis

Statistical analysis was performed using SPSS 13 software program (SPSS Inc, Chicago, Illinois). Categorical data were presented as frequencies (%) and compared with the chi-square statistics or Fisher's exact tests (if an expected frequency is <5). Continuous variables were presented as mean±SD and compared using the Student *t*-test or Mann–Whitney *U*-test and correlation coefficients. A *P*-value <0.05 was considered to indicate a significant difference.

3. Results

3.1. Baseline characteristics

There were no significant differences between the DES and BMS groups in terms of baseline clinical characteristics except that the patients of the DES group were older, had a higher ratio of insulin treatment for diabetes mellitus, and had a more frequent history of previous PCI (Table 1). The patients in the DES group had more unfavorable lesion characteristics and more frequent involvement of the left main coronary artery than those in the BMS group (Table 2). The DES group had smaller reference vessel diameter and longer lesion length than the BMS group (Table 3). The BMS group had a smaller minimal lumen diameter and more severe diameter stenosis than the DES group.

3.2. Procedural results and in-hospital outcomes

Angiographic and procedural results are shown in Tables 2 and 3. The angiographic success rate did not differ significantly between the DES and BMS groups (98 versus 96%; $P=0.758$). The deployed stent length was longer in the DES group, and the number of implanted stents per patient was also greater in the DES group than in the BMS group. The acute gain and post-intervention minimal lumen diameter were larger in the BMS group.

Table 1
Baseline clinical characteristics

	DES (N=104)	BMS (N=50)	P value
Weight (kg)	65±10	65±9	0.891
Age (years)	64±10	60±9	0.008
Male sex	68 (65%)	34 (68%)	0.856
Creatinine clearance (ml/min)	30±19	30±11	0.978
Treatment modality			0.813
Medical	64 (59%)	31 (62%)	
Hemodialysis	36 (35%)	16 (32%)	
Peritoneal dialysis	4 (6%)	3 (6%)	
Diabetes mellitus	64 (62%)	29 (58%)	0.726
Insulin treatment	31 (30%)	4 (8%)	0.001
Oral medication	33 (32%)	25 (50%)	0.004
Hypertension	77 (74%)	39 (78%)	0.691
Current smoking	11 (11%)	8 (16%)	0.433
Hypercholesterolemia (≥200 mg/dl)	26 (25%)	15 (30%)	0.561
Previous PCI	20 (19%)	3 (6%)	0.032
Previous CABG	8 (8%)	2 (4%)	0.501
Previous MI	20 (19%)	5 (10%)	0.168
LV ejection fraction	55±12	52±14	0.344
Indication for intervention			0.063
Stable angina	33 (32%)	7 (14%)	
Unstable angina	57 (55%)	35 (70%)	
Acute myocardial infarction	14 (13%)	8 (16%)	

DES: group treated with drug-eluting stent, BMS: group treated with bare metal stent, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft surgery, MI: myocardial infarction.

In-hospital events are summarized in Table 4. Death during hospitalization occurred in no patient in the DES group (0%) and four patients in the BMS group (8%) (P=0.010). Of those, two cases were cardiac death (cardiogenic shock due to poorly controlled heart failure after successful intervention, and cardiac arrest after failed intervention) and the others were non-cardiac deaths (sepsis and progressive pneumonia). Post-procedural MI developed in four patients in the DES group (4%) and three patients in the BMS group (6%) (P=0.683). While composite in-hospital MACE (cardiac death, non-fatal MI and TVR) appeared to occur more frequently in the BMS group (10%) than DES group (4%), this difference was not found to be statistically significant (P=0.151). There were no cases of stent thrombosis in either group during hospitalization.

Table 2
Baseline angiographic and procedural characteristics

	DES (N=104)	BMS (N=50)	P value
No. of lesions	142	70	
Target vessel			0.076
Left anterior descending	77 (54%)	34 (49%)	
Left circumflex artery	11 (8%)	11 (16%)	
Right coronary artery	40 (28%)	24 (34%)	
Left main	13 (9%)	1 (1%)	
Graft vessel	1 (1%)	0 (0%)	
ACC/AHA lesion class			<0.001
A	2 (1%)	10 (14%)	
B1	24 (17%)	22 (32%)	
B2	17 (12%)	12 (17%)	
C	99 (70%)	26 (37%)	
Multivessel involvement (≥2)	43 (30%)	30 (60%)	0.039
Chronic total occlusion	6 (5%)	3 (4%)	1.000
Ostial lesion	16 (12%)	5 (7%)	0.465
Bifurcation lesion	15 (12%)	5 (7%)	0.618
Direct stenting	26 (17%)	4 (6%)	0.012
Stents per patient	1.9±1.0	1.0±0.2	<0.001
Stent length per lesion (mm)	24.8±6.7	20.8±5.8	<0.001
Balloon-to-artery ratio	1.3±0.2	1.1±0.1	<0.001
Maximal balloon size (mm)	3.6±0.4	3.7±0.6	0.076
Maximal inflation pressure (atm)	15.7±3.8	12.6±3.4	<0.001
Guidance of IVUS	43 (42%)	12 (24%)	0.048
Use of GP IIb/IIIa inhibitors	0	2 (4%)	0.104
Angiographic success	98%	96%	0.758

ACC/AHA lesion class: American college of cardiology/American heart association lesion class, IVUS: intravascular ultrasound, GP: glycoprotein.

Table 3
Quantitative angiographic characteristics

	DES (N=104)	BMS (N=50)	P value
No. of lesions	142	70	
Reference vessel diameter (mm)	2.8±0.5	3.3±0.7	<0.001
Lesion length (mm)	28.8±17.0	20.5±9.2	<0.001
Minimal lumen diameter (mm)			
Before procedure	1.1±0.5	0.9±0.6	0.023
After procedure	2.9±0.5	3.2±0.5	0.002
Acute gain (mm)	1.9±0.6	2.3±0.7	<0.001

3.3. Follow-up clinical outcomes

The mean follow-up duration was 359±3 days for the DES group, and 360±4 days for the BMS group (P=1.000). Clinical events during the 1-year follow-up are summarized in Table 4. During that time there was no significant difference between the two groups in terms of cardiac death, non-fatal MI or TVR. However, the composite MACE rate higher for the BMS group (26%) than the DES group (12%) (P=0.042). There was one case of subacute stent thrombosis in the BMS group during the follow-up period. Dialysis-dependent patients did not show more mortality propensities compared with medically treated patients regardless of used stent types (dialysis dependent versus dialysis non-dependent; 2/19 (10.5%) versus 4/31 (12.9%) in the BMS and 1/40 (2.5%) versus 2/64 (3.1%) in the DES group).

Table 4
Adverse cardiac events during initial hospitalization and after one year

	DES (N=104)	BMS (N=50)	P value
In-hospital events			
Death	0	4 (8%)	0.010
Cardiac death	0	2 (4%)	0.104
Non-fatal MI	4 (4%)	3 (6%)	0.683
TVR	0	0	1.000
Composite MACE	4 (4%)	5 (10%)	0.151
One-year clinical events			
Death	4 (4%)	10 (20%)	0.002
Cardiac death	3 (3%)	6 (12%)	0.059
Non-fatal MI	4 (4%)	3 (6%)	0.715
TVR	6 (6%)	4 (8%)	0.729
Composite MACE	13 (12%)	13 (26%)	0.042

Composite MACE included cardiac death, non-fatal MI and TVR.
TVR: target vessel revascularization, MACE: major adverse cardiac event.

3.4. Comparison between the SES and PES groups

Baseline clinical, angiographic and procedural data between the SES and PES groups showed similar characteristics. During hospitalization, there were two cases of non-fatal MI in each group (SES 3% versus PES 7%; $P=0.293$) without cardiac death or TVR. There was no difference between these two groups in terms of composite MACE during the one-year follow-up (SES 9 cases [12%] versus PES 4 cases [14%]; $P=0.741$).

4. Discussion

The major finding of this study was that DES implantation for *de novo* coronary lesions in patients with significant CKD showed the more favorable clinical outcomes compared with BMS implantation. The 1-year clinical efficacy between SES and PES implantations in patients with significant CKD was similar.

Patients with CKD have diffuse and accelerated progressive atherosclerosis [13,14]. It is related with many risk factors of CKD such as increased prevalence of hypertension or hypervolemia, lipid abnormalities, insulin resistance and physical inactivity. CKD has been found to be directly associated with a premature atherosclerosis. The outcomes of revascularization in CKD patients have been disappointing, with a more than 60% of restenosis rate following balloon angioplasty [15]. In addition, while the use of BMS has lowered the incidence of subacute vessel closure, angiographic restenosis occurs in up to 30% of hemodialysis patients [16]. Best and colleagues demonstrated a 16.6% of MACE rate (death, MI or TVR) and a 32% angiographic restenosis rate in the 9 months subsequent to PCI in significant CKD patients [17].

It has been established that the risk of cardiovascular disease increases as CKD has progresses [17,18]. Even though mild renal insufficiencies increase cardiovascular events, significant CKD (CrCl<60 ml/min) markedly increases the risks of congestive heart failure, left ventricular hypertrophy and coronary artery disease [19]. Although previous studies showed that significant CKD or dialysis patients had a higher MACE rate after PCI – mostly death – than patients without significant CKD, they have not found different rates of repeat revascularization after BMS implantation, regardless of the severity of renal failure [5,6,14,20]. In the era of DES, the TAXUS-IV trial documented a reduced 1-year MACE (cardiac death, MI or TVR; 13.9%) and angiographic restenosis rates (2.1%) in significant CKD patients [21]. Restenosis rate, although high after BMS implantation both in patients with both normal and depressed renal function, was actually slightly lower in patients with baseline renal insufficiency. TVR rates at 1 year was also similar or tended to be lower in patients with greater degrees of renal insufficiency. This data may suppose at a minimum that significant CKD in the DES era is no risk factor for increased clinical or angiographic restenosis. However, more large-sized investigations will be needed to confirm the findings of TAXUS-IV trial due to the use of polymer-based PES only, and significantly lower restenosis rate in that study compared with previous BMS and our DES data.

Our preliminary study enrolled the patients with significant CKD which has been known as a determinant of post-procedural MACE. We sought to compare differences of long-term clinical events after DES versus BMS implantation in such a critical condition. There were considerable differences of baseline clinical, procedural, and angiographic characteristics between DES versus BMS patients. Patients treated with DES were older, more often insulin-treated, with more severe and complex coronary artery disease and higher BMI. Procedural characteristics were also different, being IVUS-guidance and direct stenting more frequent in the DES group. Despite unfavorable baseline characteristics of patients treated with DES, the present study demonstrated that use of DES significantly reduced the incidence of 1-year MACE (cardiac death, MI or TVR; 12%) compared with use of BMS (26%) ($P=0.042$). The only significant difference was observed in the rate of both in-hospital and one-year death, and no difference was found in the TVR rate. Although six-month follow-up angiography rate was low (DES 38.7% [55 lesions] versus BMS 34.2% [24 lesions]), QCA data of the DES group showed lower restenosis rate (9.1 versus 37.5%, $P=0.008$) and smaller late loss (0.49 ± 0.65 versus 1.42 ± 0.80 mm, $P<0.001$) than those of the BMS group. It might propose that DES is superior to BMS for reducing long-term angiographic restenosis in significant CKD patients. In the present study, the lesion complexity and a high possibility of complication after PCI made difficult to perform repeat revascularization, which led to no difference of TVR according to degrees of renal insufficiency. There were no significant differences between the SES and PES groups in terms of clinical outcomes and angiographic restenosis. These finding suggest both SES and PES implantations have greater efficacy and safety compared to BMS implantation for *de novo* coronary lesion in significant CKD patients. Our findings in the current study are not only showing that DES could be a preferred strategy in CKD patients than conventional BMS, but also consistent with previous studies demonstrating that CKD are significantly associated with worse clinical outcomes compared to those without CKD.

The present study had some limitations. The study was a retrospective, observational analysis from a single center and the sample size is relatively small. Despite these shortcomings, clinical long-term follow-up was available in all patients and the current data clearly indicated that DES was superior to BMS in terms of long-term clinical adverse events.

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