Int J Clin Exp Med 2017;10(7):11220-11225
www.ijcem.com /ISSN:1940-5901/IJCEM0053047

Original Article

A real world analysis of the angiographic patterns of in-stent restenosis and clinical outcome of second drug-eluting stent implantation

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Received March 16, 2017; Accepted June 25, 2017; Epub July 15, 2017; Published July 30, 2017

Abstract: *Objective:* To investigate the medium-term outcome of patients with in-stent restenosis (ISR) who received second drug-eluting stent implantation. *Methods:* Totally 5993 patients received drug eluting stents during the review period, and 52 of them (74 lesions) who had a symptomatic cardiovascular event and developed ISR angiographically after they undergone angiography and received drug-eluting stents were included. Stent restenosis was classified by visual estimation on angiography. Data on major adverse cardiac events (MACEs) were retrieved and analyzed. *Results:* Angiography revealed that 31 patients (59.6%) had pattern I ISR, 9 patients (17.3%) had pattern II ISR, and 12 patients (23.1%) had pattern IV ISR. Twenty-four patients with ISR were treated with drug-eluting stents only, involving seven types of drug-eluting stents. Symptoms disappeared in 39 (75%) patients and were relieved in 13 (25%) patients. After 22.8 ± 17.5 months of follow up, 7/24 (29.2%) patients developed angina pectoris requiring hospitalization, three (3/24, 12.5%) patients required revascularization, and one (1/24, 4.2%) patient had myocardial infarction and one (1/24, 4.2%) patient died. Noticeably, no (0/8) patients receiving Xience drug-eluting stent had a cardiovascular event or died. *Conclusion:* Second drug-eluting stent placement was effective in alleviating patient symptoms, but MACEs developed in these patients within 2 years of follow up.

Keywords: Drug-eluting stent, in-stent restenosis, angiographic pattern, major adverse cardiac events (MACEs)

Introduction

Drug-eluting stent implantation such as everolimus-eluting stent implantation is the standard therapy for coronary artery disease and has yielded an overall favorable long term clinical outcome [1]. Although the newer generation drug-eluting stents are more effective and safer than the first generation drug-eluting stents, restenosis following implantation with the newer generation drug-eluting stents continues to represent a major challenge, hampering the clinical usefulness of this procedure [2-4].

The angiographic patterns of in-stent restenosis (ISR) have been classified for individual drug-eluting stents and their implications for long-term outcome have also been investigated [4, 5]. Recent randomized controlled trials on in-stent-restenosis have analyzed different treatment strategies and the medium term follow-up. However, these studies tended to limit the comparison of efficacy and safety to only two different types of drug-eluting stents or to that between drug-eluting stent and drug-eluting balloon [6], while in real practices, multiple types of drug-eluting stents may be used at one institution, especially in China. But no comparative study is available on the clinical outcomes of multiple drug-eluting stent types, particularly in patients with ISR who received second implantation of drug-eluting stents. For in-stent stenosis, even though many treatment strategies, such as cutting balloon, re-implantation of drug-eluting stents, coronary artery bypass grafting (CABG) and drug-eluting balloon are employed to treat restenosis following drug-eluting stent implantation, the optimal therapeutic strategy currently remains undefined. Furthermore, the morphology and characteristics of ISR based on recurrent cardiac ischemia

symptoms after second implantation of different types of drug-eluting stents has remained unclear.

In this single center retrospective study, we sought to investigate the medium term outcome of patients with ISR who received second drug-eluting stent implantation, and further delineate relationship between the angiographic patterns of ISR and types of drug-eluting stents implanted.

Patients and methods

Patients

In this retrospective observational study, we enrolled patients who had a symptomatic cardiovascular event and were confirmed angiographically to have ISR after receiving drug-eluting stents at Beijing Friendship Hospital, Capital Medical University, Beijing, China, between January, 2003 and January, 2013. In stent restenosis was defined by coronary angiography as a luminal stenosis of >50% in the diameter of a previously treated vessel. Stent restenosis was classified by visual estimation on angiography according to the geographic distribution of intimal hyperplasia in reference to the implanted stent as previously described by Mehran *et al* [7].

Patients who presented with recurrent angina or objective evidence of ischemia and had >50% diameter stenosis on angiographic assessment were included, while patients with ISR in small vessels (≤2.0 mm in diameter) or very diffuse lesions (>30 mm in length) were excluded. Patients whose recurrent myocardial ischemia was due to causes other than ISR, or whose vascular lesion and myocardial ischemia symptoms were confirmed by coronary angiography to be not caused by ISR, were also excluded.

The study protocol was approved by the local institutional review board at the authors' affiliated institution and patient consent was not required because of the retrospective nature of the study.

Percutaneous interventions

Stent implantation was performed by two cardiologists (LW and HC) with more than 15 years of experience in percutaneous intervention. All patients were pretreated with aspirin and clopidogrel. Unfractionated heparin with an initial bolus of 100 mg/kg was used during the procedure targeting for an activated clotting time >250 seconds. After adequate lesion pre-dilation, appropriate drug-eluting stents were implanted with a final balloon-to-artery ratio of 1.1:1. Stent expansion was assessed with the use of intracoronary imaging techniques at the discretion of the physician. Clopidogrel (75 mg/day) was recommended for 1 year after stent implantation and all patients were treated with aspirin indefinitely.

Follow up

Patients were followed up at 6 to 9 months and at 1 year. Angiographic follow-up was scheduled at 6 to 9 months, and early angiography was recommended in patients with symptoms. Data on major adverse cardiac events (MACEs: all cause death and myocardial infarction) and target vessel revascularization were retrieved. All deaths were considered cardiac unless a clear non-cardiac cause was established. Myocardial infarction was diagnosed when patients met the following two criteria: 1) prolonged (>30 min) chest pain; 2) a rise in creatine kinase levels more than twice the upper normal value (with abnormal MB fraction); 3) development of persistent ischemic electrocardiographic changes.

Statistical analysis

All data were retrospectively entered into a dedicated database. SPSS13.0 statistical software was used for data processing. Continuous variables following a normal distribution were presented as mean ± standard deviation. Non-normally distributed data were presented as median. Categorical variables were presented as frequency (%). Chi-square test was used to compare the differences among sets of categorical variables. T-test was employed to compare the difference between two sets of continuous variables, and ANOVA or Wilcoxon rank sum test was used to compare multiple sets of continuous variables. A probability value of $P<0.05$ was considered as statistically significance.

Results

Patient and lesion characteristics

Totally 5993 patients received drug eluting stents during the review period, and 52 of

Table 1. Patient characteristics and in-stent restenosis pattern following primary stent placement

		Time to 2nd angiography, months	Patterns of in-stent restenosis, n (%)			
			I	II	III	IV
All patients	52	43.8 ± 28.1	31 (59.6)	9 (17.3)	0 (0)	12 (23.1)
Mean age (range), years	64.5 ± 11.2 (46, 89)	-				
Male gender, n (%)	40 (76.4)	-				
Hypertension only, n (%)	27 (52)					
Diabetes only, n (%)	4 (7.7)					
Hypertension and diabetes, n (%)	13 (25)					
Drug eluting stents, n						
Cypher	18	50.8 ± 27.1	8	5	0	5
Taxus	10	49.9 ± 34.1	8	1	0	1
Firebird	8	44.2 ± 21.6	5	0	0	3
Endeavor	7	17.8 ± 19.7	5	1	0	1
Others	9	49.33 ± 31.72	5	2	0	2
Causes of admission, n (%)						
Angina pectoris	31 (59.6)					
Myocardial infarction	21 (40.4)					

Table 2. The average interval time between stenting and angiographic restenosis with cardiac ischemia symptoms

DES Type	Cypher	Taxus	Firebird	Endeavor
Interval time, months	50.8 ± 27.1	49.9 ± 34.1	44.2 ± 21.6	17.8 ± 19.7
DES Type	Partner	Excel	Janus	Cypher+Taxus
Interval time, months	20.3 ± 17.0	49.87 ± 27.8	53	74

them (74 lesions) who had a symptomatic cardiovascular event and developed ISR angiographically after they undergone angiography and received drug-eluting stents were eligible for inclusion in this analysis. The demographic and lesion characteristics of the study subjects were listed in **Table 1**. Their mean age was 64.5 ± 11.2 years and the majority of the patients were male (76.4%). Eighteen patients (34.6%) received Cypher sirolimus-eluting stent, 10 patients (19.2%) received Taxus paclitaxel-eluting stent, 8 (15.4%) received Firebird sirolimus-eluting and 7 patients (13.5%) received Endeavor zotarolimus-eluting stent. Nine patients (17.3%) received other types of drug-eluting stents.

Angiography was performed in 31 (59.6%) patients who had angina pectoris and in 21 (40.4%) patients who had myocardial infarction. The median duration from initial drug-eluting stent placement to second angiography was 47 months (range 4 to 108 months). Patients receiving Endeavor zotarolimus-eluting stent had the shortest time to second angiography (17.8 ± 19.7 months) while the time to second angiography was comparable between patients receiving Cypher sirolimus-eluting stent (50.8 ± 27.1 months) and those receiving Taxus paclitaxel-eluting stent (49.9 ± 34.1 months) (**Table 2**). Angiography revealed that 31 patients (59.6%) had pattern I ISR, 9 patients (17.3%) had pattern II ISR, and 12 patients (23.1%) had pattern IV ISR. For all types of drug-eluting stents, pattern I ISR appeared to be dominant. However, the angiographic patterns of ISR were not associated with the type of drug-eluting stent implanted.

Outcomes of second drug-eluting stent placement

Twenty-four patients received drug-eluting stents only, involving seven types of drug-eluting stents. Eight patients received Xience everolimus-eluting stent, seven patients received Excel sirolimus-eluting stents and six patients received Taxus paclitaxel-eluting stent. Nine remaining patients received other types of drug-eluting stents (**Table 3**). Procedural success was achieved in all patients except one patient who had broad anterior myocardial infarction due to complete blockage and received a second drug-eluting stent. The patient died of postoperative heart failure and pulmonary infection. Symptoms disappeared in 39

Table 3. Characteristics of second drug-eluting stent placement

	N	Angina pectoris requiring hospitalization	Revascularization	Myocardial infarction	Death of all causes
Drug-eluting stents	24	7	3	1	1
Cypher	2	0	0	0	0
Taxus	6	3	0	1	0
Partner	2	0	0	0	0
Endeavor	4	1	2	0	0
Xience	8	0	0	0	0
Excel	7	3	1	0	0
Firebird	1	0	0	0	1

(75%) patients and were relieved in 13 (25%) patients.

The patients were followed up from the date of confirmed restenosis for a median duration of 19 months. Seven (7/24, 29.2%) patients developed angina pectoris requiring hospitalization, three (3/24, 12.5%) patients required revascularization, and one (1/24, 4.2%) patient had myocardial infarction and one (1/24, 4.2%) patient died. Four (4/6, 66.7%) patients receiving Taxus drug-eluting stent had a cardiovascular event, and four (4/7, 57.1%) patients receiving Excel sirolimus-eluting stents had a cardiovascular event and 4 (4/9, 44.4%) patients received other types of drug-eluting stent had a cardiovascular event or died. Noticeably, no (0/8) patients receiving Xience drug-eluting stent had a cardiovascular event or died.

Discussion

ISR still remains a not insignificant issue for percutaneous intervention. Compared to other types of drug-eluting stents, Endeavor zotarolimus-eluting stent had the shortest time to second angiography. Though pattern I ISR appeared to be dominant for all types of drug-eluting stents, the angiographic patterns of ISR were not associated with any particular type of drug-eluting stent implanted. Significantly, three in ten patients (29.2%) receiving second ISR had a MACE, suggesting that restenosis following implantation with the newer generation drug-eluting stents poses a serious therapeutic challenge.

More than half of the patients had pattern I ISR. Pattern I lesions are focal lesions≤10 mm in length and are positioned at the unscaffolded segment, the body of the stent, and the proximal or distal margin [7]. Our finding is consistent with other studies demonstrating that most of ISR lesions are more likely to be focal than non-focal [2, 3, 8, 9]. However, diffuse stent lesions also appear to be a significant clinical issue; 40.4% of our patients had diffuse stent lesions (pattern II, 17.3% and pattern IV, 23.1%).

Our patients underwent second angiography within two years of initial stent placement (median duration, 47 months; range 4 to 108 months). The mean duration between initial stenting and the presence of cardiac ischemia symptoms with angiographic restenosis was the shortest for Endeavor zotarolimus-eluting stent and apparently less than that for Cypher sirolimus-eluting stents and Taxus paclitaxel-eluting stents. In this retrospective study, 78.8% (41) of the patients with recurrent cardiac ischemia symptoms received intervention therapy. The angiographic and clinical outcomes after treating ISR with balloon angioplasty, drug-eluting stents and other intervention approaches have been intensively studied [10-13]. Compared with conventional therapies for ISR [12], drug eluting stents are associated with a lower recurrent restenosis rate. However, our study showed that a significant proportion (45.9%) of our patients receiving second stent placement had angina pectoris (29.2%) or myocardial infarction (4.2%), or required revascularization (12.5%). Noticeably, Xience everolimus-eluting stent was not associated with a MACE while MACE occurred in 66.7% patients receiving Taxus drug-eluting stent and 57.1% patients receiving Excel sirolimus-eluting stents. Because this study had a small sample size, a definite conclusion is hard to be drawn based on the data. A recent randomized study of 2,771 patients who were followed up for 5 years showed that compared to sirolimus-eluting-stents, everolimus-eluting stents were associated with a significantly lower MACE rate [14]. The SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions) also showed a lower MACE rate for everolimus-eluting stents

than paclitaxel-eluting stents (13.2% *vs.* 20.7%, P=0.007) [15].

The current study had several limitations. It was a retrospective, non-randomized study and had a small sample size. Furthermore, analysis of ISR was based on visual estimation on angiography. Despite these limitations, this study provides some useful insights into the relationship of restenosis patterns and the type of drug-eluting stents implanted in real world situations.

In conclusion, a significant proportion of patients receiving drug-eluting stents developed ISR within 4 years of initial stent implantation. Second drug-eluting stent placement was effective in alleviating patient symptoms, but MACEs developed in these patients within 2 years of follow up.

Disclosure of conflict of interest

None.

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