Incidence, Predictors, Treatment, and Long-Term Prognosis of Patients with Restenosis after Long Drug-Eluting Stent Implantation for Coronary Arteries

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Received 24 September 2014; revised 13 November 2014; accepted 27 November 2014

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Abstract

Background: Few data on the clinical course and management of patients experiencing restenosis after implantation of long drug-eluting stents treatment for coronary arteries was available. Objectives: The aim of this study was to evaluate the incidence, predictors, and long-term outcomes of patients with in-stent restenosis (ISR) after percutaneous coronary intervention (PCI) with long (33 mm & 38 mm) drug-eluting stents (DES) for long lesions in coronary arteries including left anterior descending artery (LAD), Lt circumflex artery (Lt Cx), right coronary artery (RCA), obtuse marginal artery (OM) & posterior descending artery (PDA). Methods: Between July 2009 and October 2010, 421 long DES had being implanted in 421 consecutive patients with significant coronary artery stenosis, with 371 patients (88%) undergoing routine follow up, clinical follow up done by exercise stress test at 6 & 12 months after stenting for 126 patients (34%), in 124 patients (33.5%) follow up was done by Computed Tomography angiography & 121 patients (32.5%) with clinically driven angiographic follow-up. A major adverse cardiac event was defined as the composite of death, myocardial infarction (MI), or target-lesion revascularization (TLR) within 15 months. Results: All patients who underwent clinical follow up were asymptomatic. The overall incidence of angiographic (CT or conventional) ISR with long (33 mm & 38 mm) DES was 4% (15 out of 371 stents) with 8 (53.3%) focal-type and 7 (46.7%) with diffuse-type ISR. Six patients (40%) underwent repeated PCI, seven (46.7%) underwent bypass surgery, and 2 (13.3%) were treated medically. During long-term follow-up (ranging from 12 - 26 months), there were no deaths, 3 (0.8%) MI, and 13 (3.5%) repeated target-lesion revascularization (PCI or CABG) cases. The incidence of major adverse cardiac event was 5.3% in the medical group, 10.1% in the repeated PCI group, and 21.4% in the bypass surgery group. Multivariate analysis showed that the occurrence of DES-ISR...
did not affect the risk of death or MI. Conclusions: The incidence of ISR was 4% after long DES stenting for coronary arteries. The long-term clinical prognosis of patients with long DES-ISR associated with coronary artery stenting might be benign, if the patient has optimal treatment.

**Keywords**

Coronary Arteries, Restenosis, Long Stent

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**1. Introduction**

Percutaneous coronary intervention (PCI) was introduced as an alternative means of coronary revascularization to CABG surgery in 1979 [1]. Restenosis or reduction in lumen diameter after angioplasty and stent implantation has been historically considered the most significant problem in coronary interventional treatment [2]. The mechanism of restenosis after stent implantation is the result of arterial damage with subsequent neointimal tissue proliferation (hyperplasia), as stents resist arterial remodeling [3]-[6]. Binary angiographic restenosis is defined as ≥50% luminal narrowing at follow-up angiography.

Four types of ISR have been defined: 1) Focal (≤10 mm in length); 2) Diffuse (ISR > 10 mm within the stent); 3) Proliferative (ISR > 10 mm extending outside the stent); and 4) Occlusive ISR. Type I has been further subdivided into types IA to ID based on the site of focal ISR in relation to the stent [7]. An additional type of ISR has been proposed, that of “aggressive ISR”, defined as ISR that is longer and/or more severe than the original lesion [8], this type is noteworthy in that the clinical course is not benign, with patients more likely to have more severe symptoms and higher rates of myocardial infarction [8].

The most widely accepted definition of clinical restenosis, assessed as a requirement for ischemia-driven repeat revascularization, was proposed by the Academic Research Consortium. This definition requires both an assessment of luminal narrowing and the patient’s clinical context [9]. Neointimal hyperplasia is strongly inhibited by Drug-eluting stents DESs [10], thus dramatically diminished but not eradicated in-stent restenosis (ISR). Despite the significant advances in the technology to reduce DES restenosis, conservative estimates still suggest that the incidence of in-stent restenosis (ISR) requiring target vessel revascularization (TVR), so-called DES failure, to be 5% - 10%, with one estimate suggesting >200000 repeat revascularizations in the United States alone [11]. Several randomized trials have shown that diabetes, small vessel size, and long lesions may increase the risk of restenosis after DES implantation [12]-[14]. Emerging evidence now suggests that between 30% - 60% of ISR cases present with an acute coronary syndrome with unstable angina being the most common presentation and up to 5% of patients even reported to present with ST-elevation myocardial infarction (STEMI) [15]-[16].

Yet there is a lack of solid evidence pertaining to the safety and effectiveness of long DES stents for treating long lesions and there is a great need to demonstrate this; therefore, we evaluated the clinical and angiographic outcomes of long lesion coverage using long (33 mm & 38 mm) Everolimus-eluting stents (XIENCE PRIME) in the real world clinical practice.

**2. Patients**

Between July 2009 and October 2010, at Sulaimany Cardiac Hospital more than 1250 PCIs were performed in a year, 421 long (33 mm, 38 mm) (XIENCE PRIME LL, Abbott Vascular, USA) had been implanted in 421 consecutive patients with significant coronary artery stenosis. All the patients had both the clinical indications for PCI and an angiographic diameter stenosis ≥ 50% - 60% with 371 patient (88%) undergoing routine follow-up, the inclusion criterion was the presence of de novo coronary lesions that were implanted with either (33 mm or 38 mm) XIENCE PRIME LL stent. Patients with previous in-stent restenosis, lesions in saphenous vein grafts, end stage renal disease on hemodialysis, severe allergic reaction to contrast & patients with severe concomitant disease had being excluded from angiographic follow-up.

Written informed consent was obtained from all patients, the design of the study & use of the data had being proved by Ethics Committee of the hospital.
3. Methods

3.1. Stenting Procedure

Drug eluting stent (XIENCE PRIME LL, Abbott Vascular, USA) (33 mm & 38 mm) was used in all patients; the operator selected the stent and the implantation done according to the standard techniques. Complete lesion coverage was recommended, any segment with stenosis ≥ 20% were completely covered with stents, as well as angiographic optimization, with <10% - 20% residual stenosis by visual estimate. The length and number of the required stents were decided upon by the operating doctor according to visual estimation. All the procedures were performed without intravascular ultrasound guidance.

For the scheduled procedures, all the patients were on Aspirin 100mg/day at least 10 days before the procedure & received 300 mg loading dose of Clopidogrel 8 - 12 hours prior to the procedure, the emergency patient received 300 mg loading dose of Aspirin, 600 mg Clopidogrel & some of them received either abciximab or tirofiban. During the procedure, patients received a bolus of 7.500 unit of un-fractionated heparin, with a repeat bolus of 2000 unit to maintain activated clotting time ≥ 300 seconds. After the procedure, the patients received 300 mg aspirin for 30 days and then 100 mg daily indefinitely with clopidogrel 75 mg for one year.

3.2. End Points and Definitions

The primary end point was the incidence of major adverse cardiac events, defined as the composite of death, acute myocardial infarction (MI), or target lesion revascularization (TLR) (repeat angioplasty or coronary artery bypass surgery) after stent implantation. All events were based on clinical diagnosis and re-judged by a couple of independent clinicians. Death was defined as death from any cause. Myocardial infarction was based on the development of electrocardiographic changes in form of ST segment elevation or new Q waves in at least two contiguous leads with an elevated creatine kinase myocardial band fraction or elevated serum creatinine kinase-MB level of more than three times than the upper limit measured 24 hours after the procedure. A target lesion revascularization (TLR) was defined as percutaneous or surgical revascularization for stenosis either within the stent or within 5 mm of the stent. Stent thrombosis was assessed according to the Academic Research Consortium definitions, with pre-specified key end point being definite or probable [17], and the timing of the presentation, stent thrombosis was classified as acute occurred within 24 hour, sub-acute (2 - 30) days, late ≤1 year and very late >1 year. Restenosis was defined by a diameter stenosis of ≥50% occurring in the segment inside the stent or 5 mm segment proximal or distal to the stent at the follow-up angiography.) Restenotic lesions were classified as focal (type I, <10 mm), diffuse (type II), proliferative (type III), or total occlusion (type IV) [7].

3.3. Follow-Up

Patients were divided in to three groups for the follow up, the first group (n = 126, 34%) were completely asymptomatic during the follow-up period underwent exercise stress test at 6 & 12 months with meticulous clinical follow-up after stenting, the occurrence of inducible ischemia on stress test (with or without ischemic chest pain) or the recurrence of ischemic chest pain subjected the patients for angiographic follow-up. As long as Multi Detector Computed Tomography Angiography (MDCTA) has a good negative predictive value for ruling out coronary artery stenosis [18]-[20]; a group of asymptomatic patients (n = 124, 33.5%) were followed-up using MDCTA, if there was evidence of in-stent restenosis by MDCTA the patient was subjected for conventional coronary angiography. The third group of patients (n = 121, 32.5%) with clinical suspicion of restenosis and the majority of patients with small size stent (2.5 mm & 2.75 mm) have underwent coronary angiography for follow-up which done after (10 - 16 months) for recommended patients. If any clinical evidence of myocardial ischemia developed at during follow-up time, then coronary angiography was recommended. Angiographic binary restenosis was defined as a narrowing of ≥50% of the vessel diameter inside the previously implanted stent.

3.4. Angiographic Analysis

Quantitative coronary angiographic analysis was performed according to two observers. At least two orthogonal projections were selected for analysis; these were obtained after 100 - 200 mgs of intra-coronary nitroglycerin, the minimal lumen diameter, the lesion length and the percentage diameter stenosis were analyzed for a group of patients.
3.5. Statistical Analysis

The data was analyzed by SPSS (Statistical Package for the Social Sciences-version 16.0) package software program for statistical analysis. Descriptive statistics (numbers and percentages) were calculated for variables, as well as analytical statistics was done to find the relations between variables. Association between variables was detected by using the appropriate statistical tests such as Chi-square and, t-test. A p-value ≤ 0.05 was considered as significant.

4. Results

4.1. Incidence, Pattern, and Clinical Presentation of Long Drug-Eluting In-Stent Restenosis

During long-term follow-up period of 15 months ranging from (12 - 26 months), angiographic (conventional & MDCTCA) ISR was 6.1% (15 out of 245), but the overall incidence of ISR in all patients groups who underwent clinical & angiographic follow-up was 4% (15 out of 371) patients. The restenosis pattern was focal in (n = 8, 53.3%) & diffuses in (n = 7, 46.7%). Eight patients (53.3%) presented with stable angina, four patients (26.7%) presented with silent ischemia, two (13.4%) presented as unstable angina and one patient (6.6%) presented as non fatal ST elevation myocardial infarction. During the follow-up period, the cumulative incidence of definite or probable stent thrombosis was (0.8%), three patients; 1 definite and 2 probable. The different characteristics of patients are shown in Table 1.

4.2. Predictors of Long DES ISR

This study showed that diabetes mellitus, ejection fraction, ostial lesions and small stent diameter had an impact on occurrence of long DES ISR (Figures 1-4) whereas hypertension, hyperlipidemia, smoking, family history of coronary artery disease and which coronary artery being stented failed to show significant effects (Figures 5-9).

4.3. Treatment and Long-Term Prognosis of Long DES ISR

Among 15 patients with long DES ISR, 2 (13.3%) treated medically, 6 (40%) patients treated by repeat PCI (2 with only balloon angioplasty and 4 with additional DES implantation), and 7 (46.7%) underwent CABG surgery. All patients who underwent clinical follow up were asymptomatic. The overall incidence of angiographic (CT or conventional) ISR with long (33 mm & 38 mm) DES was 4% (15 out of 371 stents) with 8 (53.3%) foc-
al-type and 7 (46.7%) with diffuse-type ISR. Six patients (40%) underwent repeated PCI, seven (46.7%) underwent bypass surgery, and 2 (13.3%) were treated medically. During long-term follow-up (ranging from 12-26 months), there were no deaths, 3 (0.8%) MI, and 13 (3.5%) repeated target-lesion revascularization (PCI or CABG) cases. The incidence of major adverse cardiac event was 5.3% in the medical group, 10.1% in the repeated PCI group, and 21.4% in the bypass surgery group. Multivariate analysis showed that the occurrence of DES-ISR did not affect the risk of death or MI (Tables 2-4).
Figure 3. Shows that the incidence of ISR after long DES implantation was higher with ostial lesion compared to other arterial locations.

Figure 4. Shows that the smaller the stent diameter the higher the incidence of ISR after long DES implantation.

Figure 5. Shows that hypertension did not have an impact on ISR after long DES implantation.
Figure 6. Shows that hyperlipidemia had no effect on ISR after long DES implantation.

Figure 7. Shows that there was no relation between smoking & long DES ISR.

Table 2. Follow-up results of patients with angiographic ISR.

<table>
<thead>
<tr>
<th>Event-free (death, MI, TLR)</th>
<th>450 (365 - 775)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up in days</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>TLR</td>
<td>13 (3.5)</td>
</tr>
</tbody>
</table>
5. Discussion

We have demonstrated that the rate of in-stent restenosis after long (33 mm & 38 mm) everolimus DES implantation in routine clinical practice is nearly similar to the restenosis rate for shorter (≤28 mm) DES size reported in clinical trials.

Lesion length and stent length correlated weakly with restenosis, the stent length is not an independent predictor of restenosis. These results indicate that, for DESs stent length has less influence on restenosis than it does with bare metal stents, supporting the current strategy of complete lesion coverage.

Our results have also showed that the major determinant of long DES ISR were post intervention final lumen size, diabetes mellitus, location of the stent; the ostial stent has higher incidence of ISR compared to proximal, mid and distal part, stent diameter; the smaller stent diameter the higher incidence of ISR, the decrease in ejection fraction < 45% has higher incidence of ISR, and deployment pressure also is an important predictor of ISR; the higher deployment pressure the lower ISR rate.

In the era of bare metal stent, restenosis was a major limiting factor for angioplasty when many studies shows...
Table 3. Clinical, lesion, and procedural characteristics in patients with or without ISR among those receiving angiographic follow-up.

<table>
<thead>
<tr>
<th>Variables</th>
<th>With angiographic follow-up (n = 245)</th>
<th>ISR (n = 15)</th>
<th>No ISR (n = 230)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>52.9 ± 10.4</td>
<td>53.7 ± 10.1</td>
<td>52.7 ± 10.7</td>
<td>0.59</td>
</tr>
<tr>
<td>Male</td>
<td>125 (51.01)</td>
<td>71 (473.33)</td>
<td>196 (85.2)</td>
<td>0.49</td>
</tr>
<tr>
<td>Female</td>
<td>120 (48.9)</td>
<td>55 (366.6)</td>
<td>175 (76.08)</td>
<td>0.51</td>
</tr>
<tr>
<td>Cardiac or coexisting conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>123 (50.2)</td>
<td>14 (93.3)</td>
<td>109 (47.39)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>142 (57.9)</td>
<td>9 (60)</td>
<td>133 (57.82)</td>
<td>0.852</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>109 (44.48)</td>
<td>8 (53.3)</td>
<td>101 (43.91)</td>
<td>0.461</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>99 (40.4)</td>
<td>6 (40)</td>
<td>93 (40.43)</td>
<td>0.921</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2 (0.8)</td>
<td>0 (0)</td>
<td>2 (0.86)</td>
<td>0.717</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>114 (46.5)</td>
<td>7 (46.66)</td>
<td>107 (46.52)</td>
<td>0.899</td>
</tr>
<tr>
<td>Previous PCI or CABG</td>
<td>29 (11.83)</td>
<td>3 (20)</td>
<td>26 (11.30)</td>
<td>0.312</td>
</tr>
<tr>
<td>Ejection fraction &gt; 55%</td>
<td>198 (80.8)</td>
<td>6 (40)</td>
<td>192 (83.47)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ejection fraction &lt; 45%</td>
<td>42 (17.14)</td>
<td>5 (33.33)</td>
<td>37 (16.08)</td>
<td>0.083</td>
</tr>
<tr>
<td>STEMI</td>
<td>14 (5.7)</td>
<td>1 (6.66)</td>
<td>13 (5.65)</td>
<td>0.962</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>112 (45.7)</td>
<td>7 (46.66)</td>
<td>105 (45.06)</td>
<td>0.59</td>
</tr>
<tr>
<td>Chronic stable angina</td>
<td>48.57</td>
<td>7 (46.66)</td>
<td>112 (48.69)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Table 4. Clinical and angiographic characteristics of patient with ISR, according to treatment strategy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medical therapy (n = 2, 13.3%)</th>
<th>Repeated PCI (n = 6, 40%)</th>
<th>CABG (n = 7, 46.7%)</th>
<th>P value</th>
<th>Variable</th>
<th>Medical therapy (n = 2, 13.3%)</th>
<th>Repeated PCI (n = 6, 40%)</th>
<th>CABG (n = 7, 46.7%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical indication</td>
<td></td>
<td></td>
<td></td>
<td>0.036</td>
<td>location involved</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.251</td>
<td>Ostium</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td></td>
<td>Proximal</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Chronic stable angina</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td></td>
<td>Mid part</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lesion characteristic of ISR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Distal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td></td>
<td>Focal pattern (n = 8)</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
<td>Diffuse pattern (n = 7)</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td></td>
<td>MACE %</td>
<td>5.3</td>
<td>10.1</td>
<td>21.4</td>
<td></td>
</tr>
<tr>
<td>OM</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PDA</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
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that post intervention final lumen diameter is the most powerful predictor of restenosis after bare metal implantation [21]-[23] and our study shows the same effect.

Coronary artery disease is more aggressive in diabetic than in non-diabetic patients and coronary revascularization procedures are associated with less favorable outcomes in diabetic patients. Many randomized trials, demonstrates durable clinical and angiographic benefits for diabetic patients after DES implantation, but it was unclear whether diabetes increased the risk of restenosis after DES implantation [12]-[14]. Our results have
demonstrated that diabetes is a predictor of restenosis after long DES implantation.

In-stent restenosis, which is secondary to neointimal hyperplasia, presents in different patterns. Focal in-stent restenosis was the most favorable pattern with respect to late outcome after repeat intervention [7]. Our study has shown that, similar to previous results with shorter DESs, [2] [3] in-stent restenosis occurred mostly (about 53.3%) as a focal pattern. In addition our results suggest that long DES implantation is highly effective in routine clinical practice, providing a rationale for its use.

There are several potential limitations in our study, first, only one kind of everolimus eluting stent had been used which may lead to possible bias, second, our study was limited by incomplete angiographic follow-up, thus possibly leading to potential error for the restenosis rate.

6. Conclusion

The incidence of ISR 15 months after successful long DES implantation in consecutive real-world patient with significant coronary artery lesion was approximately 4%. Diabetes mellitus, ostial location, low ejection fraction > 45%, stent diameter & pressure of employment were identified as major predictors of long DES-ISR. The clinical consequences of long DES ISR, seem to be benign. Different modalities for long DES ISR don’t have significant impact on the incidence of major adverse cardiac events given that these patients treated optimally by their clinicians.

References


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