

Major clinical and angiographic outcome of drug eluting stents in native ostial coronary artery disease

Khaled R. Abd El Meguid¹, Hesham B. Mahmoud¹, Fouad R. Amin², Jonathan R. Clague³

¹Division of Cardiology, Beni-Suef University Hospital, Beni-Suef, Egypt

²Division of Cardiology, Heatherwood & Wexham Park Hospitals, London, UK

³Division of Cardiology, Royal Brompton Hospital, Imperial College, London, UK

Email: krefaat20@hotmail.com

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ABSTRACT

Objectives: The study was designed to evaluate the efficacy and safety of drug eluting stents (DESs) in aorto-ostial (A-O) coronary artery lesions, in terms of early and late restenosis rate; including clinical assessment, non-invasive stress testing and angiographic follow-up. Also, the study was aimed to compare the results of implantation of drug eluting stents (DES) to that of bare metal stents (BMS) in aortoostial lesions done over a previous 5 years in Royal Brompton Hospital. **Background:** The safety and effectiveness of DESs for the treatment of aorto-ostial lesions. **Methods:** We included 161 consecutive patients with symptoms subjective of angina pectoris or objective evidence of myocardial ischemia; who underwent percutaneous coronary interventions (PCI) in coronary ostial lesions using DES. The patients were divided into two groups based on the site of ostial lesion. The control group consisted of 125 consecutive patients who underwent percutaneous coronary intervention for ostial lesions using bare metal stents (BMS) implantation in the period immediately before the introduction of DES. **The incidence of major adverse cardiac events (MACE), including death or Q-wave myocardial infarction (MI), need for repeated revascularization procedure CABG or angioplasty, were recorded in-hospital and at twelve months \pm 3 months. Follow-up angiography was only performed in case of recurrent symptoms subjective of myocardial ischemia or if there was objective evidence of myocardial ischemia by stress testing. Results:** The initial procedure was successful in 149 patients (92.5%) in the DES arm. There were no statistically significant major in-hospital complications in the DES group, compared to BMS group which showed 4 cases of in-hospital deaths ($p = 0.017$). At Twelve months \pm 3 months follow-up, MACE were

significantly less frequent in the DES group compared to the BMS group, including death (0.8% vs. 6.4%, $p = 0.004$) and need for CABG (1.7% vs. 10%, $p = 0.012$). **Conclusions:** The main finding of our study is that, compared to the BMS, implantation of the DES in coronary ostial lesions appears safe and effective. It is associated with high procedural success rate, low immediate and in-hospital complication rate, infrequent late adverse events and favourable long-term clinical and angiographic outcomes compared with bare metal stents implantation at 12-month follow-up. Advanced age, previous myocardial infarction and acute coronary syndromes at presentation were all found to be independent positive predictors for clinical events after drug eluting stent implantation in ostial lesions.

Keywords: Bare Metal Stent; DRUG Eluting Stent; Ostial Coronary Lesions

1. INTRODUCTION

Ostial coronary artery lesions constitute a distinct substrate for percutaneous intervention, as they differ from other lesion sites in management strategies and in clinical out-come. The high concentration of elastic muscle fibers around the ostium, and the presence of atherosclerosis and fibrosis of the aortic wall in case of aorto-ostial (A-O) and proximal left main coronary artery (LMCA), has been proposed as a possible mechanisms of elastic recoil and high restenosis rate in these sites [1,2]. In addition, the presence of ostial calcification contributes to further lesions rigidity [3]. Hence these lesions appear to be both rigid and elastic at the same time [4].

Percutaneous intervention for aorto-ostial (A-O) lesions have been associated with lower procedural success

rates of 70% - 97%, more frequent in hospital complications of 5% - 12%, and greater likelihood of late restenosis of 28% - 52% when compared with treatment of non aorto-ostial lesions [5,6]. Excimer laser coronary angioplasty had a high initial angiographic and clinical success rates but restenosis was a limitation [7].

The beneficial action of stents has been attributed to maximizing the initial luminal gain and overcoming the aorto-ostial elastic recoil [8,9]. Silvestri *et al.*, on 2000 [10] confirmed the feasibility and safety of stent-supported angioplasty of the left main coronary artery leading to acceptable morbidity, with a 6 month target lesion revascularization (TLR) rate of 17%. Stenting of ostial left anterior descending artery (LAD) lesions were associated with better event-free survival, and less target lesion revascularization (TLR) of 10.5% compared to directional atherectomy alone 50% [11].

Drug eluting stents have a potent anti-inflammatory, immunosuppressive, and anti-proliferative effect [12,13].

Drug eluting stents (DES) have been shown to reduce the incidence of restenosis even in very complex lesions [14,15], but critical aorto-ostial lesions were not included in many trials [16-18].

2. AIM OF THE STUDY

To evaluate the efficacy of drug eluting stents in aorto-ostial (A-O) coronary artery lesions, in terms of early and late restenosis rate, clinical assessment, non-invasive stress testing and angiographic follow-up.

3. METHODS

Study patients: Our study group included all patients with ostial lesions who underwent elective drug eluting stent (DES) deployment with either Sirolimus eluting stents (Cypher, Cordis/Johnson and Johnson) or Paclitaxel-eluting stents (Taxus, Boston Scientific) in a native ostial coronary artery. The population consisted of 161 patients divided into two groups with symptoms subjective of angina pectoris or objective evidence of myocardial ischemia, with suitable coronary anatomy for percutaneous revascularization. The control group consisted of 125 consecutive patients who underwent percutaneous coronary intervention for ostial lesions using bare metal stents (BMS).

Exclusion criteria:

*Target vessel reference diameter smaller than 2.5 mm.

*Stent implantation during cardiogenic shock or as a bridge to emergency CABG.

*Contraindication to antiplatelet agents.

*Myocardial infarction within 48 hours.

*Heavy calcified ostial lesions.

An aorto-ostial lesion was defined as a >70% stenosis located at the aortic junction with the left main coronary artery, right coronary artery within 3 mm of the vessel origin on the view of least foreshortened angiographic projection [19-22]. **Group I:** the aorto-ostial lesions include left main coronary artery (LMCA) and right coronary artery (RCA) ostial lesions. **Group II:** the non aorto-ostial lesions include left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), diagonal branches (D), obtuse marginal (OM), and posterior descending coronary artery (PDA).

Stenting procedures and antiplatelet medications:

Details of the stenting technique have been previously described [23,24]. All patients were pre-treated with clopidogrel and aspirin. Clopidogrel (75 mg/day) was prescribed for ≥ 12 months after DES implantation and prescribed for ≥ 3 month after BMS implantation.

Follow-up: The primary endpoints included major adverse cardiac events MACE (death, MI, need for repeat revascularization procedure CABG or angioplasty). Follow-up angiography was only performed in case of recurrent symptoms subjective of myocardial ischemia or if there was objective evidence of myocardial ischemia by stress testing.

4. RESULTS

Baseline patient and lesion characteristics: The clinical and lesion characteristics were similar between the DES group and the BMS group, except for the higher incidence of hypertension, hypercholesterolemia and patient clinical presentation (CCS III/IV functional class) in the DES group 74.4% vs. 37.6% $p < 0.001$, 79.8% vs. 64% $p 0.003$ and 69.6% vs. 37.6% $p < 0.001$ respectively. However, patients in the BMS group had higher number of smokers and previous CABG in proportion to the DES group 53.6% vs. 16.1% $p < 0.001$ and 41.6% vs. 20.5% $p < 0.001$ respectively (**Table 1**).

Table 1. Combined comparison between DES and BMS.

	Total DES	Total BMS	p Value
Age	65 (± 11.6)	66 (± 8)	0.39
Male	126 (75.0)	99 (79%)	0.4
Smoker	27 (16.1)	67 (53.6%)	<0.001
HT	125 (74.4)	47 (37.6%)	<0.001
DM	47 (28.1)	26 (20.8%)	0.152
HCL	134 (79.8)	80 (64%)	0.003
Family History	84 (50.3)	53 (42.4%)	0.181
Previous MI	82 (48.8)	66 (52.8%)	0.499
Previous CABG	35 (20.5)	52 (41.6%)	<0.001
CCS III & IV	117 (69.6)	47 (37.6%)	<0.001
EF < 50%	29 (19.5)	35 (28%)	0.172

Procedural success and in-hospital complications:

There was no statistically significant difference in terms of procedural success, MI and emergency CABG between the two groups. However, there were 4 cases of in-hospital deaths in the BMS treated patients compared to no in-hospital deaths in the DES treated patients which was statistically significant with p value of 0.017. Three of the 4 deaths in the BMS treated patient during hospitalization were in the aorto-ostial lesion group with p value 0.001, and 1 patient had emergency CABG from the non aorto-ostial lesion group. The total procedural success in the BMS treated group was 117 patients 93.6% vs. 163 patients 92.1% in the DES group (Table 2).

Long-term clinical outcomes: Twelve month \pm 3 month cumulative clinical follow-up was available in 155 out of 161 patients (96.2%) in the DES treated patients, representing 41 patients (100%) in aorto-ostial lesion group, 109 patients (95.6%) in the non aorto-ostial group vs. 109 patients out of 125 patients (87.2%) in the BMS treated patients, representing 41 patients (87.2%) in the aorto-ostial lesion group and 68 patients (80.1%) in the non aorto-ostial lesion group (Table 3).

During the follow-up period one patient in the DES treated group (0.8%) died suddenly within two month from the date of the procedure, the patient was in the non aorto-ostial lesion group with ostial Taxus stent in an OM branch. During the same follow-up period 7 patients (6.4%) in the BMS treated group died with a p value of 0.004 (Table 3). Three of the 7 patients were in the aorto-ostial lesion group (7.3%) with a p value of 0.003.

During the follow-up period 4 patients in the DES treated patients (2.3%) had MI, two patients in the non-aorto ostial lesion group (1.7%) and 2 patients in the

Table 2. Total procedural success and in-hospital complications.

	Total DES	Total BMS	p Value
Procedural Success	149 (92.5%)	117 (93.6%)	0.619
Death	0 (0)	4 (3.6%)	0.017
MI	3 (1.7)	3 (2.7%)	0.665
CABG	0 (0)	1 (0.9%)	0.233

Table 3. Long term clinical outcomes.

	Total DES 155 Patients (96.2%)	Total BMS 109 Patients (87.2%)	p Value
Death	1 (0.8)	7 (6.4%)	0.004
MI	4 (2.3)	2 (1.8%)	0.776
CABG	3 (1.7)	11 (10%)	0.012
Re-PTCA	15 (8.8)	13 (12%)	0.302

aorto-ostial group. In the BMS treated group only 2 patients (1.8%) had MI during the follow-up period being the 2 patients in the non aorto-ostial lesion group (4.7%) (Table 3).

Emergency coronary artery bypass graft was performed in 3 patients (1.7%) in the DES treated group vs. 11 patients (10%) in BMS treated group with a p value of 0.012 which was statistically significant (Table 3).

Long-term angiographic outcomes: During the follow-up period 69 patients (44%) in the DES treated group (21 patients in the aorto-ostial lesion group and 48 patients in the non aorto-ostial lesion group) had a follow-up coronary angiography because of either recurrent chest pain or objective evidence of ischemia by stress testing. Binary restenosis defined as $>50\%$ stenosis by quantitative coronary angiography (QCA) within the stented segment was documented in 20 patients (28.9%) out of the 69 patients by coronary angiography.

Four patients in the aorto-ostial lesion group representing 10% of the original 41 patients had binary restenosis, 3 patients had complete in-stent restenosis (ISR) involving ostial right coronary artery (RCA) and one patient had severe ISR involving protected left main coronary artery (LMCA) including three Taxus stents and one Cypher stent. All the 4 patients had successful redo-coronary angioplasty with good results.

Twelve patients in the non aorto-ostial lesion group representing 10.4% of the original 120 patients had documented ISR during coronary angiography involving 6 patients with ostial stenting of LCX, one patient with ostial LAD stent and another one patient with ostial PDA, and two patients in each ostial diagonal and ostial obtuse marginal lesions including 5 Taxus and 7 Cypher stents. Seven patients with ISR were treated with redo-percutaneous coronary angioplasty (PTCA), 1 patient had emergency coronary artery bypass graft (CABG), and medical treatment was recommended for 3 patients.

Figures 1-5 represent example of different patients included in the research work with different sites of ostial lesions in the Coronary tree.

The comparison of quantitative coronary angiography between DES and BMS treated patients is presented in (Table 4).

Predictors of long term clinical outcomes in DES treated patients: Combined univariate correlation between the incidences of clinical events and procedural variables in patients treated with DES is shown in Table 5. The predictors of long term clinical events include age (odds ratio {OR} 1.033, 95% confidence interval {CI} 1.005 to 1.062, p value 0.021), previous myocardial infarction (OR 2.56, 95% CI 1.387 to 4.74, p value 0.003), Previous CABG (OR 4.16, 95% CI 1.90 to 9.06, p value 0.001), Taxus stent (OR 0.46, 95% CI 0.25 to 0.85, p value 0.013), and baseline reference vessel diameter (OR

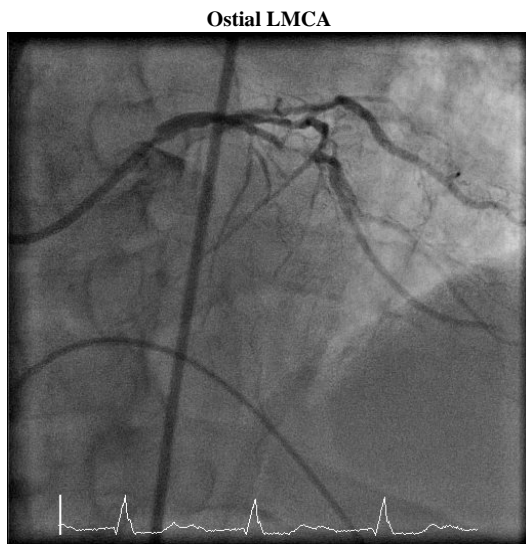


Figure 1. Base line severe ostial LMCA.

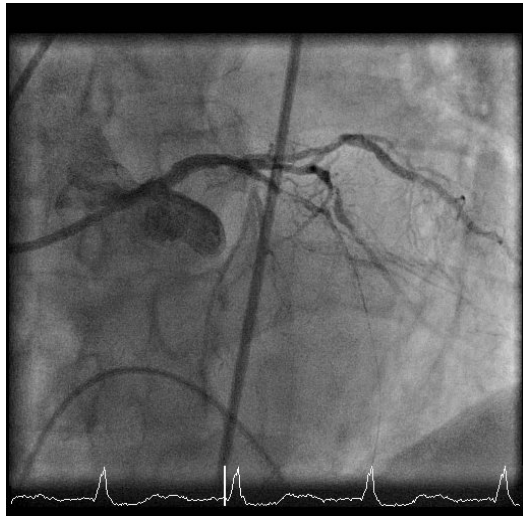


Figure 2. Taxus stent (3.5 × 8) insertion in ostial LMCA.

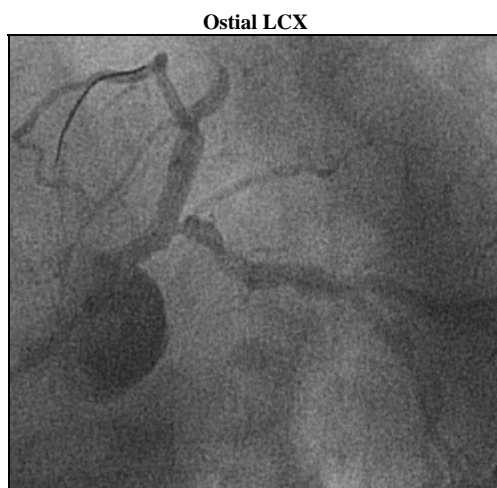


Figure 3. Base line severe ostial LCX lesion.

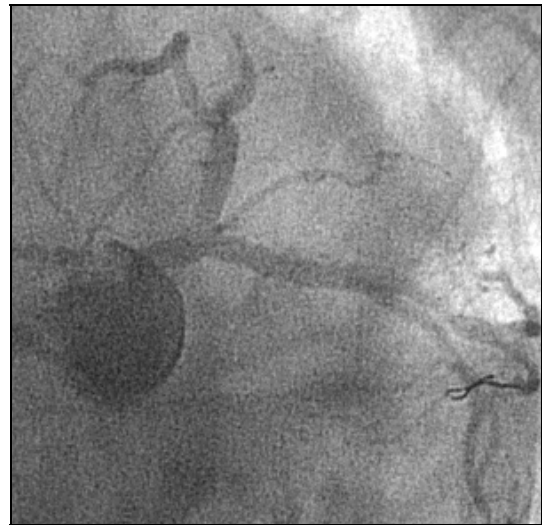


Figure 4. Cypher stent (3.0 × 33) insertion in ostial LCX.



Figure 5. Follow-up angiogram done after 5.5 months showing ostial LCX in-stent restenosis.

0.40, 95% CI 0.17 to 0.91, p value 0.03).

Predictors of long term angiographic outcomes in DES treated patients: In both groups there was no statistically significant correlation between any of the univariate predictors and the incidence of in-stent restenosis during long term follow-up period. However, in the non aorto-ostial group impaired left ventricular function in terms of ejection fraction (LV EF < 50%) was the only positive predictor of in-stent restenosis during the follow-up period (OR 4.71, 95% CI 1.169 to 19.020, p value 0.045).

5. DISCUSSION

The main finding of our study is that implantation of DES for treatment of atherosclerotic coronary ostial lesions appears safe and effective with very high proce-

Table 4. Quantitative angiographic parameters at baseline, end of procedure and follow-up.

(A)	AO (DES)	AO (BMS)	p
pre RVD*	2.6 (±0.5)	3.4 (±1.1)	0.003
pre MLD**	0.9 (±0.3)	1.24 (±0.58)	0.036
pre % Stenosis***	84 (±10.1%)	62 (±15%)	<0.001
post MLD	2.8 (±0.6)	2.9 (±0.54)	0.538
Residual % Stenosis	23.2 (±9.3%)	12.2 (±12.1%)	0.002
Follow-up MLD	2.1 (±0.8)	1.7 (±1.3)	0.217
Follow-up % Stenosis	42.2 (±24.5%)	42.1 (±35%)	0.991

(B)	Non-AO (DES)	Non-AO (BMS)	p
pre RVD	2.7 (±0.6)	2.7 (±0.7)	1
pre MLD	1 (±0.3)	0.78 (±0.62)	0.037
pre % Stenosis	84.5 (±8.1%)	72 (±19%)	<0.001
post MLD	2.5 (±0.5)	2.6 (±0.8)	0.512
Residual % Stenosis	22.6 (±9.6%)	18.8 (±15.2%)	0.203
Follow-up MLD	1.9 (±0.6)	1.9 (±1.2)	0.816
Follow-up % Stenosis	40 (±21.2%)	35.2 (±33.1%)	0.462

RVD*: Reference vessel diameter; MLD**: Minimal luminal diameter; % Stenosis***: Percent stenosis.

Table 5. Combined predictors of long-term clinical outcomes (DES).

Variable	Odds Ratio	95% CI	p value
Age	1.033	1.005 1.062	0.021
Male	1.700	0.836 3.458	0.143
Hypertension	1.561	0.764 3.188	0.222
Diabetes Mellitus	1.253	0.652 2.408	0.498
Smoker	0.540	0.226 1.289	0.165
Hypercholesterolemia	0.903	0.425 1.918	0.791
PVD*	1.813	0.918 3.583	0.087
Family History	1.256	0.690 2.285	0.456
Impaired LV EF	1.883	0.880 4.029	0.103
NYHA III	1.070	0.713 1.606	0.744
CCS IV	1.364	0.959 1.941	0.085
Previous MI [#]	2.566	1.387 4.746	0.003
High S. Creatinine	0.833	0.363 1.913	0.667
ICT	1.010	0.469 2.173	0.98
Taxus Stent	0.462	0.250 0.852	0.013
Stent size	0.813	0.372 1.775	0.603
Stent length	1.030	0.988 1.073	0.162
Base line RVD	0.400	0.174 0.915	0.03

PVD*: Peripheral vascular disease; Previous MI[#]: Myocardial infarction.

dural success rate 98.8%, no increase in major in-hospital complications 1.7% and a significant benefit in respect to the incidence of restenosis and late event rates during long term follow-up period being 8.8% and 4.6% respectively. The findings of the current study are similar to the results of the major drug-eluting stent randomized trials, which invariably showed dramatic decrease in restenosis rates major cardiac events with the use of DES [25-27]. This study has been designed so that the results of DES implantation were compared with those of BMS implantation in coronary ostial lesions that was conducted during a different period. The rate of procedural success in the BMS treated patients was 93.6%, the incidences of major in-hospital cardiac events, and long term clinical and angiographic outcomes including angiographically documented in-stent restenosis were higher than that of DES group. These results have been supported by previous studies [28,29].

A study done by Park *et al* (28) on the results of DES implantation for aorto-ostial lesions in terms of angiographic restenosis and adverse cardiac events concluded that utilization of DES to treat aorto-ostial lesions appears safe and feasible, with a very high procedural success rate 99.5%; a marked benefit with respect to rates of restenosis (60% relative risk reduction) and MACEs (51% relative risk reduction) emerged in patients with DESs compared with those with BMSs, thus confirming the results of our study and a previous observation done on the clinical and angiographic outcomes of Sirolimus eluting stents in ostial lesions [29].

The effect of base-line reference vessel diameter on long-term clinical events after DES implantation has been documented in our study as an independent predictor of long term clinical events in all ostial lesions (OR 0.400, CI 95% 0.174 to 0.915, p value 0.03), with a greater reference to the non aorto-ostial lesion group (OR 0.245, CI 95% 0.077 to 0.776, p value 0.017). In addition to reference vessel diameter, recurrent anginal symptoms and positive objective evidence of ischemia during follow-up period were considered independent parameters on in-stent restenosis in the DES treated group.

Although, the performance of the 2 drug eluting stents (Cypher and Taxus) was similar in our study, the clinical follow-up data suggested a benefit of Paclitaxel eluting stents (Taxus stents) implantation as a negative predictor of long term clinical outcomes in DES treated ostial lesions (OR 0.462, CI 95% 0.250 to 0.852, p value 0.013) which was more observed in the aorto-ostial group (OR 0.194, CI 95% 0.048 to 0.782, p value 0.021). Although, these findings are in concordance with some previous studies, other studies suggested that the luminal preservation achieved by the Cypher stent and measured by coronary angiography may be slightly superior to that of the Taxus stent [30-33].

In the initial randomized clinical trials, the incidence of DES thrombosis was less than 1% (0.4% at 1 year in the Sirolimus-Eluting Stent [SIRIUS] study [34,35] and 0.6% at 9 months in the TAXUS IV study [36]). None of the randomized data found any statistically significant difference between the incidence of thrombosis associated with DESs or BMSs. In our study, the incidence of late DES thrombosis versus BMS was high being (2.7% versus 4.6%) respectively, although the difference was statistically non significant, it is concordant with two meta-analyses that suggested that drug-eluting stents do not increase the overall incidence of stent thrombosis.

In our study, the DES group had significantly smaller base-line MLD compared to the BMS group especially in the aorto-ostial and non aorto-ostial groups (p value 0.036 and 0.037 respectively); thus it consisted of lesions more prone to restenosis. Furthermore, the base-line diameter % stenosis in the two DES groups was significantly higher than that of the BMS ostial groups, lesion rigidity might be a possible explanation for this finding. Histological data from pathologic series [37] and atherectomy specimens [38] showed that ostial lesions are frequently heavily calcified, fibrotic, and sclerotic.

Although, DES implantation has been successful in reducing TLR in ostial lesions with no increase in major in-hospital complications [39], Cosgrave *et al.* [40] reported that DES implantation in complex lesions including ostial lesions has not completely abolished the restenotic response, even though most demonstrated restenosis show more benign pattern and were more amenable to percutaneous treatment.

Based on the limited early studies evaluating restenotic lesions in Sirolimus-eluting stent (SES) and Paclitaxel-eluting stent (PES), there was a general concept that when restenosis occurs it is likely to be focal. These initial data were mainly derived from the early experiences with DES [41,42] or from selected cohorts [43]. This observation combined with the knowledge that focal restenosis in bare metal stents (BMS) carries a more benign prognosis than non-focal restenosis [44], have led to further evaluation of the pattern of restenosis in the DES era. In our study, the total incidence of focal in-stent restenosis was higher than that of non-focal type of restenosis in the DES treated patients how have documented in-stent restenosis during follow up angiograms, being 15 patients versus 5 patients respectively. Moreover, the incidence of focal pattern of restenosis in the Sirolimus eluting stent (Cypher) was lower than that of the Paclitaxel eluting stent (Taxus), but the result was not statistically significant. Our observation about the pattern of restenosis after DES agrees with the finding of previous study done by Colombo *et al.* [45], which reported that focal restenosis is the most common pattern of restenosis in DES.

In conclusion, although effective treatment of ostial coronary lesions remains technically challenging, drug eluting stent implantation in coronary ostial lesions is considered safe and feasible. It is associated with high procedural success rate, low immediate and in-hospital complication rate, infrequent late adverse events and favourable long-term clinical and angiographic outcomes compared with bare metal stents implantation. Advanced age, previous myocardial infarction and acute coronary syndromes at presentation were all found to be independent positive predictors for clinical events after drug eluting stent implantation in ostial lesions.

6. STUDY LIMITATION

1) The fact was that it was prospective and retrospective, single centre study and lacked the clear advantages of the randomized trial. 2) The study population was a heterogeneous group in terms of clinical characteristics and the nature of the treated lesions and the choice of equipment used varied at the discretion of the operator. 3) Relatively small study population in each study subgroup. 4) Two types of drug eluting stents were used in the study, where sirolimus eluting stents (Cypher) were more commonly used. 5) No debulking devices, such as directional coronary atherectomy (DCA) or rotational coronary atherectomy (RCA) were used in this study; Such devices could reduce the plaque burden before stent implantation, increase the luminal diameter, reduce the angiographic restenosis rate and improve the clinical outcomes especially in aorto-ostial lesions. 6) Intravascular ultrasound (IVUS) was not routinely used in this study; The use of IVUS may affect therapeutic strategy; provide an optimal selection of stent size and other procedures.

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