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ORIGINAL ARTICLE

Everolimus-Eluting Stent Versus Paclitaxel-Eluting Stent in Small Coronary Artery Intervention.

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ABSTRACT

Background: The relative efficacy and safety of Everolimus-eluting stents versus paclitaxel-eluting stents in the small coronary vessels (<2.75mm) remains less well defined so the objective was to assess the twelve months outcome of the Everolimus –eluting stents (EES) versus the Paclitaxel-Eluting Stent (PES) in the small coronary vessels (<2.75mm) coronary intervention.

Methods:.91patients referred for coronary intervention with reference vessel diameter (R.V. D.) <2.75mm were randomly assigned to either EES or PES. The primary endpoint was target vessel revascularization (TVR) at twelve months follow up. Out of the 91 patients enrolled, 53.8% were assigned to receive EES; 46.2% were assigned to receive PES.

Results: a significantly lower TVR among the EES group (2% versus 14.2%), p=0.03. Likewise, instant restenosis (ISR) rate was significantly lower among the EES group (6.1% versus 21.4%), p=0. 031.On the other hand; there were no significant differences in the rates of deaths; target vessel- related myocardial infarction or stent thrombosis between the two groups.

Conclusions: Both stents were similarly safe while EES is more effective.

Keywords: eluting stent, small, coronary, intervention.

INTRODUCTION

Coronary intervention outcome in small coronary vessels generally is worse compared to large vessels mainly because coronary stenting in the small vessels is associated with high late loss [1,2].

Compared to large vessels, small vessels have a smaller luminal area that is less able to accommodate more neointimal proliferation before in-stent restenosis (ISR) occurs and the ischemic threshold is achieved [3]. This can explain the link between the vessel size and ISR e.g., increased rates of ISR in small vessels. We hypothesized that EES could be superior to PES in small coronary intervention. Accordingly, this study aimed to investigate the twelve months outcome of the EES versus the PES in the small coronary intervention

METHODS

This study was carried out in the Departments of Cardiology, Faculty of Medicine, Zagazig and Banha Universities as well as Military Medical Academy, Cairo. The study was conducted from February 2017 to May 2019.

Ninety-one consecutive patients aged 18 years and older, amenable to PCI with a small coronary artery (e.g., RVD < 2.75 mm) were enrolled. Acute coronary syndrome, known intolerance to P_2Y_{12} receptor blockers that would preclude adherence to dual antiplatelet therapy or intolerance to aspirin, heparin or to antiproliferative agents (Everolimus or paclitaxel), known pregnancy or a life expectancy of less than one year were exclusion criteria. They were randomly assigned by a computer program. Patients were assigned to one of the two arms of the study either to receive Xience V®-EES (EES group; n = 49) or Taxus® Liberate-PES (PES group; n =42).

The study followed CONSROT 2010 declaration [4]. and the Helsinki Declaration and was approved by the Twente University Independent Committee in medical ethics and the Institutional Review Board of the faculty of medicine, Zagazig university. Every patient gave informed consent in writing.

Study devices:

The Xience V®-EES arm in this study used a XIence V®-ESS (Abbott Vascular, Santa Clara,

CA, USA). A detailed description of the device is provided elsewhere (http://www.abbottvascular.com/docs/coronary intervention/xience/epg. XIENCE.pdf) while the Taxus(R) Liberate-PES arm used a Taxus® Liberate-PES (Boston Scientific Corporation, USA). Also, a detailed description of the device is provided elsewhere online (www.bostonscientific.com, www.stent.com).

Invasive coronary angiography (ICA-QCA) was measured as a reference standard [5] after intracoronary NTG injection [6]. Coronary approaches have been carried out in compliance with standardized methods and protocols [7]. The lesion preparation is done once it is suggested during the procedure.

Further medical treatment was given in compliance with the recommendations and the decision of the physician [8]. Dual antiplatelet use for 12 months was obligatory.

The Academic Research Consortium has identified clinical endpoints, including an addendum on myocardial infarction [8,9,10].

Death was assumed to be cardiac if an unambiguous non-cardiac etiology was not found. Myocardial infarction was characterized by a concentration of the creatinine kinase more than double the maximum level with elevated cardiac confirmatory biomarkers [10].

A target vessel-related myocardial infarction was related to arterial territory of a previously managed target vessel; more classifications may depend on clinical, ECG, angiographic data [8,10].

Revascularization interventions were viewed as appropriately necessary i.e., appropriate evidence was identified that the stenotic lesion at angiography of the then-treated lesion is 50 per cent or greater in the presence of ischemic manifestations or if 70 per cent or more in diameters regardless of ischemic manifestations [10].

The Academic Research Consortium (ARC)) has suggested stent thrombosis [11]. A final residual in-segment percent diameter stenosis of less than 30% with TIMI flow grade 3 using the assigned device only was defined as procedural success.

In-stent restenosis (ISR) was defined as an in-stent luminal diameter narrowing of at least 50%.

12-month clinical follow-up data were obtained through the outpatient department (OPD) visits or if not feasible, by telephone follow up using medical questionnaire form.

Endpoints:

The primary endpoint was target vessel revascularization (TVR) at twelve months follow up.

Statistical analysis:

The continuous variables were represented in mean ± SD and the discrete variables in percentages.

The variations in the continuous variables were t-tested to establish their statistical value and the variations in the discrete variables were verified by X^2.

All statistical analyses were provided with p-value indicating 0,05 suggested that the difference was significant, $p < 0,001$ implied a highly significant difference, while $p > 0,05$ suggested that the difference was not significant.

The statistical research was conducted with SPSS 20 (SPSS Inc., Chicago, Illinois, USA) for windows.

RESULTS

The baseline, demographic and clinical characteristics of our study population are shown in (Table 1 and Figure 1). No statistically significant differences in the age, gender, BMI, frequency of diabetes mellitus, smokers, prior MI, or dyslipidemia. On the other hand, hypertension was more frequent among patients of the PES group ($p = 0.03$).

Angiographic and procedural variables are shown in table 2. No significant differences in the stented segment length, reference vessel diameter, minimal lumen diameter before the procedure, or immediately after, % diameter stenosis before the procedure, immediately after, SYNTAX score, frequency of class B_2/C (complex lesion), procedural failure, number of > one vessel disease, post dilatation or at the maximum balloon pressure achieved. On the other hand, there was a significantly higher frequency of right coronary artery (RCA) as a target vessel, minimal lumen diameter (MLD) at follows up among EES group ($p = 0.03, 0.007$), respectively, while % DS at follow up and ISR rates were significantly higher among the PES group ($p = 0.001, 0.031$, respectively.

Table 3 and Figure 2 indicate clinical outcome parameters at one year of follow-up. There were no significant differences in the mortality risk of cardiac, non-cardiac or dual antiplatelet, stent thrombosis or target vessel related MI cases. On the other side, the TVR in the PES arm was significantly higher ($p=0.03$)

Table (1): Baseline characteristics of studied groups

	EES group (N =49)	PES group (N = 42)	p value
Age	61 ± 8	61.5 ± 7.3	0.3
Male gender	39 (79.6%)	33 (78.6%)	0.9
BMI	28.1 ± 2.3	29 ± 2.9	0.1
Hypertension	23 (46.9%)	29 (69%)	0.03*
Dyslipidemia	27 (55.1%)	23 (54.8%)	0.97
Diabetes mellitus	10 (20.4%)	8 (19%)	0.87
Smokers	7 (14.3%)	6 (14.3%)	1
Prior MI	12 (24.5%)	10 (23.8%)	0.93
EF%	54 ± 5.0	55 ± 4.3%	0.31

Values are mean ± SD or n (%).
*p < 0.05 = Significant
BMI,body mass index; MI, myocardial infarction ;EF,ejection fraction

Table (2): Angiographic and procedural variables

	EES group (n =49)	PES group (n = 42)	p value
Target vessel			
LAD	23 (46.9%)	22 (52.3%)	0.6
CX	17 (34.7%)	13 (31%)	0.7
RCA	15 (30.6%)	5 (11.9%)	0.03*
Number of diseases (one vessel)			
> 1 vessel	16 (32.7%)	13 (30.9%)	0.86
Stented segment length (mm)	17.9 ± 3.1	18 ± 2.9	0.87
QCA analysis			
1- RVD (mm)	2.41 ± 0.46	2.43 ± 0.43	0.83
2- MLD (mm)			
a- Before procedure	1 ± 0.55	1.2 ± 0.45	0.06
b- Immediately after	2.44 ± 0.49	2.41 ± 0.38	0.74
c- Follow up	2.1 ± 0.6	1.8 ± 0.4	0.007**
3- % DS			
a- Before	58.5 ± 10	50.6 ± 15	0.0038**
b- Immediately after	1.24 ± 0.4	1.1 ± 0.3	0.06
c- Follow up	12.86 ± 3.1	26.9 ± 9.2	< 0.001**
ISR	3 (6.1%)	9 (21.4%)	0.031*
Maximum balloon pressure	14 ± 0.6	14 ± 0.7	>0.05
Post-stenting dilation	36 (73.5%)	31 (73.8%)	097
SYNTAX score	25 ± 2.0	25 ± 2.0	1
Complex lesion	10 (20.4%)	9 (21.4%)	0.9
Procedure failure	0 (0%)	0 (0%)	1

Values are mean ± SD or n (%).
*p < 0.05 = Significant; **p < 0.001 = Highly significant
CX,circumflex coronary ; LAD, left anterior descending; RCA,right coronary artery ; QCA, quantitative coronary angiography ;RVS,reference vessel diameter ; MLD,minimal lumen diameter; % DS ,%diameter stenosis ;ISR,instent restenosis ;SYNTAX, Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery.

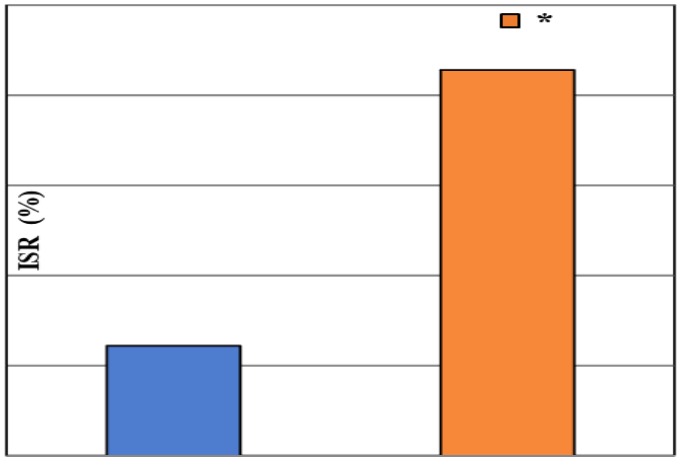
Table (3): Clinical outcome of one-year follow up

	EES group (n =49)	PES group (n = 42)	p value
Death			
Non-cardiac	1 (2%)	1 (2.4%)	0.91
Cardiac	1 (2%)	1 (2.4%)	0.91
Target vessel related MI	1 (2%)	1 (2.4%)	0.91
TVR*	1 (2%)	6 (14.2%)	0.03*
Stent thrombosis	1 (2%)	1 (2.4%)	0.91
Patient maintained on dual antiplatelet	49 (100%)	42 (100%)	1
Procedural success rate	49 (100%)	42 (100%)	1

Values are mean ± SD or n (%).
p < 0.05 = Significant
*TVR, all cases did repeat angioplasty.
TVR,target vessel revascularization ;MI,myocardial infarction .

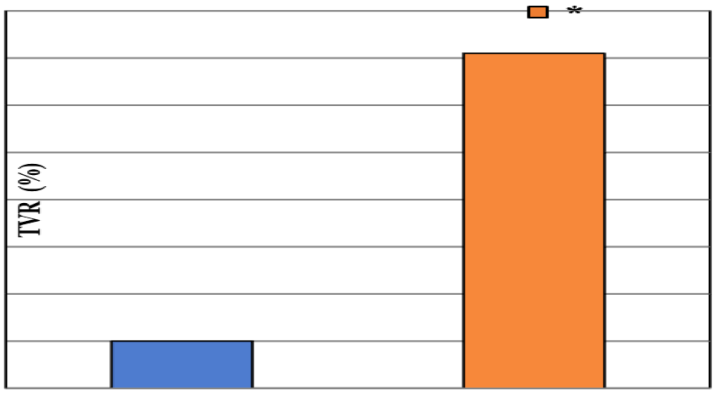
*P<0.05: means significant

Figure 1: instent restenosis % among the study groups



*P<0.05: means significant

Figure (2): target vessel revascularization at one-year follow up



DISCUSSION

We investigated the clinical outcome of two types of second-generation DES with 2 different antiproliferative drugs (Everolimus versus paclitaxel) affecting the late loss through inhibiting the intimal hyperplasia.

Results of our study demonstrated lower rates of ISR and TVR among the EES group, while the other event rates (including death, target vessel-related MI, and stent thrombosis) were similar among the two groups in patients with the small coronary vessel intervention.

The favorable outcome of the EES compared to the PES in small coronary artery intervention can be explained on basis of the manufacturer description of the device in both cases. Furthermore, **Stone et**

al. [12]. had explained the reason for the differences, They observed that the Xience-EES had a thinner polymer (7.6 µm versus 16 µm, lower overall polymer with stent strut thickness 81 µm versus 148 µm) and no webbing effect compared with the Taxus Liberte-PES. All these causes may have led to a varying degree of neo-intimal inhibition. [12].
Furthermore, according to the manufacturers Abbott Vascular, versus Boston Scientific Corporation: The Xience V-EES stent material is formed of a medical grade L-605 cobalt-chromium alloy Multi-Link Vision stent (BMS), while Taxus-PES Liberte stent material is formed of A 316 L surgical grade stainless steel Veri-FLEX stent (BMS) that is why Xience V-EES is a low profile, easy deliverable even through small diameter coronary vessels.
Previous randomized clinical trials have demonstrated the value of the EES in small coronary vessel intervention [13-15].
A pooled study of the SPIRIT II and SPIRIT III trials was performed by Antonio et al. [13]. The SPIRIT II was a multi-center prospective clinical trial , randomizing patients to obtain either the Xience V-EES, or Taxus Express 2 or Taxus Liberte PES, while the SPIRIT III was also a prospective, multi-center clinical experiment, except that patients were randomized to obtain either the Xience V-EES or the Taxus Express2 PES.
SPIRIT III proved that in the case of an intervention involving small caliber coronary artery, Xience-EES was superior to Taxus-PES [13]. The patients were selected randomly to obtain EES or PES at one year follow-up during the large volume SPIRIT IV trial[14] , the primary outcome was TLF, the rate in the EES were statistically significant lower than PES ($p < 0.001$), and MACE [Target Lesion Revascularization (TLR) , stent thrombosis and MI]. were also statistically significant lower than PES. The SPIRIT results were subsequently augmented with the (COMPARE) study [15]. for all-comers Everolimus-eluting stents and paclitaxel-eluting stents where the patients were randomly allocated to either Xience V-EES or Taxus Liberté PES. The primary outcome was 1 year MACE (death, MI, or TVR). For the EES arm, the findings were significantly lower compared with the PES at one year follow-up.
The Nasu and colleagues [16] reported two prospective multi-centric registries both conducted on a small coronary artery disease intervention (PLUM and SACRA) of Promus / Xience-EES for the first study , and TAXUS Liberté for the second, the results indicate that the rate of target lesion revascularization in the EES arm was significantly lower, while MACE was similar in the two groups . This is in accordance with our observations.
Meng and colleagues [17] conducted a meta-analysis study, they compared EES versus PES long term outcome. They concluded that, EES is safer than PES on the long term basis. MACE , all cause death , MI, TLR and stent thrombosis were significantly decreased at the EES arm but with similar TVR rate among the two groups at three years follow up. Although these findings are contradictory to our results , however this study differs from our one in that being not limited to a small coronary vessel (a vessel diameter <2.75mm at our study) , higher frequency of diabetics as well as longer follow up .
Gregg W Stone and colleagues conducted another meta-analysis [18] , analyzing EES versus PES with a primary follow-up of TLF over one year. They observed that EES in TLF and ID-TLR and stent thrombosis are superior to PES albeit with comparable cardiac deaths and MI-related vessels. In all research subgroups other than diabetic ones, rates of TLF was significantly decreased with EES relative to PES.
In a year's follow-up, Hirmiller et al[19] issued a pooled analysis of SPIRIT III and SPIRIT IV that matched the proportion of diabetics and RVD within the two stent groups (EES versus PES). They observed that MACE, TLF; stent thrombosis and TVR were decreased in the EES in comparison to PES in the small vessels subgroup. the absolute benefits in the small coronary intervention subgroup were particularly greater. Interestingly, the lower TVR in the EES arm agreed with our study, which supports the greater efficacy of the EES than the PES.
Kedhi E et al [20] stated that the very low risk of stent thrombosis observed in the EES arm, both in a one and 12 month follow-up, was very striking on the basis of findings of the COMPARE study contrasting EES and TAXUS Liberté PES. This was distinct from the present research, in which comparable frequencies of stent thrombosis were observed in both groups. This may be attributed to the comparatively limited number of our study.
Several mechanisms may explain the finding including the thinner struts of the stent together with a biocompatible fluro- polymer leading to a faster strut coverage by the endothelium [20,21]
Such fluro-polymer is proven to resist platelets aggregation as well as thrombus formation. [21].
Some limitations in our study; Firstly, the present study had a relatively short follow up period. extended follow up for 3 years or more is needed to assess all possible MACE. Secondly, the mandatory clinical follow up at outpatient clinics is preferred than the telephone interview, was not

done for all cases, instead done through over telephone interview. However, the good follow up rate in this study may compensate for such a defect. Thirdly, in the small coronary intervention, ISR may be asymptomatic thus may be missed unless follow up angiography was done on routine basis. Finally, only two versions of second generations DES being tested in the small coronary intervention. Testing for the remaining versions of DES is needed to define which is being the best in such particular subgroup.

CONCLUSIONS

Both stents were similarly safe while EES is more effective.

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