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OPTIMA Tacrolimus-eluting Stent: A Twelve-month Clinical Follow up with Two Different Periods of Dual Antiplatelet Therapy; 2-month vs. 6-month Approach

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ABSTRACT

Introduction: There are limited data comparing long-term efficacy and safety of OPTIMA tacrolimus-eluting stent (TES) with Dual Antiplatelet Therapy (DAT) in daily practice. Therefore, we evaluated the safety and performance of OPTIMA TES with 2 or 6-month dual antiplatelet therapy in a 12-month follow up period. **Methods**: In a prospective, non-randomized single center registry in which 106 patients that underwent percutaneous coronary intervention with the OPTIMA TES between January 2010 and February 2011 were enrolled. After stenting, 62 patients received DAT for 2 months and the remainder for 6 months. Major Adverse Cardiac Events (MACE), stent thrombosis rate and target lesion revascularization (TLR) were evaluated in a 12-month follow-up period for 2-and 6-month DAT groups. **Results**: No cases with death, MI or stent thrombosis were observed within the 12-month follow-up period in either of the groups. TLR and MACE rates were higher in 6-month DAT group compared to 2-month group (6.8% vs. 3.2% respectively, P=0.001) which may be due to this group having more diffuse disease (23.60±5.69 vs. 20.88±5.14, P=0.018).**Conclusions**: OPTIMA tacrolimus-eluting stent is safe and efficient with short term DAT period. A randomized trial is needed for better evaluations of OPTIMA TES in daily clinical practice.

Introduction

Drug-eluting stents (DESs) have reduced restenosis and target lesion revascularization (TLR) compared to bare-metal stents (BMS). However, long term safety of first and second generation DESs is still controversial due to concerns about late and very late stent thrombosis.[1] Durable polymers have been associated with local inflammatory and hypersensitivity reaction and subsequent delayed vascular healing and impaired reendothelialization leading to stent thrombosis.[2] To eliminate short or long-term effects of polymers on arterial healing, polymer-free DESs have been developed.

On the other hand, first and second generation DESs require a prolonged dual antiplatelet therapy period up to 1 year to reduce late stent thrombosis risk.[3] In this respect, DES use may have limitations in some patients including patients with Contraindications to long-term DAT, patients who are taking oral anticoagulants because of increased bleeding risk, patients requiring major surgery within 1 year after DES implantation, and patients with no adherence to DAT due to socioeconomic issues.

The OPTIMA tacrolimus-eluting stent (TES; SORIN, Italy) is a recently-introduced polymer-free DES. OPTIMA, possessing a proprietary drug-release system while having reservoirs on the stent outer surface, ensures a highly targeted release only focusing on the vessel wall; it also has an integral carbofilm coating providing early endothelialization.[4]

Tacrolimus, an antiproliferative agent used in the OPTIMA stent is a macrolide immunosuppressive agent that binds to cytosolic FK-506 binding protein-12; it is through this complex that it demonstrates its inhibitory effect on the T-lymphocyte signal transduction and IL-2 transcription.[5] This agent's antiproliferative effects is less than sirolimus, but in combination with its anti-inflammatory effects it represents a favorable compound reducing stent restenosis and stent thrombosis.[5]

Little is known about the OPTIMA stent use with short DAT in daily clinical practice. Therefore, we conducted a prospective single-center registry investigating safety and efficacy of OPTIMA TES, in a 12-month follow-up period, in real-world patients undergoing Percutaneous Coronary Intervention (PCI), followed by a DAT period of 2-6 months at our hospital.

Materials and methods

Patient population

Between January 2010 and February 2011, 106 patients with documented ischemia, or acute coronary syndrome (ACS) including acute myocardial infarction (AMI) were enrolled in this prospective, non-randomized single center study.

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Inclusion criteria were as follow: Patients ≥18 years, at least one angiographic coronary stenosis more than 70% with a target vessel diameter ≥ 2.5mm, < 4mm, and lesion length less than 31mm, with up to 5 lesions suitable for PCI. Exclusion criteria were as follow: intolerance or allergy to aspirin or clopidogrel, pregnant women, bleeding diathesis or contraindication to antiplatelet or anticoagulation therapy.

Written informed consent was obtained from all patients, and the study protocol was approved by the local ethical committee.

Percutaneous coronary Intervention (PCI) procedure

All patients were given a loading dose of 300mg clopidogrel and aspirin 100mg before procedure. During the procedure, all patients received an IV bolus dose of unfractionated heparin (100 u/kg) and the use of glycoprotein IIb/IIIa inhibitor was left to the discretion of the operator. Coronary angioplasty and stenting were performed based on the standard methods.[6] After stenting, all patients received Aspirin 100mg daily indefinitely.

After PCI, 62 patients received clopidogrel 75mg/d for 2 months and 42 patients for 6 months. Duration of DAT period was based at the discretion of the cardiologist treating the patient.

Follow-up

Clinical follow-up was performed by telephone contact or office visits in the following 1, 6 and 12 months. Coronary angiography was performed when there were recurrent ischemic symptoms or readmission due to unstable Angina.

Study endpoints and definitions

The study endpoint was the 12 month rate of major adverse cardiac events (MACE), defined as the composite of cardiac death, non-fatal myocardial infarction (MI) and TLR. MI was defined either as the development of pathological Q waves in at least 2 contiguous leads with or without elevated cardiac enzymes or troponin I or creatine kinase-MB enzyme elevation >3 times the upper limit of the normal value.[7]

Stent thrombosis (ST) was defined based on the Academic Research consortium (ARC) definitions for definite or probable stent thrombosis and further categorized as acute<1 day; subacute as 1 to 30 days and late>30 days. Restenosis was defined as the diameter stenosis of ≥ 50% of the target lesion.

Statistical analysis

Categorical discrete variables were compared by the chi-squared test or the Fisher exact test. Continuous variable were presented as mean ± standard deviation (SD) and were compared with the use of the Student's t-test. *P* value < 0.05 was considered statistically significant. Data were analyzed using SPSS 13.

Results

Table 1 shows baseline clinical characteristics of the study population. No significant differences were present in the baseline clinical or demographic characteristics between treatment groups with the exception of slightly more Unstable Angina presentation in the 6-month DAT group. (30.6% vs. 45.5%, *P*=0.057). Table 2 shows baseline angiographic characteristics. A trend toward higher multi-vessel disease in 6-month DAT group was seen which was statistically insignificant (*P*=0.006).

Table 1. Baseline clinical characteristics of study groups

	2 Months DAT	6 Months DAT	P value
No. of patients	62	44	
Mean age	58.55±11.42	60.15±10.13	0.45
Male gender	47(75.8%)	38(86.4%)	0.49
Hypertension	31(50%)	22(50%)	1.000
Hyperlipidemia	22(35.5%)	16(36.4%)	1.000
Diabetes	19(30.6%)	8(18.2%)	0.178
Smoking	18(29%)	19(43%)	0.52
Obesity	1(1.6%)	6(13.6%)	1.549
Family history of CAD	6(9.7%)	0	1.000
Clinical status (n=1%)			
Stable Angina	23(37.2)	15(34.1)	0.671
Unstable Angina	19(30.6)	20(45.5)	0.057
Myocardial infarction ≤24h	2(3.2)	1(2.3)	1.000
Myocardial Infarction>24h	18(29)	8(18.2)	0.254
Mea LVEF	47.91±9.08	50.18±6.96	0.068
Pathological Eca	46(79.3%)	26(65%)	0.132
Previous MI	11(17.7%)	7(15.9%)	0.143
Previous PTCA+ Stenting	4(6.4%)	5(11.3%)	0.431
CABG	2(3.2%)	1(2.3%)	0.542

For 2-month and 6-month DAT group, respectively significant differences were reported in terms of lesion length (20.88±5.14mm versus 23.60±5.69mm, *P*=0.018). Other angiographic findings like lesion classification and target vessel location were similar between two groups. Most lesions were located in the left anterior descending artery and were of the B_1 type. All patients underwent successful stent deployment in all cases (Table 3). During 1 year follow-up there was no death, MI or stent thrombosis in either group. TLR was more common in 6- month DAT (6.8% vs. 3.2%, *P*=0.007; Table 4).

Discussion

We demonstrated in this study that, the treatment of coronary artery disease (CAD) using TES OPTIMA stent in real word patients with short DAT is safe and efficacious, with no MI, cardiac death or stent thrombosis report in 1 year follow-up.

Previous studies investigating TES efficacy are controversial. The JUPITER I trial showed good safety of Janus TES with no stent thrombosis despite 2-month DAT after stent deployment.[8] Our study device, OPTIMA stent is a new version of Janus TES. In JUPITER II trial, also, there was no stent thrombosis with 6- month DAT.[9] Our study confirms these trials results with respect to safety of OPTIMA stent with no death or stent thrombosis report despite 2 or 6 months DAT and up to 1 year follow-up. However, Total MACE rate in our study was slightly less than JUPITER II trial (6.8% vs. 7.6%) which may be due to better design of OPTIMA stent compared to JANUS stent and small sample size of our study.

Table 2. Baseline angiographic characteristics

	2 Months DAT	6 Months DAT	P
RVD[1](mm)	2.84±0.25	2.77±0.45	0.324
MID[2](mm)	0.40±0.31	0.38±0.27	0.782
RVD-MID	0.30±0.15	0.29±0.14	0.751
Diameter stenosis(%)	85.03±24.41	73.33±5.77	0.430
Lesion Length(mm)	20.88±5.14	23.60±5.69	0.018
Location of Target Lesion(n%)			
LM	0	0	0.110
LAD	43(50)	24(49)	
LCX	13(15.1)	14(28.6)	
RCA	30(34.9)	11(22.4)	
Graft	0	0	
Moltiple vessels disease	52.5%	80.5%	0.006
Acc/AHA Lesion type (n%)			
A	17(28.3)	17(38.7)	0.171
B_1	22(36.7)	18(40.9)	
B_2	19(31.7)	6(13.6)	
C	2(3.3)	3(6.8)	
Bifarcation lesions(%)	16.1	6.8	0.230
Ostial lesions(%)	12.9	15.9	0.779
CTO lesions(%)	17.7	13.6	0.605
Thrombotic lesions(%)	21	9.1	0.116
heavy calaification(%)	29.5	20.5	0.4
Severe proximal Vessel Tortuosity	11.3	7	0.5
Timi Flow ≤1	16.2	23.3	0.78
Denowo lesions	90.3	83.7	0.37

[1]RVD= Reference vessel diameter, [2]MID= Minimal ivminal diameter

Table 3. Procedural characteristics

	2 Months DAT	6 Months DAT	P value
Direct stenting technique[n(%)]	24(39.3)	14(39.3)	0.309
Stent size≤3mm[n(%)]	57(91.9)	40(95.2)	0.699
Mean stent length (mm)	23.60±5.96	20.88±5.14	0.018
Stent Delivery pressure(atm)	15.11±2.17	15.23±1.6	0.759
Procedural success	100%	100%	
Residual diameter stenosis 20% (by visual estimate) after stenting procedure, Time flow =3, No urgent CABC			

Table 4. Clinical outcome according to Dat time duration (cumulative events at 12 months)

	2-month DAT	6-month DAT	P
No. of patients	62	44	
MACE	3.2%(2)	6.8%(3)	0.001
Cardiac death (n)	0%(0)	0%(0)	NA*
MI(n)	0%(0)	0%(0)	NA
Q-Wave	0%(0)	0%(0)	NA
Non Q-Wave	0%(0)	0%(0)	NA
TLR	3.2%(2)	6.8%(3)	0.001
Stent thrombosis	0%(0)	0%(0)	NA
* indicates not applicable because of zero value			

Importantly, coronary lesion in our study population consists of many complicated lesions such as ostial lesions, thrombotic lesions, CTO, bifurcations, long lesions and small vessel lesions, which reflects the "real world" of daily clinical practice PCI. Another study, the MATRIX multicenter registry of Janus flex TES deployment, evaluated safety of Janus stents with 2-or 6 month DAT at 12-month follow-up whose design is similar to our study.[10] Two-stent thrombosis cases occurred in that study which was not seen in our study suggesting better device design and profile in our study. Unlike MATRIX study, which MACE rate was not different between two study arms, in our study, However, TLR and MACE rate was significantly lower in 2-months group which may be related to more long lesion and small vessel disease seen in 6 months DAT group (Table 2).

On the other hand, the Tacrolimus-Eluting stent (TEST) study showed higher MACE rate (40.9%), mortality, MI, TLR, in 22 months clinical follow-up and high restenosis rate (39.04%).[11]

These results, contradicted to our study results, may be due to more complex lesions (66% of lesion classified as B_2/C complexity), more diffuse disease and longer duration of follow up seen in TEST study.

Study limitations

The study has several limitations. First, it was not randomized. Second, it includes small number of patients. Third, no routine angioplastic follow-up was performed and finally one-year follow-up is not enough for late events evaluation such as very late thrombosis.

Conclusion

In conclusions, our study confirms safety and efficacy of OPTIMA TES deployment even with short term DAT as short as 2 months.

Based on our study results, it seems reasonable to consider OPTIMA TES as an alternative for patients suitable for DES implantation but at high risk for bleeding or with contraindication to long-term DAT. Randomized trials with longer follow-up periods are required to achieve better evaluations of OPTIMA TES in clinical practice.

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Conflict of interests: The authors declare no conflicts of interest.

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