Research Paper

Two-year Outcome of Turkish Patients Treated with Zotarolimus Versus Paclitaxel Eluting Stents in an Unselected Population with Coronary Artery Disease in the Real World: A Prospective Non-randomized Registry in Southern Turkey

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Abstract

Background: Our purpose was to investigate the clinical outcomes of Zotarolimus- and Paclitaxel-eluting stents in Turkish patients with coronary artery disease (CAD). In general, the outcome of drug-eluting stent (DES) placement has a proven efficacy in randomized trials. However, the difference in efficacy between the Zotarolimus and Paclitaxel-eluting stents in unselected Turkish patients is controversial. Therefore, we investigated the clinical outcomes of these two drug-eluting stents in the real-world.

Methods: We created a registry and prospectively analyzed data on a consecutive series of all patients who presented to our institution with symptomatic coronary artery disease between February 2005 and March 2007 and who were treated with the zotarolimus- or the paclitaxel-eluting stent. The follow-up period was approximately two years. The primary end-point was major cardiac events, and the secondary end-point was definite stent thrombosis. Informed consent was obtained from all subjects, and the study protocol was approved by the local ethical committee.

Results: In total, 217 patients were treated with either the zotarolimus-eluting stent (n = 116) or the paclitaxel-eluting stent (n = 101). The lesions in the 2 arms of the study were treated similarly by conventional technique. At 24-month follow-up the paclitaxel-eluting stent group showed significantly higher non-Q wave myocardial infarction (2.6% vs 5.9%, p: 0.02), Q wave myocardial infarction (1.7% vs 5.9%, p: 0.049), coronary artery binding graft surgery (2.6% vs 6.9%, p: 0.002), and late stent thrombosis (1.7% vs 3.9%, p: 0.046).

Conclusions: Zotarolimus-eluting stents demonstrated better clinical outcomes than Paclitaxel-eluting stents in a daily routine practice of coronary intervention in an unselected Turkish population.

Key words: coronary artery disease, drug-eluting stent, major adverse cardiac event, stent thrombosis.

INTRODUCTION

In prospective randomized controlled trials, drug-eluting stents (DESs) have significantly reduced the rates of restenosis and target lesion revascularization (TLR) over those achieved with bare metal stents

(BMSs) in patients with symptomatic coronary artery disease of simple to moderate complexity (1-3). The use of the Zotarolimus-eluting stent (ZES; Medtronic Vascular, Santa Rosa, CA) for treating single *de novo* lesions in patients with symptomatic coronary artery disease has been examined in the first four trials of the ongoing ENDEAVOR clinical trials program. The results of these initial trials indicate that the ZES is safe and reduces the rates of clinical and angiographic restenosis in patients with symptomatic coronary artery disease (CAD; 4). Also the safety and efficacy of Paclitaxel-eluting stent (PES; Taxus, Boston Scientific Corp., Natick, Massachusetts) has been examined in the Taxus I-V studies (5-9). However, the late clinical outcome of ZES and PES in unselected patients treated in daily practice remains controversial. The long-term safety of DESs remains in question (10-11). Despite the results of meta-analyses of randomized studies refuting these concerns (12), late stent thrombosis remains a limitation of DES technology. Therefore, longer-term safety is a pressing concern when comparing ZES with PES, particularly given the differences in drug release kinetics. The longer-term outcomes of Turkish patients treated with ZES versus PES in "real world" practice are not well reported. Furthermore, with the advent of new DES systems, it is important to elucidate any differences in efficacy and safety when utilizing the currently available DESs. Therefore, we report the two-year outcomes of unselected patients with CAD treated with either ZES or PES in southern Turkey.

METHODS

Patient Population

The study population consisted of 217 patients who had undergone coronary Zotarolimus- (*n*:116) (ZES; Medtronic Vascular, Santa Rosa, CA) or Paclitaxel- (*n*:101) eluting stent (PES; Taxus, Boston Scientific Corp., Natick, Massachusetts) implantation for CAD from February 2005 to March 2007. Patients were eligible for enrollment if there was symptomatic CAD or positive functional testing, and angiographic evidence of a target lesion stenosis of ≥ 70 % in a ≥ 2.0 mm vessel. Patients with a contraindication to antithrombotic therapy were excluded from the study. The control coronary angiographies were performed when there was evidence of ischemia. The follow-up period was approximately two years. Informed consent was obtained from all subjects, and the study protocol was approved by the local ethical committee.

Medications and Percutaneous Coronary Intervention (PCI) Procedure

All patients were pretreated with aspirin and clopidogrel. A loading dose of 300 mg clopidogrel was administered before the procedure for patients who were not previously pretreated with asprin and clopidogrel. During the procedure, a bolus dose of unfractionated heparin (100 U/kg) was injected through the femoral or radial artery sheath, with repeated boli administered as needed to maintain activated and clotting time of 250 to 300 s. Patients received intracoronary nitroglycerin (0.1 to 0.2 mg) to achieve maximal vasodilatation before undergoing their initial and final angiograms. The glycoprotein IIb/IIIa inhibitor (Tirofiban) was administered at the operator's discretion. All patients maintained anti-platelet therapy following the procedure (aspirin 300 mg/d for 3 months and 100 mg/d infinitely; clopidogrel 75 mg/d for 6 to 12 months). The PCI procedure and stent implantation were performed through a femoral or radial approach using standard methods. The operators were free to use the stent approach and either the ZES or PES stent that they considered to be best.

Study End Points and Definitions

The primary clinical efficacy end points included major adverse cardiac events (MACE) at two year (MACE: Death, myocardial infarction, target vessel revascularization (TVR). Target vessel revascularization was defined as being either percutaneous or surgical revascularization of the stented epicardial vessel. The secondary end-point was definite stent thrombosis (acute, <1 day; subacute, 1 to 30 days; late, >30 days and very late, >1 year). Myocardial infarction was defined as a creatine kinase (CK) elevation >2 times above the upper limit of normal levels with any associated elevation in the CK myocardial band or the development of new pathologic Q waves in 2 contiguous electrocardiographic leads. Myocardial infarction and stent thrombosis definitions used in this study were consistent with the newest consensus of the Academic Research Consortium (13). All primary and secondary clinical end points were adjudicated by an independent clinical events committee blinded to the patient's treatment assignment.

Follow-up

Clinical follow-up was performed at 1, 6, 12, and 24 months by telephone contact or office visits. Relevant data were collected and entered into a computerized database by specialized personnel at the cardiovascular interventional heart center.

Statistical Analysis

All statistical analyses were performed with SPSS for Windows (version 10.0, Chicago, USA). Continuous variables were described as mean ± standard deviation (SD), and categorical variables were reported as percentages or proportions. Comparison of continuous variables was performed with unpaired *t*-tests (normal distribution) and nonparametric Mann-Whitney *U* test (skew distribution). Categorical variables were analyzed using Fisher's exact test and chi-square test. We used Kaplan-Meier time-to-event estimates for the primary events at the two-year follow-up, and compared the difference between the ZES and the PES treated groups with the Kaplan-Meier method and log-rank test. A *P* value < 0.05 was considered statistically significant.

RESULTS

Baseline clinical, coronary angiographic and lesion characteristics are shown in Table 1 and Table 2. No significant differences were present in the baseline clinical or demographic characteristics between patients receive ZES versus PES. Baseline angiographic characteristics were similar according to the modified ACC/AHA (American College of Cardiology / American Heart Association) classification (14). Overall, most lesions were located in the left anterior descending artery and were of the B1 and C type. The median stent for the ZES treated group was 31±4 mm in diameter and 31±5 mm (p: 0.8) for the PES treated group. Additionally, the median stent length in the ZES treated group was 26±4 mm compared to 28±8 mm (p: 0.2) in the PES treated group.

Table 1. Age and Baseline Clinical Characteristics of Patients by Treatment Cohort

Characteristic	*Zotarolimus*[a] *(n:116)*	*Paclitaxel*[b] *(n:101)*	*P Value*[c]
Age, mean (SD), y[c]	60 (9.2)	58 (10.2)	.2
History, No. (%)			
Diabetes mellitus	54 (46)	36 (36)	.7
Hypertension	76 (65)	64 (63)	.5
History of smoking	69 (59)	55 (54)	.4
Hyperlipidemia	84 (72)	69 (68)	.5
Prior MI	8 (7)	7 (7)	.4
Prior PTCA	8 (7)	6 (6)	.2
Prior CABG	6 (5)	3 (3)	.3
SAP	36 (31)	34 (34)	.6
USAP	52 (44)	47 (47)	.2
MI	28 (25)	20 (20)	.4
Serum concentrations, mean (SD), mg/dL			
Total cholesterol	228.8 (50.49	233.8 (57.4)	.8
LDL	146.3 (48.8)	150.3 (48.4)	.5
HDL	38.2 (6.5)	39.4 (8.3)	.5
Triglyceride	160.1 (101.7)	158.6 (101.2)	.8
Glucose	127.2 (62.7)	114.7 (46.4)	.2

Abbreviations: CABG, coronary artery bypass graft; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; SAP, stable angina pectoris; USAP, unstable angina pectoris.

[a]Indicates patients who received zotarolimus-eluting stents. Numbers in the column do not total 100% because some patients had more than one condition.

[b]Indicates patients who received paclitaxel-eluting stents. Numbers in the column do not total 100% because some patients had more than one condition.

[c]*P* < 0.05 defined as statistically significant.

Table 2. Baseline Angiographic Characteristics

	Zotarolimus[a] *(n:116)*	*Paclitaxel*[b] *(n:101)*	*P Value*[c]
Site of Lesion Treated, No. (%)			
LAD	81 (70)	76 (75)	.369
Cx	18 (15)	9 (9)	.056
RCA	17 (15)	16 (16)	.506
LVEF[d,e]	68.7 (5.7)	67.4 (7.3)	.6
Stent diameter, mm[e]	31 (4)	31 (5)	.8
Stent length, mm[e]	26 (4)	28 (8)	.2
Lesion length, mm[e]	21 (3)	22 (7)	.1
Type of lesion, No. (%)			
A	3 (3)	2 (2)	.9
B1	52 (45)	47 (46)	.9
B2	12 (10)	11 (11)	.8
C	49 (42)	41 (41)	.9

Abbreviations: Cx, left circumflex coronary artery; LAD, left anterior descending coronary artery; LVEF, left ventricular ejection fraction; RCA, right coronary artery.

[a]Indicates patients who received zotarolimus-eluting stents.

[b]Indicates patients who received paclitaxel-eluting stents.

[c]*P* < 0.05 defined as statistically significant.

[d]Reported as percentage.

[e]Data expressed as mean (SD).

In-hospital outcomes

In-hospital outcomes were similar between ZES and PES treated groups. In hospital incidence of MACE was 1.7% in ZES treated group and 1.9% in PES treated group (p:0.6).

Long-term clinical outcomes

Two-year clinical follow-ups were completed for 214 patients. At the end of the two years, the incidence of MACE in the group treated with ZES was 10% and 17.8% (p:0.003) was recorded for the group treated with PES. The incidence of CABG (2.6% vs 6.9%, p:0.002), Q-wave myocardial infarction (1.7% vs 5.9%, p:0.049) and non Q-wave myocardial infarction (2.6% vs 5.9%, p:0.02) was significantly higher in the PES treated group. There were no major differences in the rates of death (p:0.7), target vessel revascularization (p:0.06) and non-target-vessel revascularization

(p:0.3). Additionally, the incidence of late stent thrombosis was significantly higher in the PES treated group (1.7% vs 3.9%, p:0.046) at 24 months. There were no major differences in the incidence of acute (0.9% vs 0.9%, p:1.0), subacute (1.7% vs 3.9%, p:0.06) and very late stent (0.9% vs 0.9%, p:0.7) thrombosis in the ZES and PES groups. (Table 3)

Table 3 Comparison of Secondary End Points by Cohort

Type of Stent thrombosis	No. (%)		P value[c]
	Zotarolimus[a] *(n:116)*	*Paclitaxel[b]* *(n:101)*	
Acute	1 (0.9)	1 (0.9)	1.0
Subacute	2 (1.7)	4 (3.9)	.06
Late	2 (1.7)	4 (3.9)	.046
Very late	1 (0.9)	1 (0.9)	.7

[a]Indicates patients who received zotarolimus-eluting stents. Percentages in this column are based on a cohort of 116 patients.

[b]Indicates patients who received paclitaxel-eluting stents. Percentages in this column are based on a cohort of 101 patients.

[c]$P < 0.05$ defined as statistically significant.

Discussion

We demonstrate in this study that, the treatment of CAD using ZES in an unselected population of Turkish patients over a 24-month period, resulted in a significantly lower incidence of major adverse cardiac events, CABG and definite stent thrombosis then the PES. The safety and efficacy of ZES and PES had previously been examined in ENDEAVOR and TAXUS trials (3-9, 15-17) respectively, however, due to differences in trial design or an emphasis on angiographic rather than clinical end points, clinical trials comparing the safety and efficacy between these DES types and BMSs have yielded inconsistent results. In the ENDEAVOR I, II,II Continued Access Registry (CA) and III trials (15, 3, 16, 17), the rate of MACE ranged from 3.1%,to 12.8%, at the end of the two-year period. In our trial, however, the incidence of MACE in the ZES treated group was 10% at the end of the two year follow-up (Table 4). Additionally, the incidence of Q wave MI ranged from 0% to 0.3% in the first four ENDEAVOR trials compared to 1.7% in our ZES treated group. On the other hand, the incidence of non-Q wave MI ranged from 1%, to 5.6% in first four ENDEAVOR trials whilst registering at 2.6% in the ZES treated group in our trial. The results of the first 4 ENDEAVOR two-year trials suggested that ZES is safe and reduces the rates of clinical and angiographic restenosis in an selected patients with symptomatic coronary artery disease of simple to moderate complexity (4). Since the population used in our study was an unselected, high-risk group, four patients in

the ZES treated group were prematurely taken off their antiplatelet therapy and this likely played a role in the observed MACE events. Also noteworthy was the observation that, the lesion and the stent lengths recorded in our study were significantly longer than previously recorded for the four ENDEAVOR trials.

Table 4. Clinical Outcomes at 24-Month Follow-up

	No. (%)		
	Zotarolimus[a] *(n:116)*	*Paclitaxel[b]* *(n:101)*	*P Value[c]*
Revascularization n(%)			
Target vessel	5 (4.3)	5 (4.9)	0.6
Non target-vessel	4 (3.4)	4 (3.9)	0.3
CABG n(%)	3 (2.6)	7 (6.9)	**0.002**
Myocardial infarction n(%)			
Q-wave	2 (1.7)	6 (5.9)	**0.049**
Non-Q-wave	3 (2.6)	6 (5.9)	**0.02**
Death n(%)	2 (1.7)	1 (0.9)	0.7
MACE n(%)	12 (10)	18 (17.8)	**0.003**

[a]Indicates patients who received zotarolimus-eluting stents. Percentages in this column are based on a cohort of 116 patients.

[b]Indicates patients who received paclitaxel-eluting stents. Percentages in this column are based on a cohort of 101 patients.

[c]$P < 0.05$ defined as statistically significant.

The outcome of our study on the PES treated patients were also compared to previous studies in which the TAXUS trials (TAXUS 1, TAXUS III, TAXUS IV and TAXUS VI (5, 7, 8, 9)) were used. Whilst our study showed a MACE rate of 17.8% at the end of the two-year follow-up, the MACE rates for the TAXUS trials ranged from 3% in TAXUS I trial (5) to 29% in the TAXUS III trial (7). The TAXUS IV trial (8) represented a larger patient population and the rate of MACE was 10.8%. Interestingly the TAXUS VI trial which was designed to show whether this benefit will be reproducible in subsets of the patient population with even more complex and long lesion lengths (9) registered a MACE rate of 21.3%. It should be noted that the TAXUS VI trial and our study had a at two-year follow-up whilst results for the other TAXUS trials represent records for one-year follow-up. Seven patients in the PES treated group were prematurely taken off their antiplatelet therapy and this likely played a role in the observed MACE events. Additionally, the stent and lesion lengths recorded in our study were comparable with the Taxus VI population

To understand the safety and performance of the ZES and PES in the real-world patients, (patients not subject to any anatomic or clinical exclusion criteria) whose cases are more complex or problematic than

those seen in other trials, the E-Five Registry (18) and Taxus in Real-life Usage Evaluation (TRUE) program (19) were employed in previous studies. This multi-center global registry has an enrollment of 8,318 patients at 188 different hospitals, with 10,343 lesions treated. The in-hospital rate of MACE for the 1,989 patients receiving the Endeavor ZES was as low as 1.1%, which is comparable with the in-hospital incidence of MACE (1.7%) for the ZES treated group in our study. Despite the small population size used in our study, our results confirm the in-hospital rate of MACE of E-Five Registry. The TRUE trial shares a similar value as the E-Five Registry in that the patients were not subjected to any anatomic or clinical exclusion criteria. In-hospital MACE occurred in 3.7% patients in the TRUE trial compared to 1.9% for the PES treated group in our study.

Previous studies have shown that a potential problem with the DES is late in-stent thrombosis (20). Multiple studies have shown that the use of anti-platelet agents decreases the risk of in-stent thrombosis in DES treated patients and have been used in most of the trials described earlier. However when the antiplatelet therapy used in these trials is interrupted, in-stent thrombosis sets in (21-23). Consecutively the stent thrombosis rate at end of the two-year follow-up in first four ENDEAVOR I, II, IICA, III were 1%, 0,5%, 0%, 0%. Also in the Taxus I trial, the stent thrombosis was 0% at one year, 0.6% in Taxus IV at one year, 0.5% in Taxus VI at two year. Comparatively, the incidence of late stent thrombosis in our trial was significantly higher in the PES treated group (1.7% vs 3.9%, p: 0.046) at the end of the two-year follow-up. Also in our study, no major differences were observed in the incidence of acute (0.9% vs 0.9%, p: 1.0) and subacute (1.7% vs 3.9%, p: 0.06) stent thrombosis in the ZES compared to the PES treated groups. All the patients in this study were placed on aspirin and clopidogrel after stent implantation, as recommended, however, premature elimination of the antiplatlet therapy in addition to longer lesion and stent lengths and also the high-risk associated with an unselected patient population likely contributed to the stent thrombosis and MACE results observed in our study.

Study Limitations

The study has several limitations, the main ones being the small number of patients, lack of direct randomisation and relatively low compliance with angiographic follow-up.

CONCLUSIONS

Based on the two-year clinical results of this study it is reasonable to conclude that treatment of unselected Turkish patients with Zotarolimus-eluting stent is more effective than treatment with Paclitaxel-eluting stent in unselected Turkish patients.

Abbreviations

ACC: American College of Cardiology; AHA: American Heart Association; CABG: coronary artery binding graft; CK: creatine kinase; MACE: major adverse cardiac events; MI: myocardial infarction; PES: paclitaxel-eluting stent; ZES: zotarolimus-eluting stent; ST: stent thrombosis; TVR: target vessel revascularization.

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Conflict of Interest

None declared.

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