

One year follow-up cardiovascular outcomes of coraxel brand paclitaxel eluting stents: a single center experience

Fatih Levent¹, Sadik Volkan Emren², Nihan Kahya Eren³, Cem Nazli³, Hamza Duygu⁴

¹Izmir Su Hospital Department of Cardiology Izmir, Turkey

²Afyonkarahisar State Hospital Afyonkarahisar, Turkey

³Katip Celebi University Atatürk Training and Research Hospital Department of Cardiology Izmir, Turkey

⁴Near East University School of Medicine Department of Cardiology Nicosia, Cyprus

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Abstract

Coraxel (Alvimedica) stents are among those that contain paclitaxel and differ from other paclitaxel eluting stents (PES) in the amount of drug they contain. In this context, it is not known whether the clinical effects of Coraxel stents are different or not. In this study, the clinical effects of Coraxel stents were studied. This study was a single-centered, prospective, non-randomized real life study. Patients to whom stents of Coraxel brand were implanted were followed up in 1-, 3-, 6- and 12-month periods between May 2011 and August 2013 for target lesion revascularization (TLR), stent thrombosis and major cardiovascular events. This study enrolled a total of 78 cases. 82.1% of the cases were male. Average age was 61±11 years. Average stent length was 26.91±11.24 mm, and average stent size was 2.73±0.28 mm. 28% of the patients had TLR, 5 (6%) cases had stent thrombosis, 3 (4%) cases death from all causes, 1 (1%) case cardiac death and 55% of the cases showed major cardiovascular events. TLR, major cardiovascular event and stent thrombosis were observed more frequently in the patients using Coraxel PSS compared to those using TAXUS PSS.

Keywords: Drug eluting stents, target lesion revascularization, stent thrombosis, major cardiovascular events

Introduction

Percutaneous coronary intervention (PCI) with the use of stents has become an established means for reducing angina and intravascular restenosis in coronary artery disease. Although PCI is considered effective, re-narrowing (restenosis) in and around implanted stents can occur especially bare metal stents (BMS), which may require repeat treatment [1]. Among the first generation drug eluting stents, paclitaxel eluting stents (PES) were developed in order to reduce the re-stenosis problem seen after the common use of BMS. Paclitaxel contained in the stent is a vinca alkaloid and stops cell division during M phase by stabilizing tubulin molecules. Paclitaxel eluting stents thus reduce the development of re-stenosis by inhibiting smooth muscle cell proliferation [2]. To date, most of the data with regard to paclitaxel eluting stents have been collected from studies with PES of TAXUSTM LibertéTM brand (Boston Scientific, USA).

Coraxel (Alvimedica) stents are coated with drugs that contain polymers loaded with bio-resorbable paclitaxel.

Unlike other paclitaxel containing stents, the amount of paclitaxel per surface area in Coraxel stents is 0.25 ug/mm² [3].

It is not known whether this difference has any influence in clinical practice or not. In this study, we planned to evaluate the frequency of re-stenosis and thrombosis and the impact of clinical, laboratory and angiographic characteristics of the patients on the frequency of stent re-stenosis and thrombosis.

Materyal and Method

In this study, a total of 78 cases were assessed who underwent percutaneous coronary intervention with Coraxel stent implantation in a tertiary care setting between May 2011 and August 2013. Percutaneous coronary interventions were performed by independent operators in accordance with 2010 Myocardial Revascularization Guidelines by European Society of Cardiology [3]. The cases implanted paclitaxel eluting stents of Coraxel brand for coronary arterial disease were registered and prospectively followed up after the procedure. No intervention was made to the procedures or the treatments administered. At least one Coraxel PES was implanted to cases older than 18 years with acute coronary syndrome or with stable angina pectoris without response to medical treatment. All the patients were started on

*Corresponding Author: Sadik Volkan Emren,
Afyonkarahisar State Hospital Department of Cardiology,
Afyonkarahisar, Turkey
E-mail: vemren@hotmail.com

acetylsalicylic acid (ASA) and clopidogrel 600 mg before PCI and continued dual antiplatelet therapy for one year after the procedure [4]. Diagnosis of hospitalization, presence of hypertension (HT), diabetes mellitus (DM), hyperlipidemia, chronic renal failure (CRF), previous history of coronary arterial disease, family history, smoking status, current medical therapies, and number of affected vessels as detected by coronary angiography, intervened coronary arteries, number of stents implanted, caliber and length of stents implanted, and complications and transthoracic echocardiography findings following the procedure were recorded for all cases. The cases were clinically monitored at 1, 3, 6 and 12 months. The cases without clinical follow up were excluded from the study.

The patients were evaluated after 1 year for major cardiovascular events, total adverse cardiovascular events and stent thrombosis. Major cardiovascular event was defined as cardiac death, fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, possible or definite (confirmed) stent thrombosis, target vessel revascularization (TVR) and target lesion failure. Total adverse cardiovascular event was defined as TLR, TVR, revascularization other than target vessel, target lesion failure, angina, cardiac failure, non-ST elevation myocardial infarction (NSTEMI), ST elevation myocardial infarction (STEMI), all cause death, cardiac death and stent thrombosis. Target lesion revascularization was defined as surgical or percutaneous repeat revascularization into the stent or to 5-mm segment to the proximal or distal part of the stent. Revascularization procedure to segments of the same vessel other than stent lumen or 5-mm segments to the proximal or distal part of the stent was termed TVR. Definition of stent thrombosis was based on "Academic Research Consortium (ARC)" classification [5] in which patients that develop stent thrombosis were classified as definite, probable or possible stent thrombosis. In addition, 4 groups were defined as acute (first 24 hours), sub-acute (first 24-30 days), late (30 days-1 year) and very late (>1 year) stent thrombosis based on the occurrence timeframe of stent thrombosis. Myocardial infarction was defined based on the guideline of 'Third Universal Myocardial Infarction Definition' issued collectively by the European Society of Cardiology, American Society of Cardiology and World Heart Federation [6]. Follow-ups of the patients that developed major cardiovascular events were ended 12 months earlier. The study was approved by the local Ethics Committee. No funding was provided for this investigation.

Statistical Analysis

Analyses were performed using IBM SPSS 20.0 package software. Categorical data were given as percent, numeric data and mean $\pm$ standard deviation. Chi square or Fischer's exact test were used for comparison of categorical data. For comparison of numeric data, normal distribution was tested using Shapiro-Wilk Test. Independent Two Group t-Test was performed for

variables that comply with normal distribution, while Mann-Whitney U Test was chosen for those showing incompliance. All hypothesis checks were made at a significance level of $\alpha=0.05$ meaning that the differences for the value $p<0.05$ were considered significant.

Results

78 patients enrolled in the study had a mean age of 61 ± 11 years. The patients were followed up for an average of 12 months and 20 days (ranging between 6 days and 24 months). Demographic, clinical and laboratory findings are shown in Table 1.

Table 1. Demographic, clinical and laboratory findings of the patients

Variables	
Age, years mean $\pm$ sd (25%-75% IQR)	61 $\pm$ 11(34-83)
Male- n (%)	64(82%)
Admission diagnosis	
Stable angina - n(%)	28(36%)
Unstable angina - n(%)	16(21%)
Subacute MI - n(%)	6(8%)
NSTEMI	19(24%)
STEMI primer pci - n(%)	3(4%)
STEMI rescue pci - n(%)	2(3%)
STEMI facilitated pci - n(%)	4(5%)
Silent ischemia - n(%)	0(0%)
Hypertension - n(%)	50(64%)
Diabetes Mellitus - n(%)	28(36%)
Hyperlipidaemia- n(%)	37(47%)
Family history - n(%)	35(45%)
Smoking n(%)	37(47%)
Previous PCI - n(%)	30(39%)
Previous CABG - n(%)	14(18%)
Previous MI - n(%)	19(24%)
CRF (GFR<60 ml/dk) - n(%)	7(9%)
Noncritical CAD history- n(%)	2(3%)
Laboratory	
LDL (mg/dl) mean $\pm$ sd	123.32 $\pm$ 42.23
HDL (mg/dl) mean $\pm$ sd	37.33 $\pm$ 9.21
EF(%) mean $\pm$ sd	51.28 $\pm$ 10.7

CABG :Coronary Artery Bypass Grafting, CAD:Coronary Artery Disease, CFR :Chronic Renal Failure, EF:Ejection Fraction LVDD: Left ventricle Diastolic dysfunction MI:myocardialinfarction,NSTEM:non-ST-segment elevation myocardial infarction ,PCI :Percutaneous coronary intervention,STEMI: ST-segment elevation myocardial infarction n:number Sd:standart deviation

Stent was implanted into de novo lesions in 72 (92%) of the patients enrolled while Coraxel stents were implanted into stent re-stenosis in 6 (8%) patients. Coraxel stents were implanted to single vessel lesions in 74 (95%) patients and to 2-vessel lesions in 4 (5%) patients. In none of the patients Coraxel stents were implanted to 3-vessel lesions. LMCA was not performed and no Coraxel stents were implanted to saphena graft vessel lesions. Also, no slow flow or no-reflow occurred after percutaneous stenting of the patients. Findings with regard to

angiography and percutaneous coronary intervention are shown in Table 2.

Table 2. Findings with regard to angiography and percutaneous coronary intervention

Variables	
Findings with regard to angiography - n.(%)	
1 coronary disease	8(10%)
2 coronary disease	20(26%)
3 coronary disease	50(64%)
SYNTAX score<22*	24(92%)
SYNTAX score22-32*	2(8%)
SYNTAX score >33*	0(0.0%)
Finding with regard to percutaneous coronary intervention	
LAD stent - n(%)	39(50%)
CX stent - n(%)	24(31%)
RCA stent - n(%)	16(21%)
Stent restenosis- n(%)	6(8%)
Total stent length (mm)mean±sd (min-max)	26.91 ± 11.24 (14-87)
Total stent length ≥ 28mm - n(%)	30(39%)
Stent diameter (mm)mean ±sd (min-max)	2.73 ± 0.28 (2.5 – 4)
Stent diameter < 3mm - n(%)	73(94%)
Stent number mean ± sd (min-max)	1.17 ± 0.46 (1-4)
Stent number >1- n(%)	11(14%)
Overlapping - n(%)	10(13%)
Predilatation n(%)	52(66%)
Postdilatation - n(%)	9(12%)
dissection after procedure - n(%)	1(1%)
residue after procedure - n(%)	1(1%)
Elective procedure - n(%)	26(33%)
Primary procedure - n(%)	3(4%)
procedure within the same session - n(%)	49(63%)

CX: circumflex LAD:left anterior descending, RCA: Right coronary artery n:number sd:standart deviation

Rates of clopidogrel and Aspirin use during 1 year were 89% and 96%, respectively. 89% of the patients demonstrated complete compliance to dual antiplatelet therapy. 14 (18%) patients continued smoking after stent implantation.

Total adverse cardiovascular events

TLR was performed for a total of 22 (28%) patients. Of these 22 patients, 5 required TLR for development of stent thrombosis. For the remaining 17 patients, TLR was performed for stent re-stenosis. Major cardiac events were observed in 43 (55%) patients. No stroke was seen during the study period. Adverse cardiovascular events were listed in Table 3.

Mean age was found to be significantly higher in patients that developed stent thrombosis compared to those without thrombosis (72.4±7.4 vs. 59.8±10.9, p=0.01). Similarly, CRF (6.8% vs. 40%, p=0.01), stent implantation to Cx artery lesions (27.4% vs. 80%, p=0.01) and interruption of dual antiplatelet therapy earlier than one year (8.2% vs. 60%, p=0.01) were determined as significant variables for

stent thrombosis. CRF was found in 2 of the patients that developed stent thrombosis while these patients were on dual antiplatelet therapy.

Table 3. Adverse cardiovascular events

Variables - n.(%)	
Major cardiovascular event	43(55%)
TLR	22(28%)
TVR	14(18%)
Target Lesion Failure	5(6%)
Heart Failure	3(4%)
Angina	43(55%)
NSTEMI	8(10%)
STEMI	2(3%)
All -cause death	3(4%)
Cardiac death	1(1%)
Non target vessel revascularization	11(14%)
Definite stent thrombosis	1(1%)
Probable stent thrombosis	4(5%)
Possible stent thrombosis	0 (0%)
Acute stent thrombosis	0(0%)
Subacute stent thrombosis	4(5%)
Late stent thrombosis	1(1%)
Very late stent thrombosis	0(0%)
In stent restenosis	14(22%)

MI:Myocardial infarction NSTEMI: Non ST-segment elevation myocardial infarction SSTEMI:ST-segment elevation myocardial infarction, TLR :Target Lesion Revascularization TVR: Target Vessel revascularization n:number

DM (22.9% vs. 46.5%, p=0.03) and impaired systolic function (28.6% vs. 53.5%, p=0.02) rates were significantly higher in patients with major cardiovascular events. Besides, major cardiovascular events occurred significantly higher in patients in whom stenting was performed within the same session (48.6% vs. 72.1%, p=0.03). No statistically significant relation was found between other variables regarding TLR, stent thrombosis and major cardiovascular events (p>0.05).

Discussion

In this study, short and medium term clinical endpoints were investigated in patients who were implanted slow paclitaxel eluting Coraxel stents with polymers that contain less amount of drug compared to TAXUS stents (0.25 ug/mm² versus 1 ug/mm²). After implantation of Coraxel stents, 28% of the patients developed TLR, 6% developed stent thrombosis and 55% developed major cardiovascular events. According to these findings, rate of adverse cardiovascular events were found to be higher for patients in whom Coraxel stents were implanted compared to the results of studies that used TAXUS stents.

Earliest important human studies with PES were performed with TAXUS stents. In TAXUS 1 study, no patient developed re-stenosis after PES implantation as assessed

by angiography at 6 months [7]. In TAXUS 2 study, rates of angiographic re-stenosis using slow eluting and rapid eluting PES were lower compared to bare metal stents at 6 months (2.3% vs. 17.9% in slow eluting group, $p=0.002$; 4.7% vs. 20.2% in rapid eluting group, $p<0.0001$) [8]. In TAXUS 3 study, angiographic re-stenosis at 6 months was observed in 16% of patients with intra-stent re-stenosis after PES implantation [9]. During 5 years of follow-up in TAXUS 4 study, TVR was observed to be significantly lower in PES group compared to controls. TLR was also significantly lower in PES group compared to controls (16.9% vs. 27.4% $p<0.05$) [10]. In TAXUS 5 study, rates of angiographic re-stenosis were lower with PES implantation in complex lesions after 9 months (18.9% vs. 33.9%, $p<0.001$) [11]. In TAXUS 6 study investigating the effectiveness of PES in long lesions, a 53% decrease was demonstrated in TLR in PES group at 9th month compared to bare metal stents [12].

Real life data evaluating the effectiveness of drug eluting stents were derived from DESIRE, T-SEARCH and ARRIVE studies. In DESIRE (Drug-Eluting Stents in the Real World) study, paclitaxel or sirolimus stent was implanted to 4500 patients and 20.4% of them showed major cardiovascular event, 5.3% TLR and 1.9% stent thrombosis during an average of 5.6 years of follow-up. Stent thrombosis was most frequently seen between years 1 to 3 following the procedure [13]. In another real life study, T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital), rates of major cardiovascular event and TVR were found to be 13.9% and 5.4%, respectively, in patients to whom PES was implanted [14]. In ARRIVE (TAXUS Peri-Approval Registry: A Multicenter Safety Surveillance) study, 2-year follow-up of patients using TAXUS PES revealed a TLR rate of 5.8% for on label PES use and 9.4% for off label PES use, while stent thrombosis was observed at a rate of 2.6% based on ARC definition [15].

Our study may be considered a real life study since 78 consecutive patients were included to whom Coraxel stents were implanted. In the end of the study, rates of TLR (28.2%), stent thrombosis (6.4%) and major cardiovascular events (55.1%) were found to be higher compared to DESIRE, T-SEARCH and ARRIVE studies. Although the average caliber of stents used in our study is similar to that in DESIRE study, the average stent length was greater (26.91 ± 11.24 mm vs. 19.2 ± 5.8 mm).

Independent risk factors for major cardiovascular events in DESIRE and T-SEARCH studies included female gender, stent implantation to left main coronary artery, intervention to saphena vein, bifurcation lesion, multiple vessel lesion, residual stenosis, DM and CRF [14,16]. In our study, no stent implantation to left main coronary artery, intervention to saphena vein or intervention to bifurcation lesions was performed. Significant variables for major cardiovascular events in our study were defined as EF lower than 55% by

echocardiography, DM, and implantation of the stent within the same session. However, the amount of drug in Coraxel stent and differences in release characteristics may be relevant beyond these data.

Important factors that have a role in the development of stent thrombosis in patients to whom drug coated stents were implanted include factors related to the stent (stent length, stent malpositioning, multiple stents), those related to the lesion (bifurcation lesion, intra-stent lesion), older age, low left ventricular ejection fraction, diabetes, CRF, stenting in acute coronary syndrome, and early discontinuation of dual antiplatelet therapy [17]. Significant variables for stent thrombosis in our study were also determined as older age, intervention to Cx artery, chronic renal failure, in compliance to dual antiplatelet therapy, clinical signs of acute coronary syndrome, stent length and insufficient expansion of the stent.

Limitations to the study

There were no control groups in our study including patients with bare metal stents. Therefore, Coraxel stents had not been compared to bare metal stents. Furthermore, the number of patients enrolled was limited. Consequently, the impact of many risk factors and variables on the outcomes could not clearly be assessed.

Conclusions

In this study, frequencies of TLR, major cardiovascular events and stent thrombosis were found to be higher in patients to whom Coraxel PES stents were implanted compared to other large studies in which TAXUS PES was used. One reason of this may be the lower amount of drug on the surface of Coraxel stents.

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