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FREQUENCY OF MAJOR ADVERSE CARDIAC EVENTS IN PATIENTS WITH DE NOVO CORONARY ARTERY DISEASE REVASCULARIZED WITH EVEROLIMUS-ELUTING STENTS

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Contribution

STS conceived the idea, planned the study, did statistical analysis and drafted the manuscript. IS Collected data, conducted data analysis, edited manuscript and critically revised the manuscript. SU & NUH helped acquisition of data and did help in statistical analysis. All the authors contributed significantly to the research that resulted in the submitted manuscript.

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ABSTRACT

Objective: The aim of this study was to determine the frequency of major adverse cardiac events in patients with de novo coronary artery disease revascularized with everolimus-eluting stents.

Methodology: This prospective cross sectional study was carried out in the department of cardiology, Lady Reading Hospital Peshawar from October 2011 to November 2012. Patients with de novo coronary artery disease, who were revascularized with everolimus-eluting stents, were included in the study. Their baseline clinical and procedural characteristics were recorded from hospital record. Data regarding MACE defined as composite of myocardial infarction, stent thrombosis, recurrence of ischemia and death were obtained on follow up.

Results: A total of 420 patients were included in the study in which 320(76.2%) were male. Risk factors for coronary artery disease were; diabetes mellitus 147(35%), hypertension 256(61%), hypercholesterolemia 147(35%) and smoking 100(23.8%). Most of patients had stable angina 285(67.9%). On coronary angiography, 98(23.3%) of patients had single vessel disease, 152(36.2%) had two vessel disease and 170(40.5%) had three vessel disease. Left anterior descending artery was most frequently affected vessel 242(57.6%). Mean lesion length was 25±8.1 mm. Mean stent length/lesion was 26.03±7.09 mm while mean stent diameter/lesion was 3.14±0.29mm. Tirofiben (Agrastate) was used in 19(4.5%) of patients.

On follow up, MACE occurred in 16(3.8%) patients, 6(1.4%) patients developed myocardial infarction, 5(1.2%) developed recurrence of ischemia, 6(1.4%) of patients developed stent thrombosis and 6(1.4%) of patients died during study period.

Conclusion: Everolimus-eluting stents carries a lower risk of major adverse cardiac events in patients with de novo coronary disease.

Key Words: Major adverse cardiac events, De novo coronary artery disease, Everolimus-eluting stents.

INTRODUCTION

Charles Theodore Dotter and Melvin P. Judkins described the first angioplasty in 1964.[1] Thirteen years later, Andreas Grüntzig performed the first balloon coronary angioplasty, a revolutionary therapy that leads to the birth of a new specialty, interventional cardiology.[2] Since that first procedure, there are extensive developments; first bare metal stents followed by drug eluting stents. Today percutaneous coronary intervention (PCI) is the most frequently performed invasive medical procedures in clinical practice.[3]

Drug-eluting stents (DES) are widely used for percutaneous coronary interventions in routine clinical practice. These stents had a major favorable clinical impact on the treatment of patients with ischemic heart disease. First generation DES releasing sirolimus or paclitaxel from durable polymers has reduced angiographic restenosis and the need of repeat revascularization compared with bare-metal stents (BMS).[4] Based on the results of randomised controlled trials, drug eluting stents are increasing used for more complex lesions.[5] However, problems still exist. Instent restenosis still occurs, although at lower rate as compared to bare metal stents. The incidence of late stent thrombosis is increased with DES compared with BMS. The main reasons for it are chronic inflammation and delayed healing of the arterial wall.[6] These adverse events were more pronounced for "off-label" indications, including higher-risk lesion subsets. Therefore, newer generation drug eluting stents have been developed with the aim to improve upon the efficacy and safety profiles of early generation devices.[7]

The new second generation drug eluting stents, including the everolimus-eluting stent (EES), have been designed to improve the overall safety of earlier DES while maintaining anti-restenotic efficacy. Compared to earlier DES, the antiproliferative agent in the EES is released from a thin biocompatible fluoropolymer that is coated onto a low profile flexible cobalt chromium metallic stent platform.[8] Experimental animal data have indicated that stent strut endothelialization was more rapid with the EES compared to other DES, which might yield a lower thrombotic risk.[9] Similarly, several clinical trials suggest a reduction in both clinical and angiographic restenosis with EES implantation.[10,11]

Few studies have been conducted on the outcome of everolimus-eluting stents (EES) in Europe and United States of America.[10-12] According to those studies; everolimus-eluting stents (EES) are superior in term of safety and efficacy to first generation sirolimus or paclitaxel eluting stents. However very few studies have addressed this issue in our local population. The aim of the present study was to find out the frequency of major adverse cardiac events in patients with de novo coronary artery disease using everolimus-eluting stents (EES) for revascularization.

METHODOLOGY

This prospective cross sectional study was carried out at the Department of Cardiology, Postgraduate Medical institute, Lady Reading Hospital Peshawar from October 2011 to November 2012 for a total period of 13 months. In a study by Kim WJ et al., the frequency of major adverse cardiac events defined as death, myocardial infarction and ischemia-driven target lesion revascularization in patients with de novo coronary artery disease revascularized with everolimus-eluting stents was 5.3%.[13] Using World Health Organization (WHO) table for sample size calculation and the aforementioned response distribution, the estimated sample size was 420, keeping margin of error at 5% and confidence level at 95%. Purposive non probability sampling technique was used for patients' recruitment in the study. The institutional review board approved the study protocol and all patients provided written consent. The protocol and consent forms were consistent with the International Conference on Harmonization Guidance for Industry E6 Good Clinical Practice, the Declaration of Helsinki and all local regulations.

Study populations was consisted of patients having coronary artery disease, age 40 years and above, both genders and had at least 1 coronary lesion (defined as stenosis of $>70\%$ and visual reference diameter $\geqslant 2.5$ mm) suitable for stent implantation. Coronary artery disease was defined as stable angina, unstable angina and myocardial infarction. Patients with recent myocardial infarction (occurred within last 30 days) were included. Patients with stable angina were recruited from outpatient department while those of unstable angina and myocardial infarction were recruited from both ward and outpatient department. Patients were excluded if they had contraindication to aspirin or clopidogrel; unprotected left main disease (diameter stenosis $\geqslant 50\%$ by visual estimate); graft vessel disease; history of PCI, left ventricular ejection fraction $<30\%$; recent history of hematologic disease or leukocyte count <3000 per mm^3 and/or platelet count $<100{,}000$ per mm^3; hepatic dysfunction with aspartate aminotransferase or alanine aminotransferase $\geqslant 3$ times the upper normal reference limit; history of renal dysfunction or serum creatinine level $\geqslant 2.0$ mg/dL; serious noncardiac comorbid disease with a life expectancy <1 year; primary angioplasty for acute myocardial infarction (MI) within 24 hours; or inability to follow the protocol.

Baseline demographics, clinical and risk factors data were collected from hospital record and by interviewing patients. Only conventional risk factors including diabetes mellitus, hypertension, dyslipidemia, smoking and positive family history for coronary artery disease as defined in operational definitions were assessed in this study. The clinical presentations of patient were categorized as stable angina, unstable angina and recent myocardial infarction as explained above.

Coronary angiography was performed through standard femoral or radial artery approach. Angiographic data was collected by analyzing the angiograms by two interventional cardiologists. Atherosclerotic coronary artery disease was defined as >1 epicardial coronary segment with stenosis > 25% and was diagnosed visually and using quantitative coronary angiography (QCA) software (Toshiba's Infinix-i system). Quantitative Coronary Analysis (QCA) is a technique that provides objective and reproducible measurements of coronary artery dimensions. Patients were grouped as having Single Vessels Disease (SVD), Double Vessel Disease (DVD) and Triple Vessel Disease (TVD) according to the number of vessels involvement.

After analysis of coronary angiograms and decision for PCI, coronary arteries were engaged with EBU, VODA, IMPLANTZ and Judkin right and left guiding catheters depending on operator's choice. Lesions were crossed with the help of BMW and PT-graphix PCI wires. Most of the lesions were predilated with help of sprinter or Maverick balloons up to recommended inflation pressure. For stenting everolimus eluting stents (Xience V, Cobalt-Chromium metal alloy made; Abbott Vascular and PROMUS® Element™ Plus Everolimus-Eluting Platinum Chromium Coronary Stent System; Boston Scientific Corporation) were used. Before or during the procedure, all patients received at least 100 mg aspirin and a 300- to 600-mg loading dose of clopidogrel. Heparin was administered throughout the procedure to maintain an activated clotting time of $\geqslant$ 250 seconds. Administration of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. After the procedure, all patients received 100 mg/d aspirin indefinitely and 75 mg/d clopidogrel for at least 12 months. A 12-lead ECG was obtained after the procedure and before hospital discharge.

The primary end point of this study was occurrence of major adverse cardiac events at 8 months. It included nonfatal myocardial infarction, recurrence of angina, stent thrombosis during the study period and death due to any reason. Clinical follow-up visits were scheduled at 30, 120, and 240 days. A telephonic call was made to each patient at the expected day of follow up and was invited to OPD. At every visit, physical examination, ECG, cardiac events and angina recurrence were monitored. We defined MI as creatine kinase-MB elevation >3 times or creatine kinase elevation >2 times the upper normal limit with at least one of the following: ischemic symptoms, development of pathological Q waves, and ischemic ECG changes. Stent thrombosis was assessed according to the Academic Research Consortium definitions and was classified by the timing of the event (acute, 0 to 24 hours; subacute, 0 to 30 days; late, >31 days).[17] Recurrence of angina was assessed by asking from patients about typical ischemic type of cardiac pain and evidence of ischemia on exercise electrocardiogram.

Confounding variables were controlled by following exclusion criteria. Bias in the study was controlled by following strict inclusion criteria for patient's selection, measurable operational definitions for the diagnosis of end points, reporting all angiographies by same two cardiologists and using same QCA software for lesions measurement.

Statistical analysis was performed using statistical package for social sciences (SPSS) version 19. Numerical variables were presented as Mean±SD. Categorical variables were presented as frequencies and percentages. Comparison between two groups was performed by using student-t test for numerical variables and Chi-Square test for categorical variables. $P \leqslant 0.05$ was considered significant. Results were presented in tables.

Stable angina was diagnosed on the basis of clinical (chest pain typical or atypical) and non - invasive evaluation (1mm horizontal or down sloping ST –depression on exercise ECG or perfusion defects on technetium 99 scan).

Myocardial infarction (MI) was diagnosed in the presence of two of the following criteria: pain suggestive of myocardial ischemia lasting for at least 30 min; unequivocal new electrocardiographic alterations; or increase of creatinine kinase (CK- MB isoenzyme) to more than two times the upper limit. Patients with both ST elevation (STEMI) and non-ST elevation MI (NSTEMI) were included. ST segment elevation myocardial infarction (STEMI) was diagnosed when ST elevation of $\geqslant$2 mm in $\geqslant$2 contiguous precordial leads, or 1 mm in $\geqslant$ 2 contiguous limb leads or when new left bundle branch block was found on the qualifying ECG.

Unstable angina was diagnosed in presence of typical ischemic chest discompart of increasing severity and ST segment depression of 1 mm on limb leads and 2mm on chest leads with negative results for troponin T or I measured with help of ROCHE diagnostic kits for troponin T or I.

Diabetes mellitus (DM) was defined as chronic use of antihyperglycaemic drugs or previously documented diagnosis from medical record or established during hospital stay by repeated fasting blood glucose estimation to be $\geqslant$ 126 mg/dl.

Hypertension was defined as chronic use of antihypertensive drugs or a previously documented blood pressure $\geqslant$ 140/90 mmHg for nondiabetics and 130/80 for diabetics from medical record.

Positive family history for CAD was fined as ischemic heart disease in the father or a brother diagnosed before age 55 years and in the mother or a sister diagnosed before age 65 years.

Smoking: Any present or previous use of cigarettes was

considered smoking.

Dyslipidemia: Fasting LDL level ⩾130mg/dl was considered as dyslipidemia.

Lesion length: Lesion length was measured by caliper as the distance from the proximal to distal shoulder of the lesion in the projection that best elongated the stenosis using quantative coronary angiography, QCA. Stenosis of 10-20 mm length were defined as tubular and those of >20mm length were defined as diffuse.

RESULTS

A total of 420 patients were included in the study in which 320(76.2%) were males while 100(23.8%) were females. Risk factors for coronary artery disease were; diabetes mellitus 147(35%), hypertension 256(61%), hypercholesterolemia 147(35%), smoking 100(23.8%), positive family history for CAD 91(21.7%) and body mass index above 24.9Kg/m^2 148(35.2%). Most of patients had stable angina 285(67.9%). About 90 (21.4%) patients had unstable angina/NSTEMI while 102(23.3%) had history of recent myocardial infarction. Mean LV Ejection fraction (%) was 48.1±9.6. These findings are summarized in Table 1.

On coronary angiography, 98(23.3%) of patients had one vessel disease, 152(36.2%) had two vessel disease and 170(40.5%) had three vessel disease. Left anterior descending artery was most frequently affected vessel 242(57.6%) followed by right coronary artery 98(23.2%) and left circumflex coronary artery 83(19.8%). Mean lesion length was 25±8.1 mm. Mean stent length/lesion was 26.03±7.09 mm while mean stent diameter/lesion was 3.14±0.29 mm. Stents per patient deployed were 2.2±0.8.

Table1: Clinical and Angiographic Characteristics of Patients (n=420)

CHARACTERISTICS		FREQUENCY (n)	PERCENTAGE (%)	MEAN±SD
DEMOGRAPHIC FEATURES	Age (yrs)			54.02±9.3
	Male	320	76.2	
	Female	100	23.8	
RISK FACTORS FOR CAD	Hypertension	256	61.0	
	Diabetes mellitus	147	35.0	
	Hypercholesterolemia	147	35.0	
	Current smoker	100	23.8	
	Positive family history for CAD	91	21.7	
	BMI >24.9Kg/M^2	148	35.2	
CLINICAL PRESENTATION	Stable angina	285	67.9	
	Unstable angina/NSTEMI	90	21.4	
	Recent MI	102	24.3	
LESIONS LOCATION	Left anterior descending	242	57.6	
	Left circumflex	83	19.8	
	Right coronary artery	98	23.3	
NO OF VESSEL DISEASED	1-vessel disease	98	23.3	
	2-vessel disease	152	36.2	
	3-vessel disease	170	40.5	
LV EJECTION FRACTION (%)				48.1±9.6

Table 2: Procedural Characteristics of Study Population (n=420)

PROCEDURAL VARIABLE	FREQUENCY (n)	PERCENTAGE (%)	MEAN±SD
LESION LENGTH (MM)			25±8.1
MEAN STENT LENGTH/LESION			26.03±7.09
MEAN STENT DIAMETER/LESION (MM)			3.14±0.29
STENTS/PATIENT, N			2.2±0.8
MEAN INFLATION PRESSURE (ATM)			12.2±3.4
BALLOON DILATION	367	87.4	
DIRECT STENTING	53	12.6	
GLYCOPROTEIN IIB/IIIA INHIBITORS USED	19	4.5	

Table 3: Clinical Outcomes at 8 Months of Follow Up (n=420)

OUTCOMES		FREQUENCY (n)	PERCENTAGE (%)
MAJOR ADVERSE CARDIAC EVENTS (MACE)		16	3.8
MI	Total	6	1.4
	Q-wave	3	0.7
	Non–Q-wave	3	0.7
RECURRENCE OF ISCHEMIA		5	1.2
DEATHS	Total	6	1.4
	Cardiac death	4	1.0
	Non cardiac	2	0.4
STENT THROMBOSIS		6	1.4

Stents were deployed with a mean atmospheric pressure of 12.2±3.4 atm. Pre-stenting balloon dilation was performed in 367(87.4%) while direct stenting was done in 53(12.6%). Tirofiben (Agrastate) was used in 19(4.5%) of patients. These findings are summarized in Table 1and 2.

On follow up, MACE defined as composite of myocardial infarction, recurrence of ischemia, stent thrombosis and death occurred in 16(3.8%) of patients, 5 (1.2%) developed recurrent ischemia, while 6(1.4%) of patients developed myocardial infarction in which half were Q-wave MI and half non-Q wave MI. About 6(1.4%) of patients died during study period in which 4 deaths were due cardiac causes. Stent thrombosis developed in 6(1.4%) of patients. These findings are summarized in Table 3.

DISCUSSION

This study demonstrated that treatments with everolimus eluting stents carries a lower risk of major adverse cardiac events in patients with de novo coronary artery disease. In our study, the frequency of major adverse events was 3.8% in patients with de novo coronary artery disease revascularized with everolimus eluting stents which is accordance with the published literature. In a study by Kim WJ et al., the frequency of major adverse events was 2% in patients with ischemic heart disease revascularized with everolimus eluting stents. [13] In another study by Jensen LO et al., the frequency of major adverse events was 10.3% in patients treated with everolimus eluting stents.[12] The MACE rates in these studies are similar to our study which shows our patients carry the same risk of adverse events as patients in those international studies.

Myocardial infarction occurred at rate of 1.4% in our patients in which Q wave MI and Non Q wave MI were equal i.e. 0.7% each. It is similar to other published studies. In study by Jensen LO et al., the frequency of myocardial infarction in patients with ischemic heart disease treated with everolimus eluting stents was 0.5%.[12] In another study by Kalesan B et al., in which patients with acute coronary syndrome revascularized with everolimus eluting stents were studied, the frequency of myocardial infarction was 2.1%.[14] The lower frequency of death in our study as compared to this study can be explained by the fact that our study included both patients with stable and unstable coronary syndromes. In our study patients with acute coronary syndrome were 21.4% only and rest of patients have either stable angina or sustained an MI in the past.

Recurrence of ischemia at follow up is an important event needing target lesion or vessel revascularisation.In our study it was 1.2% which is similar to other studies. In study by kim WJ et al., recurrence of ischemia after revascularization with everolimus eluting stents needing target vessel revascularization was 0.7%.[13] In similar study by Jensen LO et al., recurrence of ischemia needing target vessel re-vascularization was 3.1%.[12] The slightly increase frequency of recurrent ischemia in this study as compared to our study can be explained by the fact that our study had less number of diabetic patients as compared to that study. Diabetic patients have increase recurrence of ischemia after revascularization with drug eluting stents as compared to nondiabetic patients.[12]

Stent thrombosis is an important cause of morbidity and mortality in patients revascularized with drug eluting stents. In study by kim WJ et al., the frequency of stent thrombosis including acute, subacute and late stent thrombosis was 0.7%.[13] In another study Park DW et al., the frequency of stent thrombosis in patients revascularized with everolimus eluting stents was 0.7%.[7] In another study in which patients with acute coronary syndrome were studied it was 3.8% [14]. In our study it was 1.4% which is similar to first two studies. It is less in our study as compared to studies in which patients with acute coronary syndrome were studied. This can be explained by the fact that patients with acute coronary

syndrome have increase frequency of stent thrombosis as compared to patients with stable angina revascularized with drug eluting stents.[13,14] Our study population consisted of patients with both stable angina and acute coronary syndrome.

The frequency of death rate in stable angina patients revascularized with everolimus eluting stents was from 0.4% to 1.4% in various studies.[7, 13] It is 7.8% in patients with acute coronary syndrome revascularized with everolimus eluting stents.[14] In our study it was 1.4% which is similar to other studies. The increase mortality in some studies can be explained by the fact that those studies included patients with acute coronary syndrome only as compared to our study in which patients with both stable angina and acute coronary syndrome were included. Patients with acute coronary syndrome have high mortality after revascularization with drug eluting stents as compared to patients with stable angina[13, 14]

LIMITATIONS

This study addressed only major adverse cardiac events in patients' revascularized with everolimus eluting stents. We did not performed angiographic follow up due to logistic and financial reasons and not studied instent restenosis, target vessel and lesion revascularization which are important to know the efficacy of stents. We performed only short term follow up and long term results were not studied.

CONCLUSION

The frequency of major adverse cardiac events (MACE) in our patients population with ischemic heart disease revascularized with everolimus eluting stents is similar to other populations. Revascularization with everolimus eluting stents in patients with de novo coronary artery disease carries low risk of major adverse cardiac events (MACE) at 8 months.

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