IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 20, Issue 5 Ser.6 (May. 2021), PP 29-36
www.iosrjournals.org

Bare Metal stents with hybrid cell design and thin struts are safe and effective in treatment of coronary artery stenosis : Real world data analysis of Protea CoCr Stent

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Abstract
Bare metal stent (BMS) was considered as the gold standard for safety after PCI, in terms of rate of Stent thrombosis. However, often restenosis is an issue with older generation BMS.
Methods and Results: The data in hospital's record for 122 patients who completed 18-24 months after PCI with Protea hybrid design thin strut CoCr BMS by MIV therapeutics India was evaluated for MACE and ST events. Average age of the population was 59.85± 10.26 years. There were 68.03% males, 48.36% tobacco consumers including 18.03% smokers, 40.98% Diabetic, 77.05% Hypertensive and 81.15% Dyslipidaemic. Previous MI was present in 11 - 9.02%, 46 patients (37.70%) were thrombolysed and 100% lesions were de novo. The Average BMI was 27.21 ±3.9. AMI was presenting complaint in 61.48%, old infarct in 13.97%. Stable angina in 2.46% and 9.02% were asymptomatic. Systolic BP was mean 132.31± 30.26 and diastolic BP was mean 75.8±15.39.
Of 160 lesions detected, 150 lesions were treated (average 1.31 lesions). LAD had 45.63% lesions, RCA had 31.25% Circumflex had 19.38% lesions. One lesion per patient was treated in 70.74%, patients Two lesions per patient in 27.87% and three lesions per patient in 1.64% patients. Mean RVD was 2.97± 0.36 which had 83.84±17.55 percent diameter stenosis and 20.07±8.36 mean length. Total 152 stents were implanted in 152 lesions of 122 patients (average 1.25 stent per patient, 1.01 stent per lesion). The mean stent Diameter was 2.99±0.34 and average stent length was 22.41 ± 7.89 mm. In 148 patients, 1 stent was implanted and 2 stents were implanted 2 patients.
There were total 9 (7.38%) MACE which including 3 (2.46%) cardiac deaths, 2 cases of non-fatal MI and 4 (3.28%) Clinical TVR. In the back ground of MACE, there were 5 (4.1%) binary restenosis identified, and no cases were reported to have stent thrombosis. The mean event free survival probability for the interval of 18-24 months was 93.44% by K-M analysis (Chi-sq 0.898, p=0.1). Most patients (111 - 90.98%) took antiplatelet therapy for at least 6 months.
Conclusion: The study revealed that in the real world population based upon demographic characteristics and event rates, the Current generation Protea BMS was found to be safe and efficacious.

Date of Submission: 05-05-2021 Date of Acceptance: 18-05-2021

I. Introduction

Treatment of coronary artery stenosis has greatly evolved after invention of balloon catheter. The journey from a plain old balloon angioplasty (POBA) to introduction various scaffolds have been quite dynamic. Metal stent or Bare metal stents (BMS) was the second important innovation in the field of interventional cardiology before the most accepted treatment of current time, the Drug Eluting Stents (DES). Clinically coronary stent is evaluated based upon rate of Major Adverse Cardiac Event (MACE) after its implant. The MACE is defined as composite endpoint of cardiac death, TVR, and Myocardial Infarction (MI)[1]. The main two pathological pathways leading to these clinical outcomes are restenosis (usually gradual) or stent thrombosis (usually sudden). Off late, the trends shifting from DES to BMS mainly emphasize on the DES efficacy in terms of low restenosis or Target Vessel Revascularization (TVR) rates and safety in terms of stent thrombosis similar to the BMS[2,3,4]. However, from the clinical practice in cardiology, it is evident that BMS, cannot be completely replaced by DES.

While DES have been effective in controlling restenosis, the stent thrombosis (ST) issues[5] added to its risk profile as observed in even recent studies of DES[6,7] like Orsiro[8,9]GenXSync[10,11], and Xience[4-8,12]family.Considering that lower risk probability of ST in BMS as compared with DES;certain patients such as having limitations to long term dual antiplatelet therapy or sensitivity to drug or polymer, still need treatment by BMS[4,13]. Besides these rare conditions that necessitate use of BMS, the use of BMS is mainly based upon budget[14]. The studies of BMS are conducted only with old generations of BMS. Most of the clinical data on BMS is as a control arm in the studies for comparison of a DES Versus its BMS platform as be observed in studies as old as RAVEL[15], Endeavour I[16] or STEALTH[17]. Though some clinical investigation was performed on BMS proper such as Polish NexGen Registry[18], there is only limited data of current generation of BMS published. Therefore, we decided to study the BMS outcomes of one current generation BMS in our centre from a pooled data analysis.

The main objective of this study was to obtain data on the current generation BMS in the real world scenario and find out the effect of comorbidity factors on device related events or MACE. The BMS selected for this study was Protea™ (MIV therapeutics Surat). Proteais anultra thin struts, uniform sinusoidal strut design and alternate 'S' link design stent to offergood flexibility, deliverability and cause minimal vessel wall injury. This makes it a current generation BMS. This study is a real world pooled out data study for all the patients treated with Protea ™ Cobalt-Chromium stent, and have completed up to 17-24 months of follow-up.

II. Methods

This study was based upon the real world data, pooled out from the hospital's database. Total 122 all comer patients who were treated on clinical indication with Protea between Feb-2014 and Dec-2015, at Parkar Hospital, Ratnagiri. The data was pooled from the Electronic Health Record and paper based medical record into a pre-definedMS-Excel spreadsheet. Data of the patient who were treated with more than one type of stents, those who were treated before January 2014 and after December 2015, lost to follow-up before 1 year and those who could not be contacted between 15 and 24 months was excluded from analysis. No patients were excluded from the data for therapeutic or demographic reasons. The final data was validated by tallying the data in Excel Spreadsheet and the original hospital record.

After validation, the statistical analysis was performed on MS-Excel by a statistician independent of the hospital. The numeric data was summarized as mean and standard deviation. The time data was reported as median and quartiles and categorical data was reported as absolute frequency and percentage. The time to event analysis was performed by Kaplan-Meier method. Significance for time to event analysis was based upon chi-square test for zero event at all points in time.

III. Results

In the study, there were 83 (68.03%) males out of total 122 evaluated patients, thus the male : female ratio was 2.13. This ratio is close to the commonly observed male : Female ratio of Ischemic Heart Disease (IHD) In India. The average age of the population was 59.85± 10.26 years, indicative of older age population. In all 59 (48.36%) patients has tobacco consumption habit, out of which 22 (18.03% of the overall population) were smokers, consuming 5 - 20 cigarettes per day. The Average BMI was 27.21 ±3.9 (Range 18.41 to 40) indicating that most of the patients were marginally overweight. (table 1)

Table 1 Study Chohort Demographic characteristics

Demographics	
Number of patients in the study (n)	122
Males, n (%)	83 (68.03%)
Male : Female Ratio	2.13
Age (years) mean ± SD	59.85± 10.26
Height (cm) mean ± SD	158.4±8.03
weight (kg) mean ± SD	67.39±10.36
BMI (kg/sq m) mean ± SD	27.21±3.9
Smokers n(%)	22(18.03%)
In Smokers average cigarettes per day Mean (range)	9 (5-20)
Other Tobacco habits n(%)	37(30.33%)

SD: Standard Deviation

The evidence of comorbidity factors namely Diabetes (50 - 40.98%), Hypertension (94 - 77.05%), Dyslipidemia (99-81.15%) and Previous MI (11 - 9.02%) was marginally higher than the usual IHD population. None of the patients underwent any treatment for coronary stenosis in the past, except for 46 patients (37.70%)

who underwent thrombolysis before angioplasty. This means that all the lesions were *de novo* lesions (Table 2) Despite having high percentage of comorbidity factors, only a few patients were reported to be treated with some medication for hypertension and dyslipidemia before enrolment.

Table 2 Comorbidity factors

	Yes	
	n	%
Diabetes mellitus	50	40.98
Hypertension	94	77.05
Dyslipidaemia	99	81.15
Previous MI	11	9.02
Previous PCI / CABG	0	0
Thrombolysis done	46	37.30

MI: Myocardial infarction

Most patients 75 (61.48%) presented with acute myocardial infarction (AMI) while 17 (13.97%) other patients were diagnosed to have old infarct. Stable angina was presenting complaint in 3 (2.46%) patients while other (11, 9.02%) were asymptomatic. Among vital parameters, blood pressure records demonstrated extreme range. Systolic blood pressure ranged from 50 - 210 mmHg, mean 132.31± 30.26, and diastolic Blood pressure was not recordable in one case where the patient was admitted with critical vital parameters to 170 mmHg maximum, mean 75.8±15.39.

Table 3 Presenting complaint

Presenting Condition		
	n	%
Acute MI	75	61.48%
Old MI	17	13.93%
Unstable Angina	16	13.11%
Stable Angina	3	2.46%
Asymptomatic	11	9.02%
Systolic BP Mean ± SD, Range	132.31± 30.26	50-210
Diastolic BP Mean ± SD, Range	75.8±15.39	NR-170

MI: Myocardial infarction, BP: Blood Pressure

In all 160 lesions were detected, of which 150 lesions were treated in 122 patients, average 1.31 lesions. Most lesions (73 - 45.63%) were detected in Left Anterior Descending (LAD) artery. Right Coronary Artery (RCA) had 50 (31.25%) lesions and Circumflex had 31 (19.38%) lesions. In 86 (70.74%) patients one lesion was treated. Two lesions each were treated in 34 (27.87%) and three lesions each were treated in 2 (1.64%) patient. Average reference vessel diameter was 2.97± 0.36 which had 83.84±17.55 percent diameter stenosis. Average Lesion length was 20.07±8.36 (Table 4).

Table 4 Lesion characteristics

Lesion Details	
Total Number of lesions observed	160
Total Number of lesions treated	150
Average Lesions per patient	1.31
RCA	50(31.25%)
LAD	73(45.63%)
LCX	31(19.38%)
D1	2(1.25%)
OM	2(1.25%)
Ramus	1(0.63%)
Other	1(0.63%)
Average Reference Vessel Diameter mm, Mean ± SD	2.97± 0.36
Average Diameter stenosis %, Mean ± SD	83.84±17.55

Average lesion length mm, Mean ± SD	20.07±8.36
Number of patients with 1 lesion treated n, (%)	86 (70.74%)
Number of patients with 2 lesion treated n (%)	34(27.87%)
Number of patients with 3 lesion treated n(%)	2 (1.64%)

RCA: Right coronary artery, LAD: Left anterior descending artery, LCx: Circumflrx coronary artery, D: Diagonal artery

Total 152 stents were implanted in 152 lesions of 122 patients; calculated as average 1.25 stent per patient, 1.01 stent per lesion. The mean stent Diameter was 2.99±0.34 and average stent length was 22.41 ± 7.89 mm. In 148 patients, 1 stent was implanted and 2 stents were implanted 2 patients. (table5)

Table 5 Stent Details

stent Details	
Total Number of stents used	152
Average stents per patient	1.25
Average stents per lesion	1.01
Average stent Diameter	2.99±0.34
Average stent length	22.41±7.89
Number of patients with 1 stent treated	148
Number of patients with 2 stent treated	2
Number of patients with 3 stent treated	0

Dual Antiplatelet therapy is among the most important criteria in post angioplasty treatment for prevention of stent thrombosis. Most patients (111 - 90.98%) took antiplatelet therapy for at least 6 months to 2 years. Median Dual antiplatelet therapy was 12 months. (table6)

Table 6 Dual Antiplatelet therapy details

Antiplatelet therapy Analysis	
Median DAPT Duration	12 months
Minimum DAPT Duration	10 days
Max DAPT Duration	24 months
0-3 MONTHS	2
3-6 MONTHS	7
6-12 MONTHS	55
12-18 MONTHS	2
18-24 MONTHS	56

DAPT: Dual antiplatelet

Clinical outcomes of angioplasty are expressed composite endpoint MACE. There were total 9 (7.38%) MACE which comprised of 3 (2.46%) cardiac deaths, 2 cases of non-fatal MI and 4 (3.28%) cases requiring Target Vessel Revascularization based upon clinical presentation. One other death reported in the study was due to non cardiac reasons, hence there were overall 4 (3.28%) deaths in the study. In the back ground of MACE, there were 5 (4.1%) binary restenosis identified, and no cases were reported to have stent thrombosis. (Table 7) The mean event free survival probability for the interval of 18-24 months was 93.44% by K-M analysis (Chi-sq 0.898, p=0.1). (table8, figure 1)

Table 7 Composite endpoints at 24 months

MACE at 2 years from the date of deployment		
Total Cumulative Hierarchical MACE	9	7.38
All cause deaths n (%)	4	3.28
Cardiac Deaths n (%)	3	2.46
Myocardial Infarction n (%)	2	1.64
Clinically driven Target Vessel Revacularization n (%)	4	3.28

Stent Thrombosis n (%)	0	0
In-lesion binary restenosis n (%)	5	4.1

Table 8 Time of Event Analysis (K-M)

Time to event Analysis	Number of events	Event free Survival
0-3 MONTHS	1	121
3-6 MONTHS	0	121
6-12 MONTHS	3	118
12-18 MONTHS	3	115
18-24 MONTHS	1	114

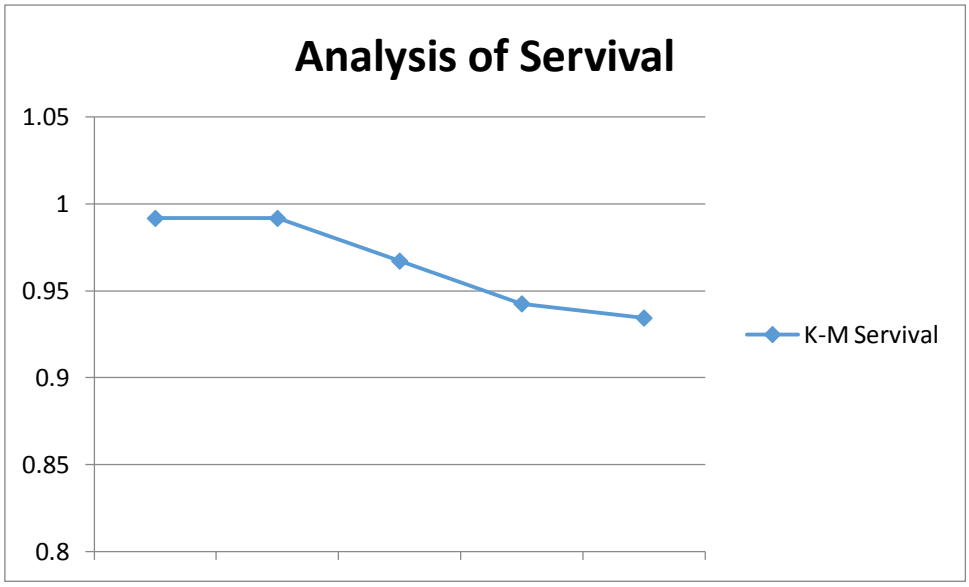

Figure 1 K-M Analysis for event free Survival (atypical excel line diagnram)

Of the 4 death cases reported, 3 were males. There were no smokers, but 2 were tobacco chewers. All had hypertension, 1 had ACS and all 4 had history of MI in the past. One patient died of Acute renal failure on 10th day of angioplasty, one other patient died due to Acute Left ventricular failure and 2 patients had Fatal MI. Out of 4 cases of revascularization, 3 underwent CABG and 1 underwent PCI. Two cases who reported non fatal MI, were managed with medicinal therapy. (Table 9)

Table 9 Event Causal Analysis

Event	Frequency	DM	Hypertension	Smoking	ACS	History of MI	Critical at admission	Details
Death	4	1	3	None Tobacco chewer 1	1	4	1	Acute LVF1, MI 2 ARF 1
TVR	4	3	1	None	1	1	None	CABG 3 , PCI 1
MI	2	2	2	None	1	1	None	Medical Therapy

IV. Discussion

This publication is based upon a real world incidence of treatment of IHD by angioplasty including a BMS implant. Diabetes mellitus, hypertension, dyslipidemia, smoking and tobacco habits previous MI history and family history of MI are often observed as the demographic risk factors or precursors of MACE after angioplasty in all the publications on IHD. In this study, the same criteria were identified as the demographic risk factors. In this population, there the frequency of hypertension and dyslipidemia were in a frequency higher than the usual, typical IHD population[19].

Most of the clinical data of BMS is generated as a control arm in randomized control trials (RCT) conducted for DES. In an old clinical study comparing paclitaxel eluting stent with bare metal stent in 1156 patients, the TVR rate for BMS was observed as 17.3%. In this study, the incidence rate of in-stent restenosis was 31.9% for the BMS arm[20]. PRODIGY was another bench-marking RCT, which compared first or second generation DES with BMS in a 2013 patients. In this study, the MACE rate was 32.1%. The TVR rate in this

study at 2 years was 18.3%[21]. In the second generation of BMS, these rates are reduced to an extent, as an impact of improved deployment environment and technology of stent. In EXAMINATION trial, the reported rate of TLR in ST Elevation subgroup was 5.6% and the MACE rate was 17.3%[22]. In the current cohort, cases of AMI were a little more than 60% of the cohort, which include STEMI, n-STEMI both. As AMI is an important precursor of MACE, the current cohort was marginally less complex than the cohort of EXAMINATION study. However, in PRODIGY study, the disease characteristics were close to the current cohort.

The novel platinum chromium REBEL BMS had 9 month TLF rate 11.5%, and one-year event rates were low including a TLF rate of 12.8%. This is a good event of efficacy. As an evidence of safety, the ST rate was 0.6% at 12 months[23]. The study performed on current generation BMS in NexGen Polish Registry revealed that in complex population, the MACE rate was 25.21%[18]. As compared with many other studies in the past, the clinical outcomes in this data evaluation were quite better. At 18 to 24 months, the MACE rate was 7.38%, which resembles to many DES study results. However, this result may be deviated in the population with more complex subset. In the current study, the reference vessel diameter was close to 3mm, due to which a moderate late lumen loss may not result into restenosis and thereby TLR. The lesion length was close to 20 mm, this in may be in general indicative of a simple lesion. However, even if the direct quantification is not possible, the significantly low rate of MACE at time more than 18 months is a considerable evidence of safety and efficacy.

In cases of non-cardiac surgery, where the risk of bleeding is relatively higher, the use of dual antiplatelet therapy (DAPT) is restricted and often limited to less than 6 months. In such cases, the dilemma of selection of a stent for treatment of IHD is between choosing a DES which requires minimum 12 months of DAPT but has better control on restenosis or a BMS in which DAPT can be stopped in less than even 3 months but has a limited control on restenosis[24,25,26.] Often in this situation a BMS that has lower TVR rate can help. This is leading reason why several patients still receive BMS despite large amount of data available to demonstrate superiority of DES in all types of lesions, as compared to BMS[27]. The same idea was observed by Marie-Claude Maurice et al. in a prospective study, and demonstrated that the use of a BMS was directly driven by a concern about either bleeding or DAPT compliance in 301 (40.5%) cases. In this study having 31 centers in Europe and Asia to identify744 consecutive BMS PCI cases were included. Other than the DAPT and costing, indications for using BMS were identified as: large vessel diameter, 241 (32.4%); ST-segment elevation myocardial infarction, 132 (17.7%); reimbursement/regulatory/other reasons, 70 (9,4%); advanced age, 92 (12.4%); concomitant oral anticoagulant treatment, 84 (11.3%); increased bleeding risk, cancer, or anemia, 71 (9.5%); planned noncardiac surgery within the next year, 41 (5.5%); and anticipated poor DAPT compliance, 13 (1.7%).[28]To conclude, BMS (<3 mm diameter and short length <20 mm) can be used when there is limitation for using dual antiplatelet therapy.

Limitations of the study:

This study was a single centre single investigator lead study, which was based upon a non-protocol based data pooled from the hospital's health record. Therefore, the information retrieved had limitations. The cohort was a real world cohort, in whom, main reason behind deployment of the BMS was limitations for using dual antiplatelet therapy, budgetary consideration/ reimbursement. Hence, unlike a planned clinical trial, this study data was more realistic, but could not be evaluated in the same way as a clinical trial. Usually, STEMI is considered to be the most important clinical indication of BMS. However, in this study there was no break-up of AMI sub-types. Hence, a relationship between BMS oriented composite endpoints and STEMI could not be established critically.

V. Conclusions

The study revealed that in the real world population based upon demographic characteristics and event rates, the Current generation Protea BMS was found to be safe and efficacious. There was no stent thrombosis in the cohort, which complies with the conventional consideration about BMS. The in stent restenosis was also low (4.1%) despite typical angioplasty challenges in terms of demographics and disease characteristics.

Acknowledgements:

The authors acknowledge copy editing support from Dr. Srinivas Reddy Boreddy of Tata Consultancy Services and Data Validation support from Mr. Jay Vaidaya of MIV therapeutics.

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