



Original article

Evaluation and efficacy of long length Pronova XR Bioabsorbable Polymer stent in the treatment of long coronary lesions



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ABSTRACT

Aim: The study aims an observational registry of the long and extra-long length (>33 mm) Pronova XR stents in patients with long coronary lesions (>30 mm) in a prospective real world study.

Methods and results: Current study was conducted at Ruby Hall Clinic Pune, between July 2012 and July 2013 including 30 patients who underwent PTCA using long and extra-long Pronova XR stents. Among the stents used, one stent - 33 mm, 2 stents - 38 mm, 5 stents - 43 mm and 25 stents were of 48 mm in length. In particular average stent length for the study was 46.03 mm and the average stent diameter was 3.09 ± 0.41 mm.

For this study coronary angioplasty was performed using femoral approach and standard practice. Lesions were predilated using undersized balloons and study stent was deployed at pressure 7–26 atm. (12.8 ± 3.2 atm.) The successful delivery of stent at the intended lesion with visual residual stenosis less than 50% was defined as Procedural success. Follow up studies were conducted for all the patients at 30 days, 3 months and 6 months intervals. The predefined QCA parameters were calculated using Sanders Data System QCA plus software (Palo Alto, CA, USA).

No procedural complication was observed during the whole study. 100% successful stent placement was achieved in all patients. Six months clinical follow-up was available for all patients. No adverse events (Acute closure, angina, REPCI, MI, death, sub acute stent thrombosis) or hospitalization was reported for any of the patients except one. The Quantitative Coronary Core Lab analysis post 6 months showed well-flowing stent with average late lumen loss $0.10 \text{ mm} \pm 0.26$.

Conclusion: In patients with long coronary lesions and very long length stent implantation series, Pronova XR showed excellent in 6 months results. This is for the first time reported that use of long length Pronova XR stents has shown so low restenosis rate and absent of mortality in six month period. These results offer a new opportunity to single long length stenting.

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1. Background

In spite of a steep development of percutaneous coronary angioplasty, long coronary lesions are still a formidable challenge for the coronary stenting. It is known that, the excessive neointimal proliferation around and within the stented segment causes the in-stent restenosis. Therefore, a return of coronary symptoms is observed in 20–50% of cases, according to complexity and size of the stenosis.^{1,2} Consequently, the lesion length is known as the independent predictor of in-stent restenosis.^{3,4} Patients in India annually spent about 2500 crore for stenting, which is a three

times import price for stents. In order to save money it is more expedient to go for single stenting. However, the stent length has been shown to correlate with the occurrence of restenosis.^{5,6}

Nevertheless, the significant development of drug-eluting stents has improved treatment efficiency in patients with long coronary lesions.⁷ Also, sirolimus eluting coronary stents have shown to be substantially higher to the bare metal stents (BMS) in reducing restenosis and target vessel revascularization, as examined in various randomized trials.^{8–10}

The Pronova XR stent represent this new generation of Bioabsorbable Polymer sirolimus-eluting stents (SES). In this device, a pharmaceutical excipient is used for the timed release of sirolimus from the XR stent platform instead of a polymeric coating.¹¹ The longer configurations of Pronova XR stents (33 mm–48 mm) are expected to provide physicians with greater flexibility and higher efficiency in long coronary lesions treatment. However, this matter requires further investigation.

Abbreviations: SES, sirolimus-eluting stents; BMS, bare metal stents; PTCA, percutaneous transluminal coronary angioplasty; QCA, Quantitative Coronary Angiography; TVF, Target Vessel Failure.

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2. Methods

2.1. Study population

Our study had included 30 patients who underwent PTCA using long and extra-long Pronova XR stents. Among the stents used in the study, one stent - 33 mm, 2 stents - 38 mm, 5 stents - 43 mm and 25 stents were 48 mm in length. In particular average stent length was 46.03 mm and the average stent diameter was 3.09 ± 0.41 mm. (Table 1). In all cases, general clinical examinations were performed, including blood pressure and heart beat monitoring. Additionally, coronary lesions were classed in morphological type by American College of Cardiology/American Heart Association (ACC/AHA).¹²

Patients undergoing elective or urgent percutaneous transluminal coronary angioplasty (PTCA) were enrolled consecutively after obtaining informed consent. The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by Local Ethical Committee of Poona Heart Hospital and Research Foundation.

Inclusion Criteria were age more than 18 years old, coronary lesion length more than 30 mm, one or multiple vessels of 2.5 mm–4.00 mm in diameter and patients with signs of ischemia were eligible for PCI. Exclusion Criteria were patients who have major bleeding and hematological problems, patients who are non-compliant to the dual antiplatelet therapy (DAPT) protocol and exposure to any other investigational device or drug in the recent past.

2.2. Study procedures and medications

Coronary angioplasty was performed using femoral approach and standard practice. Lesions were predilated using undersized balloons and study stent was deployed at pressure 7–26 atm. (12.8 ± 3.2 atm.) Post dilatation of the stents was performed using a noncompliant balloon for suboptimal deployment assessed visually. Procedural success was defined as the successful delivery of stent at the intended lesion with visual residual stenosis less than 50%.

The angiograms were sent to the Quantitative Coronary Angiography (QCA) core lab to Krakow Cardiovascular Research Institute Poland for further analysis. QCA parameters included lesion length, percent diameter stenosis, stent length, and stent diameter.

2.3. Data collection and core laboratory analysis

All patients were clinically followed at 30 days, 3 months and 6 months intervals. 26 of these underwent check angiography after six months of the implant and three also underwent IVUS during the follow-up angiography. The remaining 4 patients who could not undergo check angiography were followed up telephonically through a clinical follow-up a questionnaire and were asymptomatic. The predefined QCA parameters were calculated using Sanders Data System QCA plus software (Palo Alto, CA, USA)

Table 1
Lesions and stents parameters.

| | |
|---------------------|--------------|
| Lesion length (mm) | 40.03 ± 7.49 |
| Stenosis (%) | 89.33 ± 5.83 |
| Stent Length (mm) | 46.03 |
| Stent Diameter (mm) | 3.09 ± 0.41 |

2.4. Study endpoints

The primary endpoint was late lumen loss and death. The secondary endpoint was major adverse cardiac events (MACE) such as death, myocardial infarct or TVF (Target Vessel Failure), Stent Thrombosis (as per ARC definition), and Peri stent Stenosis.

2.5. Statistical analysis

Continuous variables were presented as mean and standard deviation. A probability < 0.05 was considered to be statistically significant. For angiographic parameters one-sided-test or Wilcoxon signed-rank test (depending on normality) was used, because measurements were dependent, and direction of the difference was known; only the significance of observed differences was investigated.

3. Results

30 patients undergoing elective or urgent PTCA at our center were included in the study. The patient population was predominantly male (26 males and 4 females). The mean age of the enrolled patients was 60.5 ± 9 years. 53% patients had hypertension and 56% suffered from diabetes mellitus. Hypertension was defined as blood pressure of 140 mm Hg and greater systolic or 90 mm Hg or greater diastolic pressure. Of the total population, no one was a smoker and only one patient (3.3%) had a family history of premature coronary artery disease. In 53.3% of patients, Acute Coronary Syndrome was the indication for urgent PTCA. Accordingly, in 46.6% of cases the indication for PTCA was the stable angina. In the study population, average left ventricular ejection fraction (LVEF) was $52.9 \pm 13.8\%$. In particular the 16.7% (5 patients) of all cases had LVEF less than 45%. It was significant to note that one patient with the positive outcome has been with 25% LVEF. The resting heart rate varied in the range of 61 – 102 beats per minute. The details of angina status and LV ejection fraction are summarized in Table 2.

Of the total population, 70% (21 patients) had single vessel disease and double vessel disease was present in 30% (9 patients). Accordingly, 20 patients (66.7%) underwent PTCA to single artery only while double vessel PTCA was performed on 9 patients (30%). One patient (3.3%) underwent triple vessel stenting. A total of 39 lesions were treated with 41 stent implantations. The average stent diameter was 3.09 ± 0.41 mm and average stent length was 46.03 mm (Table 1). One stent was 33 mm in length, 2 stents - 38 mm, 5 stents - 43 mm and 25 stents were 48 mm in length. The other 8 stents had a length less than 33 mm and were not included in the study.

In most of the cases, treated vessels were Right Coronary Artery (RCA) (33.3%) and Left Anterior Descending Artery (LAD) (30%). Details of the stented vessels are shown in Fig. 1.

Maximum of cases in the study, the regions of lesion were proximal and middle-proximal parts of coronary vessels in 13 patients (43.3%) and 6 patients (20%) approximately. Four patients (13.3%) had lesion in middle region of artery, and 2 patients (6.7%) had lesions in distal, ostial and middle-distal regions. It should be

Table 2
Angina status among different types of patients.

| Type of patients | Percentage of total population | Number of patients |
|----------------------------|--------------------------------|--------------------|
| Diabetic Patients | 56% | n = 17 |
| Acute Coronary Syndrome | 53.3% | n = 16 |
| Stable angina | 46.6% | n = 14 |
| LV ejection fraction | $52.9 \pm 13.8\%$ | |
| Patient with LVEF $< 45\%$ | 16.7% | n = 5 |

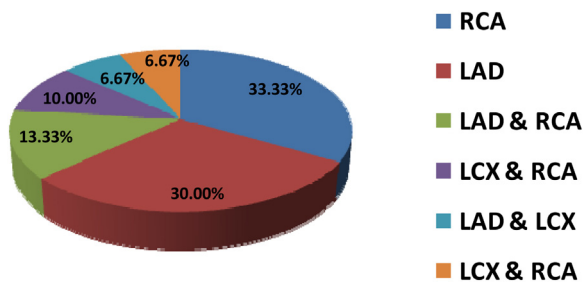


Fig. 1. Vessels Treated.

added that, one patient had the long (44 mm) atherosclerotic lesion over a length of Right Coronary Artery (proximal-middle-distal regions) and this patient had a positive outcome after stenting.

Based on the classification of coronary lesions type according to the Report of the American College of Cardiology/American Heart Association (ACC/AHA)[12] 12 patients (40%) had coronary lesions type B, 9 patients (30%) had type A and 8 patients (26.7%) had type C. One patient (3.3%) had B and C types of lesion at the same time. The statistic structure of coronary lesions has shown in Fig. 2.

There was no procedural complication during the whole study. 100% successful stent placement was achieved in all patients. Six months clinical follow-up was available for all patients. None of the patients had in hospital adverse event (Acute closure, angina, REPCI, MI, death, sub acute stent thrombosis). During 1 and 3 month clinical follow up there was none of the patients had any complications. After 6 month clinical follow up none of the patients developed acute or late stent thrombosis and recurrent angina. Follow-up angiography was made available for 26 patients.

The coronary angiography of a patient is clearly represented in Fig. 3. Where Fig. 3A represents angio view prior to stenting whereas 3B represents Pronova XR 3.5 × 43 mm stent in position after angioplasty. Normal flow after stenting is shown in Fig. 3C. Fig. 3D is check angiography at 6 months showing stent flowing well.

The QCA (Quantitative Coronary Analysis) Core Lab analysis done by Krakow Cardiovascular Research Institute Poland post 6 months and represented in Table 3. The data showed well-flowing stent with average late lumen loss 0.10 mm ± 0.26. Four patients were followed up telephonically through questionnaire and were found asymptomatic. Only in 1 patient (3.3%) focal restenosis had developed. This one underwent CABG for severe Long In-stent Restenosis in the non-culprit vessel. Consequently, in this study population for six months period the mortality was absent.

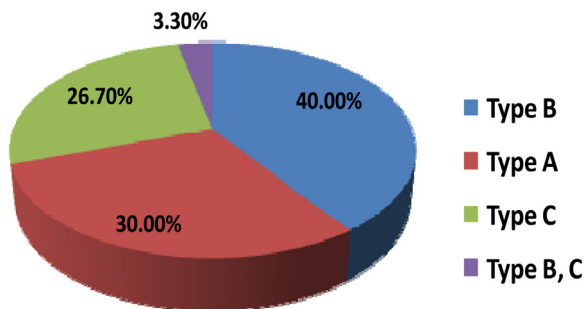


Fig. 2. Structure of Coronary Type Lesions.

3.1. Major adverse events

One patient (3.3%) developed focal restenosis. This patient underwent Coronary Artery Bypass Grafting (CABG) for severe Long In-stent Restenosis in the non-culprit vessel.

4. Discussion

Long coronary lesions are still independent variable of in-stent restenosis risk. Previous studies had shown that the lesion length more than 30 mm was confirmed as the independent predictor of TLR (Target Lesion Revascularization) and TVR (Target Vessel Revascularization).¹³ Therefore, as the long coronary lesions increase the risk of late complications due to stent edge restenosis; a treatment of long coronary lesion has required full lesion coverage with longer stents implantations. Consequently, the approach based on complete coverage of plaque is an effort to minimize edge restenosis.¹⁴ However, in the period of the bare-metal stents, longer stent length was found to be an independent factor predicting restenosis.⁶ And longer stent implantations have been associated with an increased risk of major adverse cardiac events caused by stent thrombosis.^{15,16}

Nevertheless, sirolimus-eluting coronary stents (SES) have presented the predominantly higher results, than the bare metal stents (BMS). One interesting study by Degertekin et al. demonstrated the safe and effective of very long (>36 mm) SES implantation for long coronary lesions requiring multiple stent placements.⁷ In additional, according to experience by Katritsis et al., drug-eluting stent overlap is an independent predictor of MACEs and target vessel revascularization regardless of lesion length.¹⁷ Also, in favour of long stent implantation are results from Raber et al., which suggested that stent overlap, rather than stent length is associated with subsequent myocardial infarct.¹⁸ Moreover, the use of a full-cover strategy with multiple stenting unavoidably increases the number of stents and costs.

At the present time, the significant development is in a process of novel drugs eluted stents (DES) systems generation that may improve outcomes after single long and extra long stenting. However, the clinical data of long lesions treated by the newer generation DES are still limited.

This study aimed at proving of Pronova XR, a novel polymer-free sirolimus-eluting stent, in the treatment of patients with long coronary stenoses. Additionally, our study population is at a particularly high risk due to the significant incidence of diabetes (56%). The longer configurations of Pronova XR stents (33 mm–48 mm) are expected to provide physicians with greater flexibility in long coronary lesions treatment. Moreover, long length SESs have given additional benefits from cost and clinical perspectives, such as a fewer number of stents and reversal of stent overlapping with multiple stent uses, as well as possible abridged procedural time.

Additionally, in our study we would like to highlight the row of prognosis factor such as resting heart rate and arterial hypertension. There are a lot of evidence associating an increase in resting heart rate to a grown risk of cardiovascular mortality in the general population.^{19–21} A retrospective study by Diaz et al. was reported that resting heart rate more than 83 beats per minute (bpm) has a long-term prognostic value.²² In the light of these reports, there were 10 patients (33.3%) with resting heart rate more than 83 bpm. It is also important that the arterial hypertension is the significant risk factor of in-stent restenosis in patients after transluminal coronary angioplasty.²³ And, in our study 53% patients suffer from hypertension. The reported late lumen loss in the study is 0.16 mm is highly appreciable considering the average stent length (46.03 mm). Another important factor of stenting outcome was the morphologic type of lesion. It was known that type B, C and

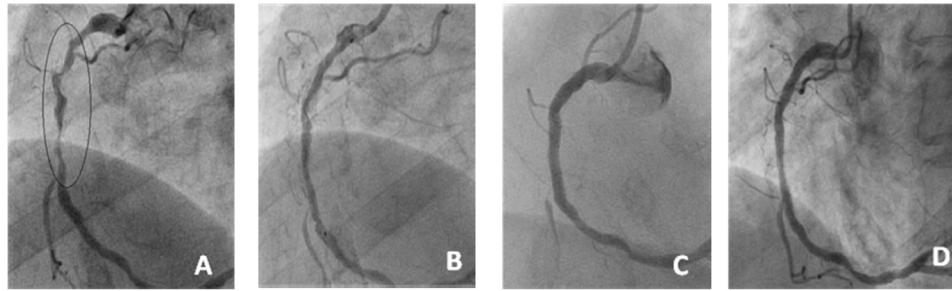


Fig. 3. Angio View Prior stenting (A), Pronova XR 3.5 × 43 mm Stent in Position (B), Flow after stenting (C), Check Angiography at 6 months showing stent flowing well (D).

Table 3
Quantitative Coronary Analysis.

| | |
|---|-----------------|
| Reference Vessel Diameter | 2.55 ± 0.11 mm |
| Lesion Length | 40.03 ± 7.49 |
| Minimal Luminal Diameter - Pre Procedure | 0.52mm ± 0.11 |
| Maximal Luminal Diameter - Post Procedure | 2.4 ± 0.013 mm |
| Acute Gain | 1.88 ± 0.012 mm |
| Minimal Luminal Diameter - Post 6 months | 2.3 ± 0.9 mm |
| Late loss | 0.10 mm ± 0.26 |
| Binary Stenosis | 3.3%(1/30) |

their combination had a most negative prognostic value.^{24,25} In our study 12 (40%) and 8 (26.7%) patients had B and C type lesions respectively. One patient (3.3%) had a combination of B and C types. In consonance with foregoing the case with in-stent restenosis has included the C type of coronary lesion.

In the light of the above, our study population had a significant high general cardiovascular risk. However, 96.6% of patient had a positive outcome after stenting with Pronova XR long and extra-long stents. The incidence of the restenosis (3.33%) in our study population was remarkably low than others trials with the long coronary lesions.²⁶ With a previously supported study by Schlij et al., shown a 25% incidence of MACE for patients treated with bare metal stents at a mean stent's length of 45 mm.²⁷ Appropriately, the analogic trials with long sirolimus-eluting stents have reported much better outcomes with 11.9% restenosis rate.⁷

Despite the superior results, one of the drawbacks of stents eluting systems is the high cost of treatment. Clearly, the long and diffuse coronary stenoses require multiple stenting in lesion's sites and entail additional costs. Against the background of the Indian economic scenario, the problem remains unresolved and topical. Patients in India annually lose about 2500 crore for stenting and this does not include the cost of blood tests, angiography, procedures, charges for a hospital stay, doctor's charges, etc. Most of the people in India were not benefited in a real sense owing to high cost of the multiple drug-eluting stents.²⁸ In the light of the above, the effective long stents implantation would be an effective way to solve this problem.

This is for the first time reported that use of long length Pronova XR stents has shown so low restenosis rate and absent of mortality in six month period. These results offer a new opportunity to single long length stenting. The advantages from cost perspectives can extend the limit of high-effective single stenting with drug-eluting systems in patients with long coronary lesions in countries with different economy status. Therefore, the further assessment of configurations Pronova XR stents in multicenter trials with a greater number of patients is still relevant and important.

5. Conclusions

In patients with long coronary lesions and very long length stent implantation series, Pronova XR showed excellent in 6 months results.

Study limitations

This study was a single center experience using long and extra long Pronova XR stent with relatively small number of patients. 26 of 30 patients underwent angiography after 6 months of stent's implant, However, the remaining 4 patients who could not undergo check angiography were followed up telephonically through a clinical follow-up questionnaire and were asymptomatic. A multicenter trial with the larger number of patients will be an advantage over the study to evaluate the long Pronova XR stents further.

Conflict of interest statement

No conflicts of interest to declare.

Impact on daily practice

The long length stents have significantly helped in reducing the no. of stents there by reducing the stent overlapping and cost wise it is more beneficial. The ultra long length stents of 43 and 48 mm have increased the scope of angioplasty as multiple lesions in the same vessel can be now treated with implantation of one long length drug eluting stent.

Acknowledgement

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