EMPIRE (Escorts Multiple ProNova Implantation Registry) Study: Evaluating the ProNova SES in *De Novo* Coronary Artery Lesions

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BACKGROUND

The main limitation of percutaneous coronary intervention with bare metal stents was the increased incidence of instent restenosis. The introduction of drug-eluting stents has decreased the rate of restenosis. Various drug-eluting stents, using different drugs and stent designs, are now being used in interventional cardiology worldwide.

The EMPIRE study was conducted to evaluate the safety and efficacy of the slow-release sirolimus-eluting ProNova stent in *de novo* coronary artery lesions in patients with single- or multi-vessel disease.

METHODS AND RESULTS

A total of 300 patients, enrolled in a single-center registry, were successfully implanted with ProNova, a sirolimus-eluting stent. They were followed up clinically, first at 30 days and then six months after the procedure for parameters like death, target vessel failure, documented myocardial infarction and restenosis. Assessment of binary restenosis was done angiographically at six months. The primary success rate of stent implantation was 100%, the percentage of acute major adverse cardiac events being 0% and 2% at 30 days and six months, respectively. Angiographic restenosis was documented in 12.6% of the patients enrolled in the study.

CONCLUSION

The ProNova stent was found to be safe and effective in this trial.

INTRODUCTION

Percutaneous invasion of coronary arteries began with Andreas Gruentzig, who performed the first human percutaneous transluminal coronary angioplasty (PTCA). Stents, which overcame many of the limitations encountered with PTCA alone, were the next big milestone in the field of interventional cardiology. However, the incidence of restenosis even with stents remained high, at 20–40%.[1–4]

Over time, a better understanding of vascular pathology and how it responds to therapy along with advances in medical technology, led to the introduction of drug-eluting stents (DESs). Restenosis is the result of neo-intimal proliferation which occurs after the deployment of a stent. The various drugs used to coat the stent are capable of suppressing neo-intimal proliferation. Sirolimus, a macrolide antibiotic with immunosuppressive and cytostatic properties, is one such drug. It interacts with the mammalian target of rapamycin (m-TOR) receptor, causing down-regulation of cyclic dependant kinase, thereby arresting cell growth.

A polymer is utilized as a vehicle to coat the surface of the stent with this drug. The polymer also controls the extended release pharmacokinetics of a drug inside the human arteries. The results of the RAVEL (RAndomized Study with the Sirolimus-eluting VELocity Balloon Expandable Stent)[5] SIRIUS (Sirolimus-Eluting Stent in *De Novo* Native Coronary Lesions),[6] RESEARCH REGISTRY,[7] E-SIRIUS (European Sirolimus-Eluting Stent in *De Novo* Coronary Lesions)[8] and many other studies have demonstrated the efficacy of and low restenosis rates following the use of sirolimus-coated stents.

Stent Characteristics and Design

ProNova is a drug-eluting ProPass coronary stent system, manufactured by Vascular Concepts Ltd. The ProPass stent (CE-marked) has been implanted in a large number of patients with good acute and long-term results. These have been attributed to its thin strut design, as proved by the ISAR–STEREO-II (Intracoronary Stenting and Angiographic

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Results–Strut Thickness Effect on Restenosis Outcome-II) trial.[9] At the Transcatheter Cardiovascular Therapeutics Conference held in Washington in 2003, Dr Thomas Ishinger presented the data gathered by a European multicentric study on the ProPass stent.[10] The polymeric matrix that elutes the drug on the stent is biocompatible and has elastomeric properties, which enable the stent to expand smoothly and allow the drug to be retained over the stent surface after deployment. Theoretically, the covalent bonding of the drug to the hydrophobic–hydrophilic polymeric matrix may facilitate elution of the drug for a much longer duration than is the case with the existing polymer coating technology.

The ProNova stent is mounted on a proprietary semi-compliant stent delivery system. This system has a low crossing profile, with excellent trackability, and a rated burst pressure of 18 atm. Its trackability is attributed to its unique design, including its variable strut thickness (VST), variable strut design (VSD), and thin 60 μ articulations in the mid-portion. This ensures ample flexibility and prevents flare-up of the struts. Its closed cell design allows the stent to provide the maximum surface area, which enhances coverage and reduces the chances of restenosis. The straight 90 μ articulations in the mid-portion give it high radial strength, while the increased metal coverage at the ends (120 μ) allows for the use of a greater quantity of the drug on the edges, thereby preventing edge restenosis.

METHODS

The EMPIRE study was a single-center registry, involving 300 patients meeting the inclusion and exclusion criteria. Multiple and overlapping stents were used—their diameters ranging from 2.5–3.5 mm and their length from 13–38 mm (Figures 1 and 2).

Ethical Considerations

The approval of the Escorts Heart Institute and Research Centre Ethical Review Board was obtained before the EMPIRE study was conducted. The informed consent of the patients was obtained, in writing, prior to the trial. The information and data sent to the hospital or the sponsors, whether on the patients or their participation in the study, was considered confidential by the sponsor. Only authorized personnel had access to these confidential files. Case report forms were used to collect data concerning the patients for the purposes of the study.

Inclusion and Exclusion Criteria

The enrolled subjects consisted of consecutive patients admitted to the Escorts Heart Institute and Research Centre, New Delhi, with *de novo* coronary lesions, of any length and type, in one or multiple coronary arteries of a diameter of 2.5–3.5 mm. The consent of the patients, who had to be a minimum of 18 years of age, was compulsory. The exclusion criterion was a prior coronary artery bypass graft (CABG) or the use of any DES other than ProNova in the treated vessel.

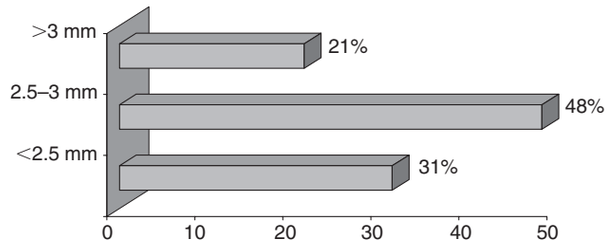

Figure 1. Diameter of stents used in the study.

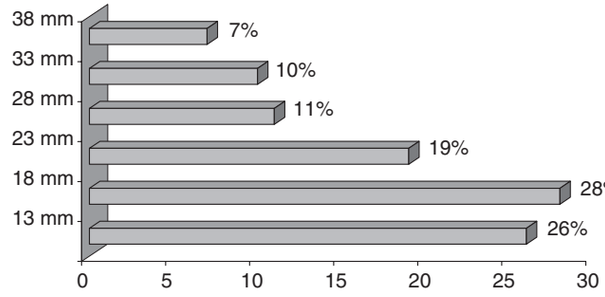

Figure 2. Length of stents used in the study.

Study Procedure

The information required for the study was assessed angiographically. It included the location of the lesion, reference vessel diameter (RVD), minimum lumen diameter (MLD), and percent diameter residual stenosis before and after treatment.

Standard operating procedures were followed for stent deployment, as per the manufacturer's guidelines. The stent to artery ratio for sizing and selection of the stent was taken to be approximately 1.1:1.0. Post-dilatation was done with a balloon of the appropriate size and length, at the doctor's discretion. All patients were followed up clinically at 30 days and at six months after being discharged from hospital. The first 101 patients to go through the procedure underwent a check angiogram at six months.

Study End Points/Success Definitions

The following end points were assessed in all patients implanted with stents. The primary angiographic end points included restenosis, as determined by angiographic evaluation and quantitative coronary angiography study, in 101 patients. The secondary end points included major adverse cardiac events (MACE), such as death, target vessel revascularization and myocardial infarction (MI), as ascertained by telephonic contact with the patients or during their visits to the clinic six months after the procedure. Restenosis was defined as stenosis of 50% or more of the luminal diameter.

Late luminal loss was defined as the difference between the MLD immediately after the procedure and that at six months.

OBSERVATIONS AND RESULTS

Of the 300 patients enrolled, 82% were males and 18% females. As for the baseline demographics, 87% had angina, 67% had a history of MI, 58% had a history of hypertension, 36% of the patients were smokers and 32% had diabetes. Patients with small vessel and thrombotic lesions were also covered. The patient demographics included in the study were more complex than those of other randomized trials on DES (Table 1).

All patients were pre-treated with oral antiplatelet therapy (aspirin and clopidogrel). During the procedure, an intravenous bolus of heparin was administered, while the use of GP IIb/IIIa inhibitors was left to the discretion of the physician/surgeon. Standard intervention techniques were used to treat lesions.

In all, 386 stents were deployed, the average being 1.29 stents per patient. Self anterior descending artery was stented in 40% of the patients whereas right coronary artery and left circumflex stented in 20% and ramus intermedium in 2%. The average length of the stents deployed was 21.4 mm per patient and the average size, 2.92 mm. All the stents were deployed successfully. Six months after the procedure, 101 patients went through angiographic follow-up, while 196 had a clinical follow-up. None of the patients suffered MACE in hospital (Table 2). However, at 30 days' follow-up, a diabetic patient with anginal symptoms was found to have a significant lesion in the left main, for which he underwent CABG (Table 3). He died subsequently due to heart failure. At 6-month follow-up, two patients had sudden cardiac arrest and died before they could reach the hospital (Table 4). The rate of angiographic in-stent restenosis was found to be 12.6% (Table 5).

The lesions treated in the EMPIRE registry trial were more complex compared to those in previous trials. Their mean length was 19 mm, which is greater than that of the lesions treated in previous studies. Overlapping stents were used in 22 (7.3%) patients. Sixty-six (22%) patients were implanted with 2 stents, 11 (3.7%) patients with 3, 2 (0.67%) with 4, and 1 (0.33%) with 5. A total of 237 (79%) patients were implanted with stents of a size of less than 3 mm (Table 6). In 78% of the patients, GP IIb/IIIa inhibitors were used (Table 7).

Primary Results

The mean MLD was 0.49 mm (SD = 0.3) before PTCA, and 2.91 mm (SD = 0.43) after PCTA. The mean RVD was 2.42 mm pre-PTCA, and 3.2 mm post-PTCA. The mean MLD for patients who consented to appear for a check angiogram (n = 101; number of lesions = 117; number of stents = 126) at a mean follow-up of 7 months 22 days was 2.34 mm (SD = 0.78). The mean early gain in luminal diameter was 2.43 mm and the mean late loss, 0.59 mm.

Table 1. Baseline demographic characteristics and risk factors in study population

	Number	Percentage
Total number of patients	300	100
Male/female	246/54	82/18
Mean age (Years)	56.8	
Diabetes	96	32
Hypertension	174	58
Family history of heart disease	93	31
Smokers	108	36
Angina	261	87
Stress test positive	60	20
Post-myocardial infarction	201	67
Recent myocardial infarction	141	47
Old myocardial infarction (>1 month)	60	20

Table 2. In-hospital major adverse cardiac events*

Major Adverse Cardiac Event	Percentage
Acute thrombosis	0
Death	0
Myocardial infarction	0
Urgent percutaneous coronary intervention	0
Urgent coronary artery bypass graft	0

*No patient needed any re-intervention procedure during hospital stay.

Table 3. Major adverse cardiac events at 30 days

Major Adverse Cardiac Event	Number of Patients
Sub-acute thrombosis	0
Death*	1
Myocardial infarction	0
Urgent percutaneous coronary intervention	0
Urgent coronary artery bypass graft*	1

*The coronary artery bypass graft and death refer to the same patient, a diabetic who was diagnosed with a new lesion and died after undergoing coronary artery bypass graft.

Table 4. Major adverse cardiac events at 6 months (0–180 days)

Major Adverse Cardiac Event	Number of Patients
Death	3
Myocardial infarction	0
Repeat procedure	3
Target lesion revascularization	2
Non target lesion revascularization	1
Coronary artery bypass graft	1

Table 5. Follow-up data of study population

Follow-up	Percentage
Angiographic	33.6
Clinical	65.3
Angiographic in-stent restenosis	12.6

Table 6. Procedural and stent details in the study

Total stents deployed	386
Average stent/patient	1.29
Average stent length	21.4 mm
Average stent size	2.92 mm
Patients with overlapping stents	22 (7.3%)
Patients with two ProNova stents	66 (22%)
Patients with three ProNova stents	11 (3.7%)
Patients with four ProNova stents	2 (0.67%)
Patients with five ProNova stents	1 (0.3%)
Patients with stents <3 mm size	237 (79%)

Table 7. Use of GP IIb/IIIa inhibitors

GP IIb/IIIa Inhibitor	Percentage
Integrilin	52
Reopro	24
Aggramed	2
Total	78

CONCLUSION

The first published non-randomized study of DESs in humans was the First In Man (FIM) Study, in which sirolimus-coated stents were implanted in 45 patients in Brazil and Europe. This pioneering study found no MACE at 1-year clinical follow-up, and neo-intimal thickening within the stent was minimal on angiographic and intravascular ultrasound follow-up.[11] This remarkable effect of the sirolimus DES was subsequently confirmed, although not with a zero restenosis rate, by the larger SIRIUS trial,[6] which included patients with longer lesions (mean length 14.4 mm); and the E- and C-SIRIUS trials[8,12] (Europe and Canada). The latter 2 trials covered 452 patients, the mean lengths of the lesions of the treated patients being 14.5 mm and 14.9 mm, respectively. In the TAXUS-II and TAXUS-IV trials,[13,14] which used polymer-based paclitaxel stents, the mean lengths of the lesions were 13.4 mm and 10.6 mm, respectively.

The cohort covered by the EMPIRE study was more complex than the those covered by the previous studies and thus, the study proves the efficacy of the ProNova sirolimus-eluting stent in a variety of complex coronary artery disease cases. The mean length of the lesions treated (19 mm) was relatively much greater, while the mean RVD (2.42 mm) was lower than that in SIRIUS (2.79 mm), E-SIRIUS (2.6 mm), C-SIRIUS (2.65 mm), TAXUS-II (2.8 mm), and TAXUS-IV (2.75 mm). The EMPIRE trial found that ProNova stents significantly increase the luminal diameter of the stenosed vessels, as is clear from the increase in the MLD following the procedure and from the check angiograms done six months later. In addition, the mean RVD increased after the PTCA. The mean early gain in luminal diameter was 2.43 mm and the mean late loss, 0.58 mm, but this could be due to the fact that the lesions treated in the EMPIRE study were more complex compared to other trials.

The EMPIRE trial demonstrates the safety of the ProNova sirolimus-eluting stent, considering that the rates of acute and sub-acute thrombosis were relatively low. There was not a single case of acute/sub-acute in-hospital stent thrombosis. Although there was no documented case of delayed stent thrombosis, it cannot be ruled out as a cause of the two sudden cardiac deaths that occurred later. The restenosis rate is comparable to various DESs used in other studies.

It was concluded that the ProNova sirolimus-eluting stent is safe and effective when implanted in patients with *de novo* coronary artery lesions.

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