

ORIGINAL ARTICLE

ASSESSMENT OF VASCULAR RESPONSE OF N-DEAVOUR® DRUG ELUTING STENT VS. XIENCE PRO™ DRUG ELUTING STENT AND MULTILINK VISION BARE METAL STENT IN THE PORCINE CORONARY ARTERY MODEL

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Objectives: The objectives of the study were to evaluate the vascular and tissue response of Pakistani manufactured novel drug eluting stent (called N-DEAVOUR®) on a swine model and compare the results with XIENCE PRO™.

Methodology: A total of 10 animals were used for the study and assigned randomly to each time-point group. The test articles were administered percutaneously and each animal was implanted with one stent in each one of the coronary arteries (3 in total) LCA (left circumflex artery), LAD (left anterior descending coronary artery), and RCA (right coronary artery). Additionally, a second test stent was implanted in some animals (4 in total). QCA (Quantitative Coronary Angiography) technique was used for measurements of the vessel at the target site. OCT (Optical Coherence Tomography) was performed only at follow up time-points which were 30, 90 and 180 days.

Results: At 30 DFU, parameters for N-DEAVOUR® were comparable to those of both control (XIENCE PRO™ and VISION) stents. At 90 days follow-up N-DEAVOUR® showed no statistically significant difference in performance for values of lumen area, stent area, area stenosis, and neointimal area against XIENCE PRO™. With reference to stent area, at 90 DFU, N-DEAVOUR® performed better than XIENCE PRO™ ($p=0.0056$). For neo-intimal area, area stenosis and lumen area, the differences between XIENCE PRO™ and N-DEAVOUR® were non-significant ($p=0.13$; $p=0.9$; $p=0.086$) respectively. These results indicate the positive potential of N-DEAVOUR® to be successfully implanted in clinical settings after necessary randomized clinical trials are executed.

Conclusion: This study proved that the drug eluting stent examined in the present study is both safe and feasible. This study supports that this stent can move forward for human trials.

Keywords: novel drug eluting stent, tissue response, late lumen loss

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INTRODUCTION

According to a report published in 2019 by World Health Organization, Coronary artery disease (abbreviated as CAD) has become major cause of human mortality. CAD is one of the most common types of heart disease which is caused by development of atheromatous in the coronary vessels. It results in narrowing or completely blocking of heart vessels. CAD is associated with many heart disorders that is, asymptomatic atherosclerosis, stable angina, acute coronary syndrome.¹ To treat coronary artery diseases, blocked vessel is opened through various methods that is, stent implantation. Coronary stents were introduced to treat the CAD patients. At first, mesh like metallic tubes were introduced which kept the vessels open for

longer period of time and later, the Drug Eluting Stents were introduced to promote the lesion healing and prevent the formation of thrombus.²

Till now, three types of stents have been brought into market: BMS (Bare metal stents), DES (drug eluting stent) and BRS (bioresorbable stents). Current bare metal stents (BMSs) are made of stainless-steel (SS), cobalt-chromium (CoCr), or platinum-chromium (PtCr). Stainless steel BMSs were the first devices used for coronary stenting. Undoubtedly, BMS were successfully able to lessen the incidence of abrupt vessel closure and also the rate of restenosis and gave better results than balloon angioplasty, thereby decreasing the rate of target lesion revascularization (TLR). One advantage of BMSs is that on average, endothelial stent coverage is complete in approximately 12 weeks, which decreases the risk of

stent thrombosis (ST). Nevertheless, despite refinements in stent design, significant restenosis within the stented segment develops in approximately 20% to 30% of lesions.³

Introduction of Drug coated stent decreased the chance of occurrence of restenosis by 50 to 70%.⁴ Studies has proved that various factors including stent, stent thickness, underlying plaque, type of coating and type of drug can influence the rate of thrombogenicity. BMS with thicker struts have more acute thrombogenicity with respect to platelet aggregation at the lesion site as compared to DES.⁵ Clinical studies of various DES have proved that prevalence of stent thrombosis (ST) is lesser in DES. The rate of ST is much lesser in CoCr DES as compared to SS DES. Among DES, Everolimus eluting stents i.e. XIENCE have lease prevalence of ST as compared to other DES and BMS.⁶

The present study was intended to evaluate the tissue response of animals through optical coherence tomography and quantitative coronary analysis for newly developed N-DEAVOUR[®] and compared it with XIENCE PRO[™] in an ex vivo porcine model.

METHODOLOGY

This animal study was conducted in 2019 at Pre-clinical Research Laboratory, Center of Cardiovascular Research and Development, American Heart of Poland and duration of study was six months. The Test Facility followed requirements specified in the approved protocol and internal SOPs which are based on 21 CFR Part 58. A total number of ten animals were included in the study comprising of eight domestic pigs of Swine breed and two Vietnamese Minipigs. The pigs and minipigs were 3 months old and 1 to 1.5 years, respectively. The animals were castrated and had 35 to 40 kg weight. The porcine model was selected for this study because of the anatomical and physiological similarities with the human coronary arteries.⁷ Porcine model has been used for decades for testing intracoronary devices.

Domestic pigs were acquired from a certified vendor Institute of Animal Production Grodziec Śląski (Domestic Swine), Poland and Vietnamese Minipigs from American Heart of Poland S.A., Poland. The herd was free from common domestic swine diseases and vaccinated according to the standard operating procedures. Animals were monitored for signs of disease during the acclimation period before enrolling them into the study.

The test article was N-DEAVOUR[®] Everolimus drug eluting stent and it was intended to be implanted in the coronary arteries and treatment of coronary artery disease by interventional technique. N-DEAVOUR[®] comprises of the following components:

- A balloon expandable Everolimus-eluting coronary stent
- A rapid exchange delivery PTCA balloon dilation catheter.

The stent was pre-mounted crimped on the balloon of a PTCA catheter for endovascular delivery and implantation at the desired site. The delivery system consisted of a rapid-exchange PTCA catheter with a balloon. Nominal pressure and Rated Burst Pressure of the balloon (for the test article) was 10 and 14 ATM, respectively. Two radiopaque platinum-iridium markers were located in the ends of the stent, and two additional markers on the proximal catheter shaft to aid in positioning. The results of test article were compared with commercially available DES XIENCE PRO[™] and Multilink Vision.

The animals were sedated before angioplasty according to the standard operating process. The test articles were administered percutaneously. Each animal received total of three stents; one in each artery left circumflex artery (LCX), left anterior descending coronary artery (LAD), and right coronary artery (RCA). On the basis of lesion size at artery, some animals received an additional stent.

After the stent implantation, angiographic data was collected to assess TIMI flow, vessel patency and presence of any aneurysms. The angiograms were analyzed using a quantitative coronary angiography (QCA) analysis software program (DICOMview[®]). The guiding catheter was used as reference for the measurement of baseline vessel diameter, reference vessel diameter and minimal lumen diameter after stenting. After stent implantation, the conditions of stents and vessels was observed by performing Optical Coherence Tomography (OCT) after 30, 90 and 180 days.

The vascular response of animals was studied at 1 day, 7 days, 30-days, 90-days, and 180-days and 1 year and one pig was recruited for each time point. The histopathology analysis were performed after 30-days, 90-days, and 180-days; and for that purpose, four pigs were recruited for 1 and 3 months, and 2 pigs for 6 months follow up. The pre-clinical outcomes of the implanted stents were mapped out numerically through Minimal Lumen Diameter (MLD), Reference Diameter (RD), % Area Stenosis (AS), % Diameter

stenosis (DS), and late lumen loss (LLL) measurements and subsequent statistical analysis.

The results were represented in the form of graphs and tables; and were analyzed through ANOVA analysis using SPSS software.

RESULTS

The success rate of stent deployment procedure was 100%. The animals remained alert and active after the procedure and did not show unresponsiveness, weight loss, fever or other health problems. During the procedure no complications including slow flow rate, thrombus formation or peri-procedural artery dissections were observed. The stents were properly expanded inside the arteries and well apposed to the vessel wall without showing any signs of strut fracture.

Quantitative Coronary Analysis (QCA): The characteristics of stent implantation including area stenosed, diameter stenosed, late lumen loss was measured through QCA and the results are demonstrated in Figure 1 and 2. Throughout the study, no significant difference was found between the results of BMS, XIENCE and N-DEAVOUR®. There was no statistical difference in Minimal Lumen Diameter (MLD), Reference Diameter (RD), % Area Stenosis (AS), % Diameter stenosis (DS), and late lumen loss (LLL) when all three stents were compared for variance. The reference diameters were similar as well as the pressures applied.

During the time period, there was no statistical difference in Minimal Lumen Diameter (MLD), Reference Diameter (RD), % Area Stenosis (AS), % Diameter stenosis (DS), and late lumen loss (LLL) at 30 DFU when all three stents were compared for variance (Figure 1).

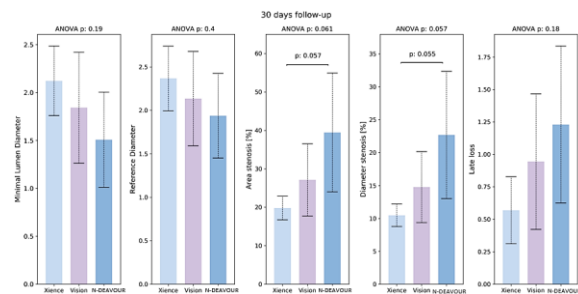


Figure 1: ANOVA analysis from QCA for different parameters between N-DEAVOUR®, XIENCE PRO™, and Vision™ at 30 DFU

During the study, there was no statistical difference between the three types of stent systems, at 90 DFU for % area stenosis, % diameter stenosis, and late lumen loss. There was no statistically significant difference with reference to minimal lumen diameter and reference diameter, however numerically, N-DEAVOUR® performed better than XIENCE™ for these two parameters. For both parameters, there was no statistical significance between Vision™ and N-DEAVOUR®; and XIENCE™ and N-DEAVOUR®, but there was a significant difference between Vision™ and XIENCE™ for both parameters.

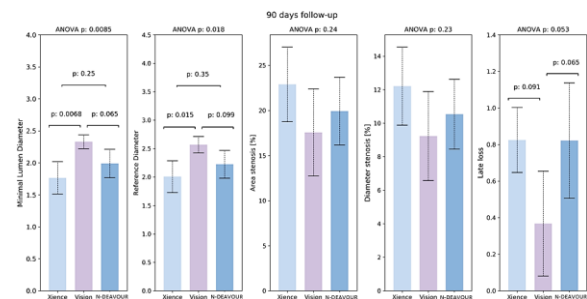


Figure 2: ANOVA analysis from QCA for different parameters between N-DEAVOUR®, XIENCE PRO™, and Vision™ at 90 DFU

Optical Coherence Tomography (OCT): Optical coherence tomography performed at 30 and 90 days confirmed that all stents were patent with no signs of thrombus. In morphometric analysis, no differences between groups regarding stent diameter.

During the study, no cases of late stent thrombosis or malapposition were found in any of the groups at 30 DFU. At 30 DFU, the difference in performance between N-DEAVOUR® as compared to the control stents, was not statistically significant, (p=0.1 for lumen area, p=0.28 for stent area, p=0.11 for stenosis area, and p=0.16 for neointima area), which confirms its functionality and performance.

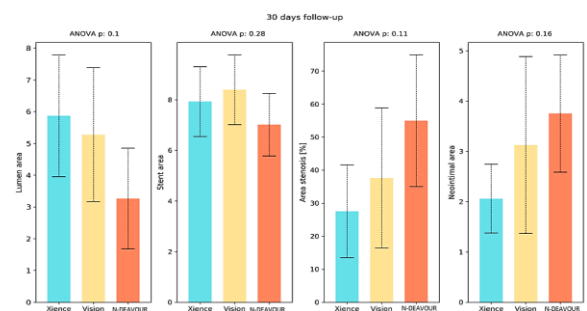


Figure 3: ANOVA analysis from OCT for different parameters between N-DEAVOUR®, XIENCE PRO™, and Vision™ at 30 DF

There was no statistical significance in lumen area when comparing N-DEAVOUR[®] against XIENCE PRO[™] ($p=0.086$). For stent area N-DEAVOUR[®] had better performance than XIENCE PRO[™] ($p=0.0056$). For area stenosis, there was no difference between N-DEAVOUR[®] and XIENCE PRO[™] ($p=0.9$). Finally, for neointimal area, XIENCE PRO[™] was matched against N-DEAVOUR[®] ($p=0.13$) with no statistically significant difference. No cases of late stent thrombosis or malapposition were found in any of the groups at 90 DFU.

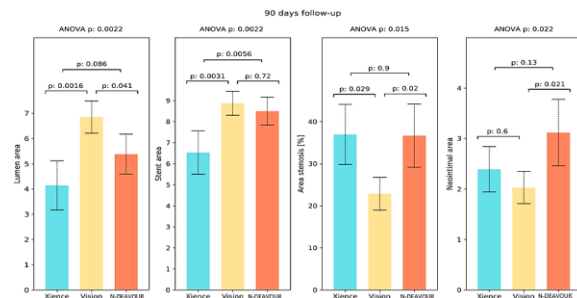


Figure 4: ANOVA analysis from OCT for different parameters between N-DEAVOUR[®], XIENCE PRO[™], and Vision[™] at 90 DFU

DISCUSSION

Human and animal pathologic sample studies have indicated that DES (first-generation) can cause delays artery healing. This is because of deposition of fibrin and lack of endothelialization; which ultimately results in thrombotic events.^{8,9} This is the first study for the assessment of healing process of N-DEAVOUR[®] in the porcine coronary artery model as compared to commercially available XIENCE PRO[™] and Multilink VISION BMS.

The N-DEAVOUR[®] is a second-generation DES and coated with Everolimus drug and permanent polymer. This stent is devised to address both the safety and efficacy of treatment of coronary artery disease. The main purpose of this stent is to reduce the rate of ST (stent thrombosis). In this study, The N-DEAVOUR[®] was compared with commercially available DES XIENCE PRO and BMS VISION. The results demonstrated that N-DEAVOUR[®] has results comparable to XIENCE and better than VISION. At 90 days follow-up N-DEAVOUR[®] showed no statistically significant difference in performance for values of lumen area, stent area, area stenosis, and neointimal area against XIENCE PRO; however, the numerical values of N-DEAVOUR were better than XIENCE PRO.

N-DEAVOUR[®] consists of three components: CoCr platform¹⁰, fluoropolymer-based coating¹¹ and Everolimus drug¹². Each component plays a key role arterial healing and has been optimized. The optimized regime reduces in-stent restenosis which has been shown in results. First, N-DEAVOUR is thin-strut metallic cobalt-chromium platform, and this metal has proven it superior results in many studies. This alloy enables the construction of stents with thinner struts, lower profile, and higher radial strength with preserved maximal elasticity, thereby allowing introduction into small and tortuous coronary vessels. Its high radial strength ensures efficient support in lesions with complex morphology located ostially and facilitates the successful closure of dissections. Moreover, according to the results of the ISAAR Stereo study, thinner struts may induce less injury to the arterial wall and consequently lower restenosis rate^[3,4]. It is also thought that thinner struts facilitate re-endothelialization. These factors favor the use of cobalt-chromium stents, especially in select clinical situations. Moreover, cobalt-chromium stents are excellent platforms for locally released drugs.

Second component of N-DEAVOUR[®] is Everolimus drug which is a Limus derivative and has proven superior results than other drugs i.e., Zotrolimus, Sirolimus or paclitaxel. It is an immunosuppressive drug which acts as an mTOR inhibitor. In N-DEAVOUR[®], the amount of drug incorporated allows rapid heart vessel healing by reducing proliferation of vascular smooth muscle cells. In the porcine coronary arterial model, N-DEAVOUR[®] has shown release kinetics which are according to the cellular phases of vascular healing. This study has proved an efficient delivery of Everolimus to the coronary arterial wall. The third component of the N-DEAVOUR[®] is the PVDF-HFP polymer. It is a fluoropolymer which has been widely used in other vascular and nonvascular applications. There are some commercially available stents which has already been using this polymer and proven safety by long-term safety and integrity studies conducted on other durable polymer-based DES systems.

The combination of thin struts of CoCr metallic platform with lowest effective dose of Everolimus, and the optimum drug delivery of biocompatible durable PVDF-HFP polymer gives the N-DEAVOUR[®] properties of rapid vessel healing which are at par or may be numerically superior to XIENCE PRO in some features; hence, by this study we can say that the N-DEAVOUR[®] may has features of optimal vessel healing, rapid re-endothelialization and less stent thrombosis.

The results demonstrated no significant differences were observed at 90 days through QCA and OCT data. During the analysis, no excessive neointima proliferation, and strut coverage was observed.

The QCA results demonstrated the 20% and 22.8% area stenosed for N-DEAVOUR® and XIENCE PRO. For the better performance of DES low percent diameter stenosis and area stenosis is required. Through results, numerically less but statistically insignificant difference was observed between three groups of stents. Additionally, when we take into consideration the late lumen loss and N-DEAVOUR® and XIENCE PRO exhibited 0.82% and 0.83%, respectively.

With reference to OCT results at 30 DFU, the performance of Xience Pro™ was marginally better for all the parameters that were investigated, with the exception of stent area. For stent area, Multilink Vision™, scored better. The performance of N-DEAVOUR® was comparable to the control stents, (p=0.28 for stent area, p=0.1 for lumen area, and p=0.16 for neointima area, p=0.11 for stenosis area). These results confirm the performance and functionality of N-DEAVOUR® at 30 DFU. Additionally, there was no case of malapposition and late stent thrombosis at 30 DFU, for any of the stents tested.

Considering OCT results at 90 DFU, for stent area, N-DEAVOUR® performed better than Xience Pro™ (p=0.0056). Lumen area performance parameters were also comparable between N-DEAVOUR® and Xience Pro™ (p=0.086). Similarly, area stenosis and neointimal area results were statistically comparable between N-DEAVOUR® and Xience Pro™ (p=0.9 and p=0.13). Additionally, there was no indication of malapposition and stent thrombosis at 90 DFU, for any of the stents tested.

Based on QCA analysis and OCT analysis at 30 and 90 days, N-DEAVOUR® and stents appeared as safe as XIENCE PRO™. One may conclude that safety profile at 90 days is similar to XIENCE PRO™ stent in the porcine coronary artery model.

Study limitations revolve around the pre-clinical investigation design, as healthy swine were utilized in the study, without co-morbidities or underlying pathologies. This study is meant to reflect potential for clinical use of the stent, after in-depth clinical investigations or randomized trials have been carried out.

CONCLUSION

The study validation was confirmed by appropriate level of injury and overstretch implanted in all stents. At 30 days, parameters for N-DEAVOUR® were comparable to those of both control stents. At 90 days follow-up N-DEAVOUR® showed no statistically significant difference in performance for values of lumen area, stent area, area stenosis, and neointimal area against XIENCE PRO™. Therefore, these values of N-DEAVOUR® are within acceptable range and comparable to XIENCE PRO™. Based on the above results for 30 and 90 days follow up, N-DEAVOUR® results show acceptable level of vascular response.

AUTHORS' CONTRIBUTION

PM, MNA, and AMK: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. MM, HA, MMA, and SH: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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