THREE-YEAR CLINICAL & TWO YEAR MULTI-MODALITY IMAGING OUTCOMES OF THIN STRUT SCAFFOLDING SYSTEM

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Aim: Although the proof of concept of **drug-eluting stent system** is well-documented, device-related adverse outcomes with firstgeneration **drug-eluting stent system** indicate longer-term surveillance. The current study provides insights into safety and performance of study device, a beyond 1-year up to 3-year follow-up (FU).

Abbreviations

BRS	Bioresorbable vascular scaffolds
DES	Drug-eluting stent
ID-TLR	Ischemia-driven target lesion revascularisation
TVR	Target vessel revascularizations
IVUS	Intravascular ultrasound
MACE	Major adverse cardiac events
MI	Myocardial Infarction
OCT	Optical coherence tomography
PLLA	poly-L-lactic acid

QCA	Quantitative coronary angiography
TIMI	Thrombolysis In Myocardial Infarction

INTRODUCTION

Percutaneous coronary intervention (PCI) with implantation of an advanced drug-eluting stent (DES) is currently the cornerstone of treatment for obstructive coronary artery disease.[1] However, the presence of permanent metallic implant in the coronary arteries also creates an ongoing risk of occurrence of very late annual adverse cardiac events at a rate of 2-3% per year up to 5 years and even beyond. It is these limitations of DES which gave rise to the concept of a temporary implant with drug-elution for acute benefits and its eventual disappearance to eliminate shortcomings due to the permanently caged metallic vessel and this led to the development of bioresorbable vascular scaffold (BRS). Since the introduction of the first-generation BRS in 2010, its use proliferated in the initial years.

Subsequent randomized trials, however, demonstrated that while the BRS was as effective as best in class DES, it was less safe and associated with an increased device thrombosis at all time frames when compared to everolimus-eluting stent up to 3-year followup. Some of the potential reasons for this increased thrombogenicity outcomes included thicker struts (>150µm) resulting in laminar flow disruptions, delayed endothelialization, unfavourable dismantling during resorption process, delayed resorption and also technique related inefficiencies leading to inadequate implantation and incomplete scaffold apposition. It was therefore hypothesized that many of the limitations of first-generation BRS could be overcome by a thin-strut user-friendly BRS, which could also be less thrombogenic at all time frames (early, late and very late).

The study device is a novel thin-strut second-generation drug eluting scaffold. The first-in-human trial demonstrated study device to be safe and effective for treatment of de novo coronary lesions as evident by low major adverse cardiac event (MACE) rate (0.93%)

at 1-year follow-up. Importantly, none of the patients experienced scaffold thrombosis at 1-year follow-up. Vascular imaging using quantitative coronary angiography (QCA), intravascular ultrasound (IVUS) and optical coherence tomography (OCT) also confirmed favourable vascular response during 6-month follow-up. As very late cardiac events related to scaffold thrombosis beyond one-year and up to 3-year have been of great concern with the first-generation BRS, we therefore analyzed 3-year clinical outcomes of second-generation BRS. Moreover, the results of multiple imaging modalities (QCA, IVUS, and OCT) at 2-year follow-up are also studied.

METHODS:

TRIAL DESIGN

The trial was a prospective, multicentre, single-arm, open-label clinical trial which enrolled 100 patients from 10 participating centres across India. All patients were enrolled based upon defined inclusion and exclusion criteria. The study complied with the ICHGCP guidelines, Declaration of Helsinki, ISO 14155 and was approved by the local ethics committee at all participating institutions. All enrolled patients (intention-to-treat population) gave informed consent for trial participation.

STUDY DEVICE

The study device is a balloon expandable polymer backbone scaffold with 150µm strut thickness, coated with a bioresorbable matrix for controlled release of an anti-proliferative drug (sirolimus, 1.45 µg/mm^2). The degradation of the scaffold is expected to occur within 2 to 3 years of implantation. The presence of three pairs of platinum radio-opaque marker that are 150º apart from each other at either end of scaffold facilitates angiographic placement.

IMPLANTATION TECHNIQUE

PCI was performed according to the standard guideline to treat target lesions and have been published previously. Dual antiplatelet therapy with aspirin (75-150 mg/day) and clopidogrel (75 mg/day) or prasugrel (10 mg/day) or ticagrelor (90 mg/day) was prescribed to all patients for a minimum of one-year duration, beyond which a switch to single anti-platelet therapy with aspirin alone was left to the operator's discretion.

ENDPOINTS AND FOLLOW-UP

Clinical end-points of the study were MACE [a composite of cardiac death, any MI, and ischemia-driven target lesion revascularisation (ID-TLR)] and scaffold thrombosis at 3-year follow-up. All major adverse cardiac events were independently adjudicated by clinical event committee, and data safety monitoring board evaluated patient safety. The major imaging endpoints for the present analysis included in-scaffold and in-segment LLL by QCA, minimum lumen area and neointimal hyperplasia (NIH) area by OCT, scaffold and lumen area by IVUS imaging at 2-year follow-up. Currently, clinical follow-up is complete through 3-year.

MULTIMODALITY IMAGING ASSESSMENTS

Quantitative coronary angiography was performed in a predefined subset of patients at baseline, 6-month and 2-year. Out of these, based on patients consent, IVUS (n=10) and OCT (n=9) was performed at pre-designated sites with technical facilities for OCT and IVUS in different subsets of patients. Hence, both OCT and IVUS were not performed in the same patient. The QCA parameters, OCT and IVUS were analysed at by an independent core laboratory.

STATISTICAL ANALYSIS

This is a feasibility study designed to provide preliminary observations and generate hypothesis for future studies. Since there is no hypothesis testing in this trial, the sample size was not calculated based on endpoint hypothesis. However, the sample size requirement

was determined by assessing the minimal number of patients required to provide reliable and non-trivial results. Continuous variables were expressed as the mean±standard deviation (SD), and categorical variables were expressed as frequency and percentages. Comparisons of clinical, angiographic or imaging outcomes of patients were performed using either paired t-test (for normally distributed data) or Wilcoxon signed-rank test (non-normally distributed data). A p-value <0.05 was considered statistically significant.

RESULTS

The trial enrolled 100 patients (116 lesions) with the mean age of 50.13±8.81 years. Among included patients, 30 (27.78%) had diabetes mellitus; 45 (41.67%) had hypertension, and 37 (34.26%) had MI. The majority (51.9%) of the patients were presented with stable angina. The baseline clinical and lesion characteristics and the study flow chart up to three-year follow-up are presented in Table 1 and Figure 2 respectively.

Table-1: Baseline clinical and lesion characteristics of the included patients

Clinical characteristics of the patients	**N = 100**
Age (mean ± SD),Years	50.13±8.81
Male n (%)	77 (77.00)
Smokers, n (%)	18 (18.00)
Diabetes mellitus, n (%)	30 (30.00)
Dyslipidemia, n (%)	14 (14.00)
Hypertension, n (%)	45 (45.00)
Previous Myocardial Infarction (>7 days), n (%)	37 (37.00)
Clinical Presentation, n (%)	
Stable Angina	56 (56.00)

Unstable Angina	37 (37.00)
Silent Ischemia/Asymptomatic	15 (15.00)
Left ventricular ejection fraction, (mean ± SD)	50.61±9.9
Lesion and procedural characteristics	
Total number of lesions	116
Lesion location, n (%)	
Right coronary artery	33 (33.00)
Left anterior descending artery	70 (70.00)
Left circumflex artery	13 (13.00)
Lesion Characteristics (ACC/AHA[1] Classification), n (%)	
Type A	8 (8.00)
Type B1	37 (37.00)
Type B2	65 (65.00)
Type C	6 (6.00)
Lesions per patient, (mean±SD)	1.07±0.35
Device success, (%)	100
Procedure success, (%)	100

Figure-2:

Event	**Screening**	**Procedure**	**Post -Procedure to Hospital Discharge**	**FU 1 1 M**	**FU 2 6 M**	**FU 3 12 M**	**FU 4 24 M**	**FU 5 36 M**
Time (Days)				**1 months ± 14days**	**6 months ± 28 days**	**1 year ± 28 days**	**2 years ± 28 days**	**3 years ±28 days**
Type of contact				**Hospital Visit or telephonic contact**	**Hospital Visit or telephonic contact**	**MSCT subgroup Hospital Visit**	**Hospital Visit or telephonic contact**	**All subjects telephonic or hospital contact**
Inclusion/ exclusion Criteria	X							
Informed Consent	X							
Physical examination	X							
Medical and Cardiac History	X							
Anginal Status	X		X	X	X	X	X	
[1]CBC, Blood chemistry, Lipids	X							
CK, CK-MB	X_2		X_3					
[4]Troponin	X		X_3					
12 lead ECG	X_5		X_6	X_7	X_7	X_7	X_7	
Medication Regimen	X	X	X	X	X	X	X	
Angiography		X	X		X_8		X_8	

Adverse Events and Serious Adverse Event Monitoring		X	X	X	X	X	X	
OCT			X[9]		X[9]		X[9]	
IVUS			X[9]		X[9]		X[9]	
MSCT						X[10]		

Clinical events up to 12-month have been previously reported. At six-month follow-up, one patient died due to aminophyllineinduced anaphylactic shock (non-cardiac death). Hence, the subsequent follow-up has been on 107 patients. Cumulative MACE rate at 12-month follow-up was 0.93% attributed by a single case of ID-TLR. Cumulative MACE rate was found to be 1.87% (n=2/107) at 3year clinical follow-up. None of the patients experienced scaffold thrombosis up to 3-year clinical follow-up. There were three (2.80%) target vessel revascularizations (TVR; non-target lesion) at 3-year clinical follow-up.

Paired QCA evaluation was performed in a selected cohort of patients (n=29) at baseline, post-procedure, 6-month, and 2year. In-scaffold LLL (0.13±0.22mm vs. 0.24±0.34; p=0.10) and in-segment LLL (0.15±0.22mm vs. 0.23±0.32mm; p=0.18) at 2-year did not differ significantly from 6-month measurements. QCA examination revealed one in-segment binary restenosis and one inscaffold restenosis.

Paired analyses for IVUS and OCT were completed in a subset of 10 and 9 patients, respectively. Neointimal coverage of struts was almost complete (99.24±2.27%) with a homogeneous pattern at 2-year. The number of discernible struts decreased from 185.67±43.77 at post-procedure to 87.44±17.26 at 2-year.

CONCLUSION

The first-in-human study device thin-strut scaffold trial demonstrated favorable clinical outcomes in patients with de novo noncomplex coronary lesions at three-year follow-up as evidenced by a low rate of adverse events and the absence of scaffold thrombosis. Moreover, multimodality invasive imaging assessment at 2-year reaffirmed favourable endpoints for safety and efficacy.

Impact on daily practice

Recent large real-world registries randomized controlled trials as well as meta-analysis with first-generation BRS demonstrated increased thrombogenicity and hence safety concerns. Consequently, more information related to long-term safety and efficacy of available BRS especially the second-generation thin-strut BRS is crucial. The present study demonstrated a low rate of adverse events with no scaffold thrombosis up to 3-year and maintained measures of safety and efficacy at multimodality imaging. These results are encouraging for the use of thin-strut scaffold in clinical practice in a selected subgroup of patients till large pivotal and long-term data is available to prove its long-term advantages.

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