Original Research Article

Decoding In-Stent Restenosis: A Single Centered Experience

ABSTRACT

Aim:

The current study aims to investigate the underlying mechanisms contributing to the development of in-stent restenosis (ISR), the effectiveness of various treatment approaches, and the role of advanced imaging techniques in its diagnosis and management. The study focuses on providing comprehensive insights to improve patient care and clinical outcomes in ISR cases.

Study design:

Retrospective observational monocentric study

Place and duration of study:

Apollo Hospitals, Chennai on 50 patients with ISR from April 2022 to October 2023

Methodology:

Patients with prior percutaneous coronary intervention (PCI) presenting with ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), unstable angina, positive stress tests, or revascularization failure in bare metal stent (BMS) or drug eluting stent (DES) were included. Exclusions were coronary artery bypass grafting (CABG), non-drug-coated balloons, left main restenosis, thrombus, or early restenosis within three months. The primary outcome, major adverse cardiovascular events (MACE), was a composite of cardiovascular death, target lesion revascularization (TLR), target vessel revascularization (TVR), and myocardial infarction (MI).

Results:

Analysis of ISR mechanisms showed stent under-expansion in 48% of cases with stent boost . On imaging Neo-intimal hyperplasia was found in 20%, and neoatherosclerosis in 14% of patients. The imaging group had a significant reduction in MACE. Most patients (78%) received DES, while 22% received Drug coated balloon (DCB), with no significant outcome differences between them. Additionally, ticagrelor or prasugrel use in ISR patients significantly reduced event rates.

Conclusion:

Our findings suggest that imaging-guided PCI can significantly reduce the incidence of major adverse cardiac events. Additionally, potent P2Y12 inhibitors like ticagrelor and prasugrel may offer superior outcomes to clopidogrel in ISR patients. While both adequate lesion preparation using ELCA or specialty balloons and understanding the mechanism of ISR using imaging followed by DCB or DES or combining both demonstrated fairly similar outcomes in our study

with a slight inclination towards imaging and ELCA for better long term results, further research and large number of studies is needed to assess their relative efficacy in ISR definitively.

Key words: in-stent restenosis, Imaging guided PCI, Drug eluting stent, Drug coated balloon

Introduction:

In-stent restenosis (ISR) is the most common cause of stent failure.[1] ISR is defined as a previous stent segment with >50% stenosis or up to 5 mm from stent edge. [2] Despite advancements in interventional techniques, such as scoring, cutting, and drug-coated balloons, as well as devices like excimer laser coronary angioplasty (ELCA), rotablation, and intra-vascular lithotripsy (IVL), ISR remains a persistent challenge. Drug eluting balloon (DEB)/ Drug coated balloon (DCB) is a new tool used in the management of ISR. Some studies suggest that DEB is non inferior to drug eluting stents (DES) in ISR.[3] Imaging plays a vital role in understanding the mechanics of ISR. The current study aims at understanding the mechanics, device synergy, treatment approach, role of imaging and long term results in patients with ISR.

Methodology:

This study was a retrospective observational monocentric study conducted at Apollo Hospitals, Chennai on 50 patients with ISR from April 2022 to October 2023. One-year follow-up information was collected through outpatient records. Patients with a prior history of percutaneous coronary intervention (PCI) who presented with ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), unstable angina, a positive stress test, or recurrent revascularization failure in either a bare-metal stent (BMS) or drug-eluting stent (DES) were included. Patients with ST-elevation myocardial infarction, those requiring coronary artery bypass graft, lesions treated with non-drug-coated balloons, left main restenosis, or evidence of thrombus were excluded. Early restenosis within 3 months of the index procedure was also excluded. The primary outcome variable was major adverse cardiac and cerebrovascular events (MACCE) which is a composite outcome that includes cardiovascular death, target lesion revascularization (TLR), target vessel revascularization (TVR), and myocardial infarction (MI). Statistical analysis was performed using SPSS (IBM, 28.0). Summary statistics were presented with Mean ± SD and frequency (percentage) for the

continuous and categorical factors respectively. Chi square/Fisher's exact test was used to determine the association between two independent categorical factors. *P*-value <0.05 was considered statistically significant.

Results:

Table 1 represents the demographic characteristics of the patient population, and clinical presentation of patients with ISR. **Table 2** demonstrates imaging and plaque modification devices used in the study. Analysis of ISR mechanisms revealed stent under-expansion in 48% of cases with stent boost. Neo-intimal hyperplasia was identified in 20% of patients and neoatherosclerosis was identified in 14% of individuals on imaging . As depicted in **Table 3,** the imaging group experienced a statistically significant decrease in MACCE. The majority of patients (78%) underwent implantation of a DES, while 22% received a DEB. No significant difference in outcomes was observed between patients treated with DEB and DES. **(Table 4**) Furthermore, the administration of ticagrelor or prasugrel to ISR patients was associated with a significant reduction in event rates. Poor drug compliance after index procedure was also a major contributor for ISR among the patients included in study.

Discussion:

In-stent restenosis refers to the narrowing of a previously stented coronary artery lesion. The reported incidence of ISR is 5% to 10%. [4] One-fourth of patients with ISR clinically present with acute myocardial infarction and the 30-day mortality varies between 10% and 25%.[5-8] In our study, 14 patients (28%) with previous history of PCI presented with acute MI. Exaggerated hemostatic healing of the arterial wall after stent implantation can lead to neointimal hyperplasia.[5] In-stent neoatherosclerosis (FIGURE-1)is characterised by the accumulation of foamy macrophages, necrotic core formation and calcification of intima at the site of stent implantation (in-stent or within 5 mm of stent edge). [9] It is a chronic process. Our analysis revealed the incidence of neointimal hyperplasia as 20%, and that of neoatherosclerosis as 14%. The primary cause for ISR was stent under expansion which was evident by stent boost and Imaging (IVUS/OCT). The utilization of imaging during index PCI could have facilitated the identification and correction of stent under-expansion, potentially leading to a reduction in the incidence of ISR. The incidence of MACCE was lower in patients who underwent imaging-guided PCI. Imaging modalities such as intravascular ultrasound (IVUS) (FIGURE-2) and optical coherence tomography (OCT) (FIGURE-1) have significantly improved the precision and efficacy of PCI. It is therefore recommended that all patients with ISR subsequently undergo

imaging-guided PCI. Ongoing randomized controlled trials are expected to further elucidate the role of OCT and IVUS imaging in optimizing therapy and improving outcomes in ISR. [10-11]

Our study suggests that potent P2Y12 inhibitors like ticagrelor and prasugrel may be a better choice than clopidogrel for ISR patients along with good compliance from patient and pre discharge counselling, regular outpatient follow ups.. This is supported by the higher MACCE rate observed in the clopidogrel group (4 out of 7 patients). Furthermore, results of the meta-analysis by Chen W et al. aligns with our findings, demonstrating the superiority of ticagrelor and prasugrel over clopidogrel in preventing ST-segment elevation ISR. [12]

Additionally, our study highlights the potential benefits of device synergy. Using two or more devices (Specialty balloons like OPN-NC balloons, cutting balloons and ELCA) for adequate plaque modification and lesion preparation in 10 patients resulted in a lower MACCE rate (only 2 events). These findings warrant further investigation.

This study was retrospective in nature and included a relatively small number of patients. Complete data regarding previous PCI procedures was not available for many participants. In cases where OCT/IVUS imaging was not performed, stent boosting was used to analyse the underlying mechanism of ISR. These factors could potentially limit the generalizability of our findings.

Conclusions:

Our findings suggest that imaging-guided PCI can significantly reduce the incidence of major adverse cardiac events. Additionally, potent P2Y12 inhibitors like ticagrelor and prasugrel may offer superior outcomes to clopidogrel in ISR patients. While both adequate lesion preparation using ELCA or specialty balloons and understanding the mechanism of ISR using imaging (IVUS/OCT/Both) followed by drug-eluting balloons (DEBs) or drug-eluting stents (DES) or combining both demonstrated fairly similar outcomes in our study with a slight inclination towards imaging and ELCA for better long term results, further research and large number of studies is needed to assess their relative efficacy in ISR definitively.

Ethical approval

Ethical clearance was obtained from the Institutional Review Board for the conduct of the study. [AMH-C-S-080/08-24]

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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1.

2.

3.

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Table 1: Demographic characteristic of the study population and clinical presentation

Parameters	(n=50), n (%)
Age in years	
Mean ± SD	62.7 ± 9.8
Gender	
Male	46 (92)
Female	4 (8)
Presentation	
STEMI	6 (12)
NSTEMI	8 (16)
USAP	28 (56)
CCS	8 (16)
Comorbidities	
DM	31 (62)
HTN	33 (66)
Dyslipidemia	22 (44)
COPD	9 (18)

CKD	6 (12)
Smoking habit Yes	9 (18)

SD: Standard deviation, STEMI: ST elevation myocardial infarction, NSTEMI: Non-ST elevation myocardial infarction, USAP: Unstable angina pectoris, CCS: Chronic coronary syndrome, DM: Diabetes mellitus, HTN: Hypertension, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease

Table 2: Clinical variables and Outcomes

Parameters	(n=50), n (%)
LVEF (%)	
Mean ± SD	51.6 ± 9.9
Angiographic Block (%)	
Mean ± SD	92.9 ± 5.3
Range	80 – 100
Imaging	26 (52)
Type of Imaging (In patients who underwent imaging)	
Optical Coherence Tomography	21 (42)
Intravascular ultrasound	5 (10)
Calcium management (FIGURE-3)	
Excimer laser coronary angioplasty	23 (46)
Rotablation	1 (2)
OPN*	6 (12)
Cutting of Balloon	14 (28)
No. of Devices used	
0	17 (34)
1	23 (46)
2	9 (18)
3	1 (2)
Drug eluting stent	39 (78)
Drug Eluting Balloon	11 (22)
P2Y12 Inhibitor	
Clopidogrel	7 (14)
Prasugrel	8 (16)
Ticagrelor	35 (70)
1-year MACCE	11 (22)

***OPN – NON COMPLIANT BALLOON**

Table 3: Association between clinical factors and MACCE at 1 year

Parameters	MACCE at 1 year		Overall, (n=50)	*P*-value*
	No, (n=39)	Yes, (n=11)		
Imaging				
Yes	24 (61.5)	2 (18.2)	26 (52)	**0.016**
No	15 (38.5)	9 (81.8)	24 (48)	
Type of imaging				
None	15 (38.5)	9 (81.8)	24 (48)	**0.036**

OCT	19 (48.7)	2 (18.2)	21 (42)	
IVUS	5 (12.8)	-	5 (10)	
DES**				
Not used	8 (20.5)	3 (27.3)	11 (22)	0.688
Used	31 (79.5)	8 (72.7)	39 (78)	
DEB***				
Not used	31 (79.5)	8 (72.7)	39 (78)	0.688
Used	8 (20.5)	3 (27.3)	11 (22)	
P2Y12 Inhibitor				
Clopidogrel	3 (7.7)	4 (36.4)	7 (14)	**0.043**
Prasugrel	6 (15.4)	2 (18.2)	8 (16)	
Ticagrelor	30 (76.9)	5 (45.5)	35 (70)	
P2Y12 Inhibitor				
Clopidogrel	3 (7.7)	4 (36.4)	7 (14)	**0.034**
Prasugrel & Ticagrelor	36 (92.3)	7 (63.6)	43 (86)	
No. of devices used				
0	13 (33.3)	4 (36.4)	17 (34)	
1	18 (46.2)	5 (45.5)	23 (46)	0.959
2	7 (17.9)	2 (18.2)	9 (18)	
3	1 (2.6)	-	1 (2)	
Device synergy				
No	31 (79.5)	9 (81.8)	40 (80)	>0.99
Yes	8 (20.5)	2 (18.2)	10 (20)	

*- Chi square/Fisher's exact test

** DES – THRID GENERATION FDA APPROVED DES WERE USED

*** DEB/DCB- SIROLIMUS OR PACLITAXEL COATED FDA APPROVED BALLOONS WERE USED

*OCT: Optical Coherence Tomography, IVUS: Intravascular * Ultrasound*

Table 4: Association between DES and DEB according to MACCE at 1 year

MACCE at 1 year	DES	DEB, n (%)		*P*-value
		Not used	Used	
No, (n=39)	Not used Used	- 31 (100)	8 (100) -	**<0.001**
Yes, (n=11)	Not used Used	- 8 (100)	3 (100) -	**0.006**
Overall, (n=50)	Not used Used	- 39 (100)	11 (100) -	**<0.001**

DES: Drug eluting stent, DEB: Drug eluting balloon

FIGURE -1 OCT IMAGES DEMONSTRATING NEOATHERESCLEROSIS, NEOINTIMAL HYPERPLASIA, PERISTENT CALCIUM & STENT UNDEREXPANSION

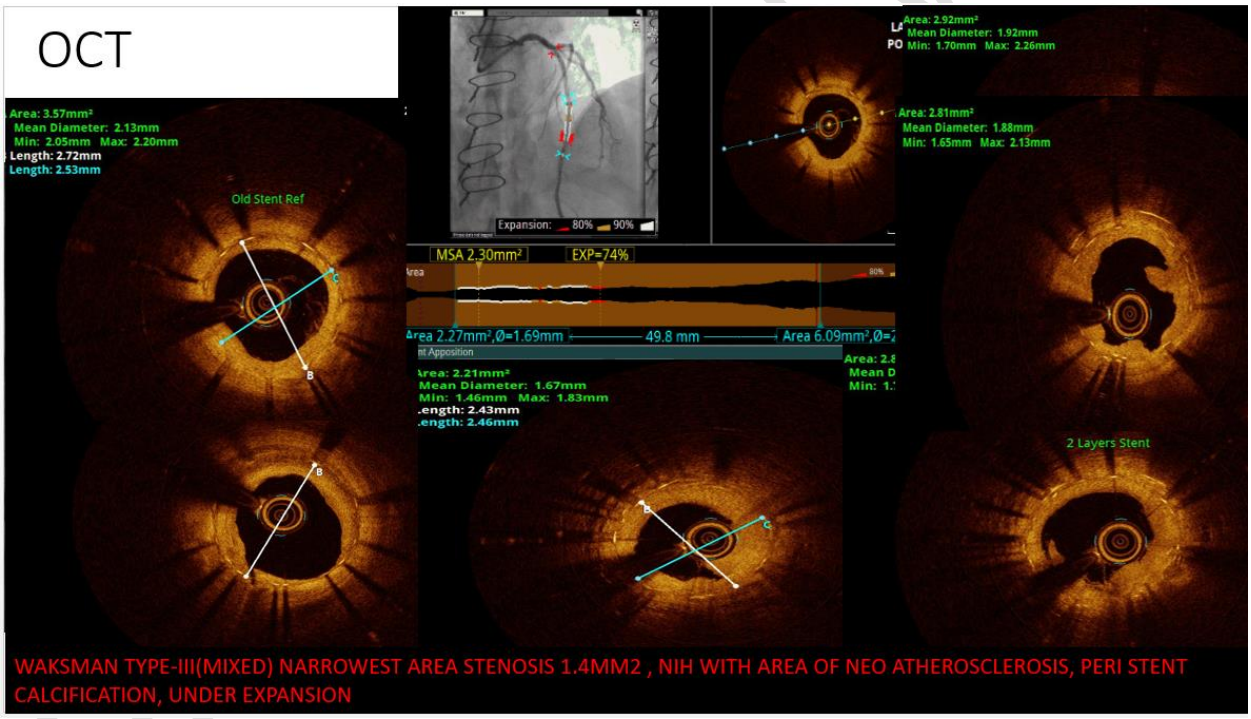


FIGURE -2 IMAGE SHOWING CINE ANGIOGRAM & INTRA VASCULAR ULTRA SOUND (IVUS) POST STENT DEPLOYMENT IN A CASE OF ISR FOR FINAL OPTIMAL RESULTS

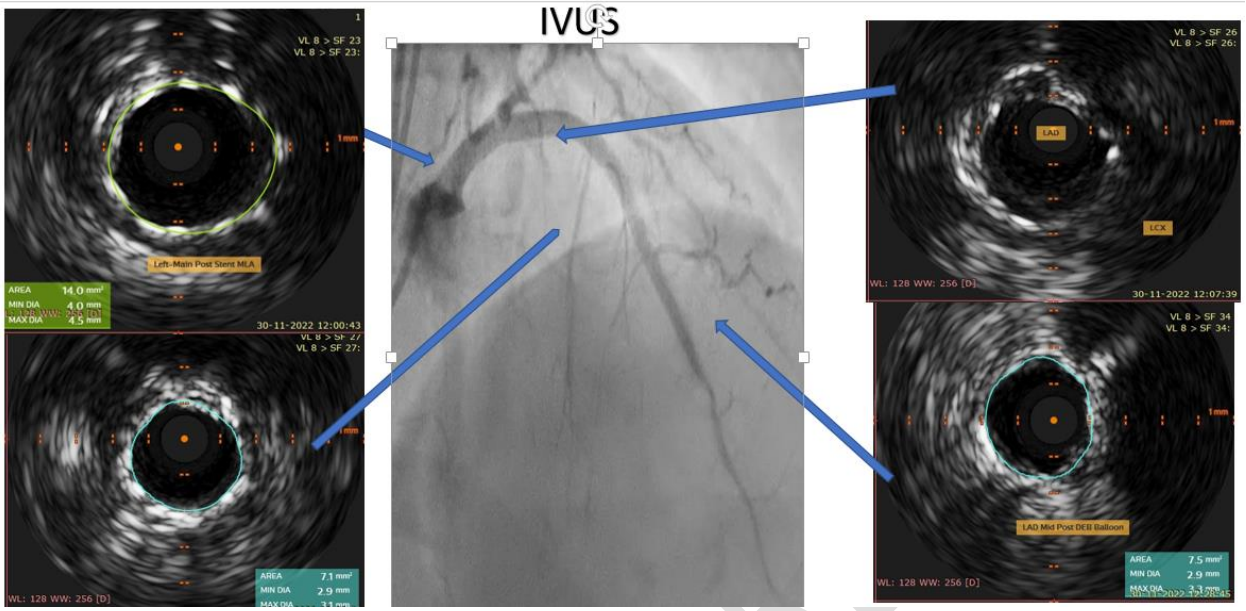
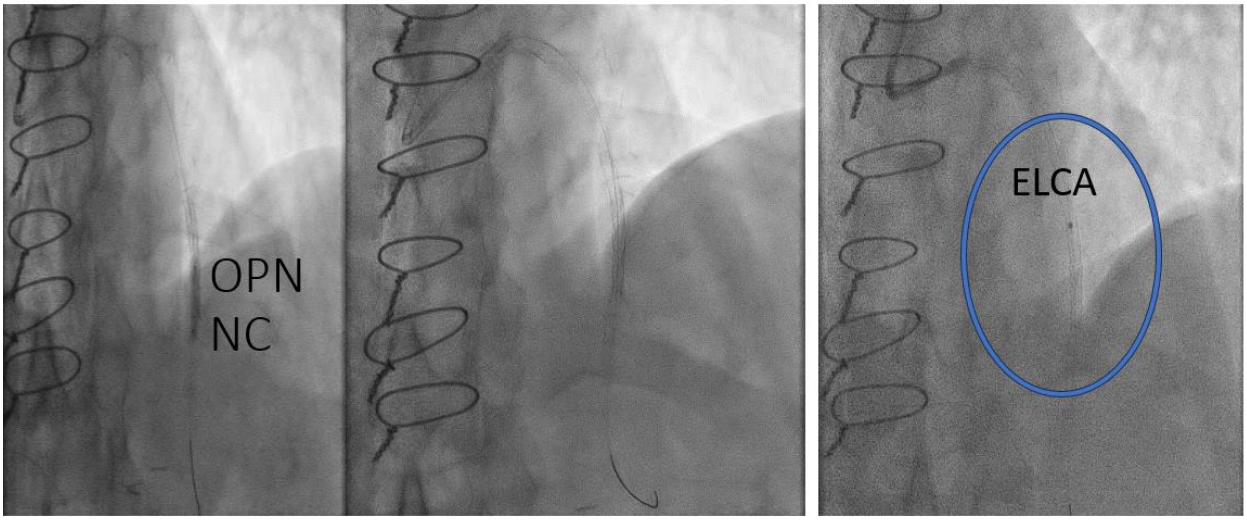


FIGURE -3 IMAGE SHOWS USE OF SPECIALITY BALLOONS OPN-NC & ELCA-EXCIMER LASER CORONARY ANGIOPLASTY FOR ADEQUATE PLAQUE MODIFICATION ,STENT EXPANSION & LESION PREPERATION



ABBEREVATIONS

- *BMS BARE METAL STENT*
- *CCS: CHRONIC CORONARY SYNDROME*
- *COPD: CHRONIC OBSTRUCTIVE PULMONARY DISEASE*
- *CKD: CHRONIC KIDNEY DISEASE*
- *DES: DRUG ELUTING STENT*
- *DEB: DRUG ELUTING BALLOON*
- *DM: DIABETES MELLITUS*
- *HTN: HYPERTENSION*
- *ELCA : EXCIMER LASER CORONARY ANGIOPLASTY*
- *IVL: INTRA-VASCULAR LITHOTRIPSY*
- *ISR : IN-STENT RESTENOSIS*
- *IVUS: INTRAVASCULAR ULTRASOUND*
- *MACE : MAJOR ADVERSE CARDIOVASCULAR EVENTS*
- *MACCE: MAJOR ADVERSE CADIAC AND CARDIOVASCULAR EVENTS*
- *MI: MYOCARDIAL INFARCTION*
- *NSTEMI: NON-ST ELEVATION MYOCARDIAL INFARCTION*
- *P2Y12 :POTENT PURINERGIC RECEPTOR TYPE Y SUBTYPE12*
- *OCT: OPTICAL COHERENCE TOMOGRAPHY*
- *SD: STANDARD DEVIATION*
- *STEMI: ST ELEVATION MYOCARDIAL INFARCTION*
- *TLR: TARGET LESION REVASCULARIZATION*
- *TVR: TARGET VESSEL REVASCULARIZATION*
- *USAP: UNSTABLE ANGINA PECTORIS,*