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# In-stent restenosis characteristics and repeat stenting underexpansion: insights from optical coherence tomography

**Dong Yin**[1,2,3], MD; Gary S. Mintz[1], MD; Lei Song[1,2,3], MD; Zhaoyang Chen[1,2,4], MD; Tetsumin Lee[1,2], MD; Ajay J. Kirtane[1,2], MD, SM; Manish A. Parikh[1,2], MD; Jeffrey W. Moses[1,2,5], MD; Khady N. Fall[2], MD, MPH; Allen Jeremias[1,5], MD, MSc; Ziad A. Ali[1,2,5], MD, DPhil; Richard A. Shlofmitz[5], MD; Akiko Maehara[1,2]*, MD

*1. Clinical Trials Center, Cardiovascular Research Foundation, New York, NY, USA; 2. NewYork-Presbyterian Hospital/Columbia University Irving Medical Center, New York, NY, USA; 3. National Center for Cardiovascular Diseases, China Peking Union Medical College, Fuwai Hospital, Beijing, China; 4. Cardiology Department, Union Hospital, Fujian Medical University, Fujian, China; 5. St. Francis Hospital, Roslyn, NY, USA*

*A list of the study collaborators can be found in the Appendix paragraph.*

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**KEYWORDS**

- bare metal stent
- drug-eluting stent
- in-stent restenosis
- optical coherence tomography

## Abstract

**Aims:** The aim of this study was to use optical coherence tomography (OCT) to predict newly implanted stent expansion for treatment of in-stent restenosis (ISR).

**Methods and results:** With OCT guidance, 143 ISR lesions were treated with a new stent. Stent underexpansion was defined as minimum stent area (MSA) <4.5 mm$^2$ and MSA/average of reference lumen area <70%. New stent underexpansion was found in 33 lesions (23%). These had a smaller old stent MSA (4.13 [3.32-4.62] versus 5.18 [4.01-6.38] mm$^2$, p=0.001), and had a higher prevalence of multiple old stent layers (51.5% versus 10.9%, p<0.001) and neointimal or peri-stent calcium (69.7% versus 37.3%, p=0.001) compared to those without new stent underexpansion. Old stent underexpansion, multiple layers of old stent, maximum calcium angle >180°, and maximum calcium thickness >0.5 mm were independently associated with new stent underexpansion. Patients with new stent underexpansion had a higher prevalence of major adverse cardiac events (35.5% vs 14.3%, p=0.009), mainly driven by a higher rate of myocardial infarction and target vessel revascularisation at two years.

**Conclusions:** When re-stenting an ISR lesion, old stent underexpansion, the amount of neointimal or peri-stent calcium, and multiple old stent strut layers are important determinants of new stent underexpansion which is then associated with adverse long-term outcomes.

**Corresponding author: Cardiovascular Research Foundation, 1700 Broadway, 9th Floor, New York, NY 10019, USA. E-mail: amaehara@crf.org*



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## Abbreviations

| | |
|---|---|
| **CSA** | cross-sectional area |
| **DES** | drug-eluting stents |
| **ISR** | in-stent restenosis |
| **MACE** | major adverse cardiac events |
| **MI** | myocardial infarction |
| **MLA** | minimum lumen area |
| **MSA** | minimum stent cross-sectional area |
| **NIH** | neointimal hyperplasia |
| **OCT** | optical coherence tomography |
| **ROC** | receiver operating characteristic |
| **TVR** | target vessel revascularisation |

## Introduction

Although advances in drug-eluting stents (DES) have substantially reduced the risk of coronary in-stent restenosis (ISR) and the need for target lesion revascularisation, ISR persists[1,2]. There are several treatment options for ISR (conventional balloon angioplasty, cutting or scoring balloons, drug-coated balloons, or bypass surgery); however, repeat DES implantation has superior clinical and angiographic outcomes to other treatment strategies[3]. Nevertheless, there are few data which evaluate the morphological predictors of new stent underexpansion when treating an ISR lesion. We hypothesised that the morphological characteristics underlying the ISR lesion, i.e., neoatherosclerotic or peri-stent calcium, would impact on the expansion of a newly implanted stent and that these morphologic characteristics could be evaluated with optical coherence tomography (OCT).

## Methods

### PATIENT POPULATION

This was a retrospective, observational study to assess morphological factors that contributed to new stent underexpansion when treating ISR lesions using OCT guidance at two hospitals (New York-Presbyterian Hospital, New York, NY, USA; St. Francis Hospital, Roslyn, NY, USA). The indication of treatment (symptoms and/or evidence of ischaemia) and treatment strategy were at each operator's discretion. Patients with pre-OCT and final (post new stent implantation) OCT evaluation were enrolled. The research protocol was approved by the ethics committee of each hospital. Clinical follow-up was performed by hospital chart review, outpatient clinic visit, or telephone contact. Major adverse cardiac events (MACE) were a composite of all-cause death, myocardial infarction (MI), or clinically driven target vessel revascularisation (TVR).

Coronary angiograms were analysed by an interventional cardiologist (D. Yin) at the Cardiovascular Research Foundation (New York, NY, USA) using QAngio XA version 7.2 (Medis medical imaging systems, Leiden, the Netherlands) using conventional methods[4]. Angiographic restenosis was classified as: (i) focal ISR (<10 mm in length); (ii) diffuse ISR (>10 mm length, but within the stent); (iii) proliferative (>10 mm in length, extending beyond the stent edges); and (iv) total occlusion[5].

### OCT IMAGING AND ANALYSIS

Pre-intervention, an OCT catheter (C7 Dragonfly™ or Dragonfly™ Duo; Abbott Vascular, Santa Clara, CA, USA) was introduced distal to the lesion, and contrast media was injected via the guiding catheter at 3-4 mL/s during pullback. Pre-OCT predilation with a 1.5-2.0 mm balloon was performed in severe ISR. OCT images were acquired using frequency-domain OCT (C7-XR™, ILUMIEN™, or ILUMIEN™ OPTIS™; Abbott Vascular) with a frame interval of 0.1-0.2 mm[6]. After successful re-stenting, OCT imaging was repeated. Off-line analysis was performed by agreement of two independent cardiologists (D. Yin and A. Maehara) using proprietary software (Abbott Vascular).

All OCT slices were evaluated; stent and intra-stent lumen cross-sectional areas (CSA) were measured at the minimum lumen CSA, minimum stent CSA (MSA), and maximum neointimal hyperplasia (NIH) CSA. Stent CSA was measured by joining strut blooming middle points. If the stent was covered by high signal attenuation tissue, stent CSA was interpolated using proximal and distal slices. Percentage of NIH was calculated as (1–lumen/stent CSA)×100. Proximal and distal reference lumen CSAs were at the slices with the largest lumen CSA within 5 mm proximal and distal to the stent edges, but before significant side branches (>1.5 mm in diameter). Stent expansion was MSA divided by the average of the proximal and distal reference lumen CSA. Stent underexpansion was MSA <4.5 mm$^2$ and stent expansion <70% based on the CLI-OPCI II study[7].

Calcium was a region with a well-delineated border and subcategorised as either within the NIH or native plaque behind the stent **(Figure 1A)**[8]. Maximum calcium angle (sum of angle in each slice) and maximum calcium thickness were measured, and lengths were calculated by the total slice number multiplied by the frame interval. Calcium fracture was defined as complete discontinuity of calcified plaque **(Figure 1B)**. Double old stent layers were two layers of old stent struts within the same OCT frame **(Figure 1C)**. There was no lesion with more than two old stent layers. Tissue protrusion, stent malapposition, and edge dissection were also assessed post re-stenting[9].

### STATISTICAL ANALYSIS

Normally distributed continuous variables were reported as mean and standard deviation and compared using the Student's t-test. Non-normally distributed continuous variables were reported as median with interquartile range and compared using the Mann-Whitney U test. Categorical variables were summarised as counts and percentages and compared using $\chi^2$ statistics or Fisher's exact test. Receiver operating characteristic (ROC) curves were used to determine cut-off values (Youden index) for maximum calcium angle and thickness associated with new stent underexpansion. A multivariable logistic regression model was performed to identify factors associated with new stent underexpansion. Included variables were chosen based on their historical or mechanistic relationship to stent

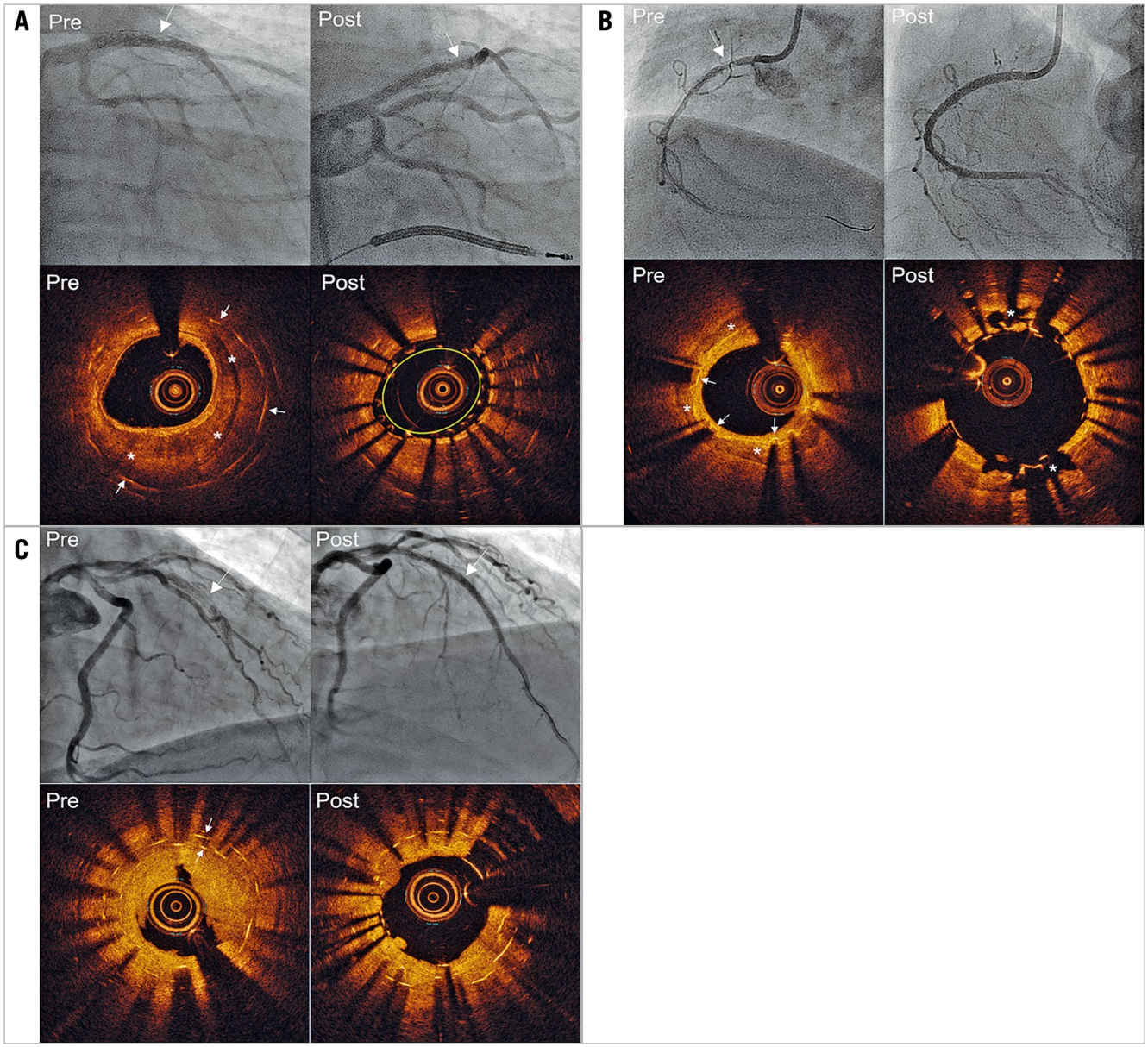


**Figure 1.** *Angiography and optical coherence tomography examples of re-stenting in-stent restenosis lesions. A) Neointimal calcium and re-stent underexpansion. The angiogram shows in-stent restenosis (arrow) in the middle of the left anterior descending coronary artery (LAD), and pre-procedure optical coherence tomography (OCT) shows neointimal calcium (asterisks) within the old stent (arrows) with minimum lumen area (MLA)=1.69 mm$^2$ and minimum stent area (MSA)=4.38 mm$^2$. Post-re-stenting angiogram and OCT show new stent underexpansion (MSA=1.86 mm$^2$, yellow circle). B) Re-stenting with good expansion due to calcium fracture. The angiogram shows in-stent restenosis (arrow) in the proximal right coronary artery, and the pre-procedure OCT shows calcium (asterisks) behind the old stent (arrows) with MLA=2.33 mm$^2$ and MSA=3.07 mm$^2$. Post-re-stenting angiogram and OCT show calcium fracture (asterisks) with MSA=5.04 mm$^2$. C) New stent underexpansion due to two old stent layers. The angiogram shows in-stent restenosis (arrow) in the middle of the LAD, and pre-procedure OCT shows two old stent layers (arrows) with MLA=1.15 mm$^2$ and MSA=3.25 mm$^2$ (inner layer). Post-re-stenting angiogram and OCT show new stent underexpansion with MSA=2.43 mm$^2$.*

underexpansion[10-12]. Time-to-first-event rates are shown as Kaplan-Meier estimates and compared with the log-lank test; $p<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software, Version 22.0 (IBM Corp., Armonk, NY, USA).

## Results

### CLINICAL CHARACTERISTICS

From February 2011 to March 2017, 655 lesions (633 patients) underwent OCT evaluation for ISR: 344 lesions did not have an intervention, 62 were treated by balloon angioplasty only, 13 were

treated with atherectomy, 58 did not have final OCT, 35 lesions had poor OCT quality, leaving 143 ISR lesions (143 patients were enrolled). Duration from implantation was 5.8±4.8 years and was >5 years in 50.7%. Ninety-four had acute coronary symptoms, 30 had stable angina, and 16 had a positive stress test without symptoms. Based on final post-re-stenting OCT measurements, 33 lesions had an MSA <4.5 mm$^2$ and stent expansion <70% and were considered to have new stent underexpansion; the rest comprised the comparison group (n=110) **(Figure 2)**. There were no differences in clinical characteristics between the groups **(Table 1)**.

## PROCEDURAL CHARACTERISTICS AND ANGIOGRAPHIC FINDINGS

Restenotic stents included bare metal stents (12.6%), first-generation DES (30.8%), and second-generation DES (56.6%). Predilation with a scoring balloon or a non-compliant balloon, maximum post-dilation pressure, and balloon/artery ratio were similar between the two groups. All but two ISR lesions were then treated using second-generation DES; new stent diameter (2.75 [2.5-3.0] versus 3.0 [2.75-3.5] mm, p=0.001) and maximum post-dilation balloon diameter (3.0 [2.75-3.38] versus 3.25 [3.0-3.5] mm, p=0.009) were smaller in patients with versus without new stent underexpansion **(Table 2)**. As shown in **Table 3**, angiographic pre-PCI and final post-PCI in-stent dimensions and acute gain were not significantly different between the groups.

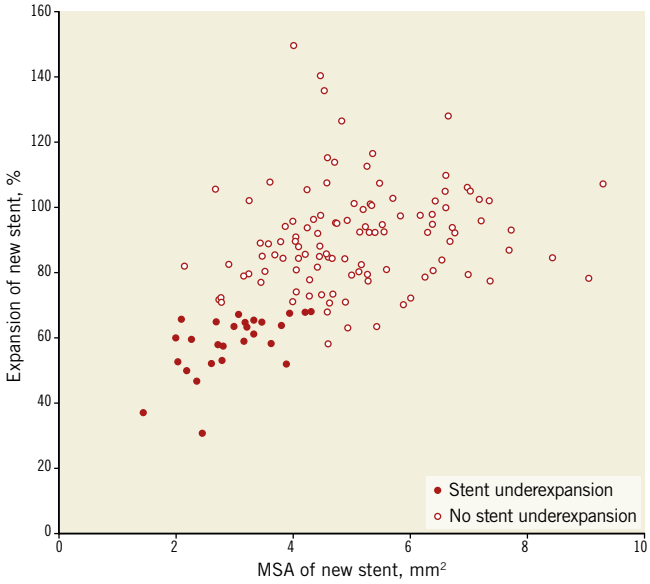


**Figure 2.** *Minimum stent area and expansion of a new stent. A new stent with both a minimum stent area (MSA) <4.5 mm$^2$ and expansion <70% was defined as stent underexpansion.*

## OCT FINDINGS

Based on pre-intervention OCT, old stent underexpansion (old stent MSA <4.5 mm$^2$ and old stent expansion <70%) were identified in 12.6% (18/143), in-stent neoatherosclerosis was identified

**Table 1. Clinical characteristics.**

| | | New stent underexpansion | | *p*-value |
|---|---|---|---|---|
| | | Yes (n=33) | No (n=110) | |
| Time since implantation, years | | 6.3±5.0 | 5.6±4.7 | 0.49 |
| >5 years | | 19 (57.6) | 53 (48.6) | 0.37 |
| Age, years | | 67.5±10.2 | 66.5±11.9 | 0.67 |
| Male | | 20 (60.6) | 75 (68.2) | 0.42 |
| Diabetes mellitus | | 14 (42.4) | 51 (46.4) | 0.69 |
| Insulin-treated | | 4 (12.1) | 20 (18.2) | 0.41 |
| Hypertension | | 29 (87.9) | 97 (88.2) | 1.00 |
| Hyperlipidaemia | | 30 (90.9) | 89 (80.9) | 0.18 |
| Current smoker | | 4 (12.1) | 18 (16.4) | 0.55 |
| Renal insufficiency* | | 3 (9.1) | 16 (14.5) | 0.56 |
| Haemodialysis | | 2 (6.1) | 6 (5.5) | 1.00 |
| Prior myocardial infarction | | 15 (45.5) | 52 (47.3) | 0.85 |
| Prior coronary artery bypass grafting | | 6 (18.2) | 21 (19.1) | 0.91 |
| Clinical presentation | STEMI/NSTEMI | 5 (15.2) | 12 (10.9) | 0.54 |
| | Unstable angina | 19 (57.6) | 58 (52.7) | 0.62 |
| | Stable coronary artery disease | 9 (27.3) | 40 (36.4) | 0.34 |
| LDL cholesterol, mg/dL | | 94±39 | 86±28 | 0.19 |
| Medication at the time of in-stent restenosis | Statin | 28 (84.8) | 100 (90.9) | 0.33 |
| | Aspirin | 30 (90.9) | 99 (90.0) | 1.00 |
| | ACE inhibitor/ARB | 17 (51.5) | 50 (45.5) | 0.54 |

Values are mean±standard deviation or n (%). *Glomerular filtration rate <60 mL/min/1.73 m$^2$ calculated using the Modification of Diet in Renal Disease formula. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; LDL: low-density lipoprotein; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction

**Table 2. Procedural characteristics.**

| | | New stent underexpansion | | *p*-value |
|---|---|---|---|---|
| | | Yes (n=33) | No (n=110) | |
| Restenotic stent type | Bare metal stent | 5 (15.2) | 13 (11.8) | 0.88 |
| | First-generation drug-eluting stent | 10 (30.3) | 34 (30.9) | |
| | Second-generation drug-eluting stent | 18 (54.5) | 63 (57.3) | |
| Predilatation | | 28 (84.8) | 87 (79.1) | 0.62 |
| Non-compliant balloon | | 8 (24.2) | 17 (15.5) | 0.24 |
| Scoring balloon | | 14 (42.4) | 45 (40.9) | 0.88 |
| Maximum predilatation pressure, atm | | 15 (12-19) | 14 (12-18) | 0.70 |
| Mean new stent diameter, mm | | 2.75 (2.50-3.00) | 3.00 (2.75-3.50) | 0.001 |
| Total new stent length, mm | | 23.0 (16.5-38.0) | 22.0 (15.0-33.0) | 0.64 |
| Maximum post-dilation balloon diameter, mm | | 3.00 (2.75-3.38) | 3.25 (3.00-3.50) | 0.009 |
| Maximum post-dilation pressure, atm | | 18 (14-20) | 20 (16-20) | 0.34 |
| Balloon-to-artery ratio* | | 1.18 (1.04-1.42) | 1.30 (1.09-1.44) | 0.22 |

Values are n (%) or median (interquartile range). *Maximum balloon diameter divided by the reference vessel diameter obtained before the procedure.

in 48.3% (69/143), and the rest of the ISR lesions were mainly due to NIH (i.e., no old stent underexpansion, no neoatherosclerosis, 39.2%, 56/143). Lesions with new stent underexpansion had a smaller old stent MSA (4.13 [3.32-4.62] versus 5.18 [4.01-6.38] $mm^2$, p=0.001), and the mechanism of old stent failure was more often underexpansion (39.4% versus 4.5%, p<0.001) **(Table 4)**. The prevalence of a double layer of old stents was higher in lesions with new stent underexpansion (51.5% versus 10.9%, p<0.001). There was no difference in new stent malapposition, stent tissue protrusion, or stent edge dissection between the two groups.

Calcium, including neointimal calcium or calcium in the plaque behind the old stent, was more common in new stent underexpansion (69.7% versus 37.3%, p=0.001) along with a larger angle and greater thickness, especially neointimal calcium **(Table 4)**. Using ROC analysis, the cut-off value to predict new stent underexpansion was maximum calcium angle (either neointimal calcium or calcium behind stent) of 177° (area under the curve [AUC] 0.75, 95% confidence interval [CI]: 0.62-0.88, p=0.001, sensitivity=68%, specificity=78%) and maximum calcium thickness (either neointimal calcium or calcium behind stent) of 0.49 mm (AUC 0.71, 95% CI:

**Table 3. Angiographic findings.**

| | | New stent underexpansion | | *p*-value |
|---|---|---|---|---|
| | | Yes (n=33) | No (n=110) | |
| Target vessel | Left anterior descending | 15 (45.5) | 60 (54.5) | 0.10 |
| | Left circumflex | 11 (33.3) | 18 (16.4) | |
| | Right | 7 (21.2) | 32 (29.1) | |
| Lesion location | Ostial | 1 (3.0) | 5 (4.5) | 0.88 |
| | Proximal | 8 (24.2) | 33 (30.0) | |
| | Middle | 18 (54.5) | 55 (50.0) | |
| | Distal | 6 (18.2) | 17 (15.5) | |
| In-stent restenosis pattern | Focal | 16 (48.5) | 74 (67.3) | 0.05 |
| | Diffuse/proliferative/total occlusion | 17 (51.5) | 36 (32.7) | |
| Pre-percutaneous coronary intervention | Restenosis lesion length, mm | 12.3 (7.2-18.1) | 10.2 (7.4-14.6) | 0.26 |
| | Total old stent length, mm | 26.5 (19.0-35.4) | 27.0 (18.8-37.0) | 0.84 |
| | Reference vessel diameter, mm | 2.44 (2.06-2.85) | 2.56 (2.12-2.93) | 0.47 |
| | Minimum lumen diameter, mm | 1.10 (0.84-1.43) | 1.05 (0.62-1.42) | 0.30 |
| | Diameter stenosis, % | 53.3 (41.5-68.8) | 56.7 (44.4-75.2) | 0.18 |
| Final | Minimum lumen diameter, mm | 2.35 (2.14-2.63) | 2.40 (2.09-2.71) | 0.48 |
| | Diameter stenosis, % | 14.0 (9.9-21.9) | 13.7 (10.0-17.3) | 0.53 |
| | Acute gain, mm | 1.26 (0.88-1.70) | 1.35 (0.98-1.93) | 0.09 |

Values are n (%) or median (interquartile range).

**Table 4. Optical coherence tomography findings.**

| | New stent underexpansion | | *p*-value |
|---|---|---|---|
| | Yes (n=33) | No (n=110) | |
| **Pre-percutaneous coronary intervention** | | | |
| Old stent MSA, mm$^2$ | 4.13 (3.32-4.62) | 5.18 (4.01-6.38) | 0.001 |
| Mean reference lumen CSA, mm$^2$ | 5.26 (4.62-6.14) | 5.08 (4.15-6.08) | 0.50 |
| Old stent expansion, % | 74.0 (56.1-105.3) | 101.0 (82.3-120.6) | 0.001 |
| Old stent underexpansion | 13 (39.4) | 5 (4.5) | <0.001 |
| Minimum lumen CSA, mm$^2$ | 1.62 (1.27-2.13) | 1.81 (1.35-2.26) | 0.21 |
| NIH area, mm$^2$ | 2.49 (1.40-3.56) | 3.37 (2.34-4.72) | 0.003 |
| Max NIH, % | 62.9 (41.9-74.0) | 66.1 (56.2-75.3) | 0.12 |
| Double layers of old stent | 17 (51.5) | 12 (10.9) | <0.001 |
| Presence of neoatherosclerosis | 16 (48.5) | 53 (48.2) | 0.43 |
| Presence of any calcium | 23 (69.7) | 41 (37.3) | 0.001 |
| Maximum calcium angle, ° | 262 (139-326) | 129 (81-170) | 0.001 |
| Maximum calcium thickness, mm | 0.62 (0.50-0.85) | 0.44 (0.39-0.58) | 0.007 |
| Calcium length, mm | 6.3 (2.4-9.8) | 3.0 (1.9-4.7) | 0.01 |
| Calcium in NIH | 11 (33.3) | 21 (19.1) | 0.09 |
| Maximum calcium angle, ° | 311 (196-360) | 129 (102-194) | 0.009 |
| Maximum calcium thickness, mm | 0.72 (0.50-0.94) | 0.47 (0.39-0.66) | 0.01 |
| Calcium length, mm | 9.2 (6.6-10.0) | 3.0 (1.8-4.7) | 0.001 |
| Calcium in native plaque | 13 (39.4) | 21 (19.1) | 0.02 |
| Maximum calcium angle, ° | 183 (108-277) | 122 (77-170) | 0.049 |
| Maximum calcium thickness, mm | 0.60 (0.35-0.70) | 0.43 (0.37-0.47) | 0.18 |
| Calcium length, mm | 2.6 (1.9-6.3) | 2.9 (1.6-5.0) | 0.86 |
| **Final** | | | |
| New stent MSA, mm$^2$ | 3.07 (2.41-3.55) | 4.86 (4.10-6.04) | <0.001 |
| New stent expansion, % | 59.0 (52.4-64.9) | 89.6 (80.0-100.1) | <0.001 |
| Calcium fracture | 2 (8.7) | 6 (14.6) | 0.70 |
| Edge dissection | 12 (36.4) | 31 (29.0) | 0.42 |
| Malapposition | 7 (21.2) | 29 (26.4) | 0.55 |
| Tissue protrusion | 14 (42.4) | 59 (53.6) | 0.26 |

Values are n (%) or median (interquartile range). CSA: cross-sectional area; MSA: minimum stent area; NIH: neointimal hyperplasia

0.56-0.86, p=0.007, sensitivity=81%, specificity=68%), especially when the two co-existed **(Figure 3)**. Calcium fracture post PCI was seen in only 8.7% (2/23 with calcium) in the new stent underexpansion group versus 14.6% (6/41 with calcium) that did not have new stent underexpansion. Among eight cases with calcium fracture post re-stenting, five fractures were in neointimal calcium, and three fractures were in calcium in plaque behind the old stent.

### PREDICTORS OF NEW STENT UNDEREXPANSION

In the multivariable analysis, old stent underexpansion (odds ratio [OR] 6.19, 95% CI: 1.82-7.61, p=0.006), double layers of old stent (OR 8.62, 95% CI: 2.15-13.3, p<0.001), calcium >180° (OR 5.80, 95% CI: 1.76-7.84, p=0.005), and maximum calcium thickness >0.5 mm (OR 4.83, 95% CI: 1.58-6.81, p=0.009) were independently associated with new stent underexpansion when re-stenting an ISR lesion. When different definitions of stent underexpansion were used, predictive factors remained consistent **(Supplementary Table 1)**.

### LONG-TERM OUTCOMES

Patients with new stent underexpansion had a higher prevalence of MACE, mainly driven by a higher rate of MI and TVR compared to no new stent underexpansion **(Table 5, Figure 4)**.

## Discussion

The present OCT study demonstrated that ISR lesions that were associated with old stent underexpansion, significant neointimal or peri-stent calcium (based on thickness and angle), and multiple

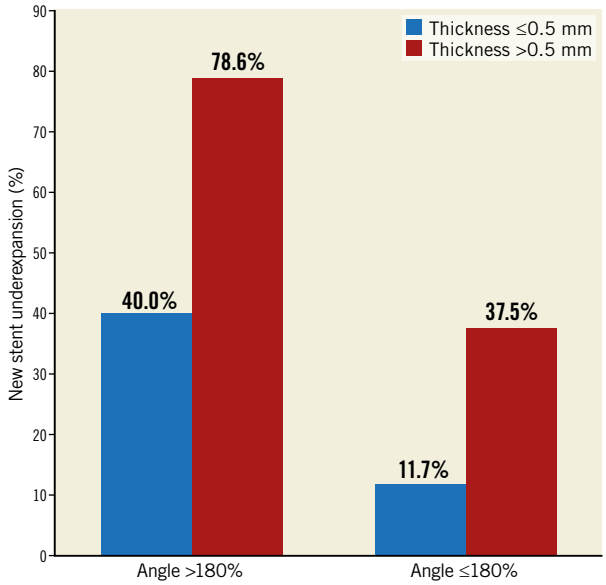


**Figure 3.** *Prevalence of new stent underexpansion in in-stent restenosis lesions stratified by maximum calcium thickness and maximum calcium angle. Calcium angle >180° and calcium thickness >0.5 mm are additive in causing stent underexpansion.*

**Table 5. Clinical outcomes at two years.**

| | New stent underexpansion | | *p*-value |
|---|---|---|---|
| | Yes (n=33) | No (n=110) | |
| Major adverse cardiac events* | 35.5% (11) | 14.3% (14) | 0.009 |
| Death | 3.3% (1) | 1.0% (1) | 0.36 |
| Myocardial infarction | 9.7% (3) | 1.9% (2) | 0.046 |
| Target vessel revascularisation | 32.4% (10) | 13.3% (14) | 0.01 |

Data are shown as Kaplan-Meier estimates (n). *Major adverse cardiac events include death, myocardial infarction, or target vessel revascularisation.

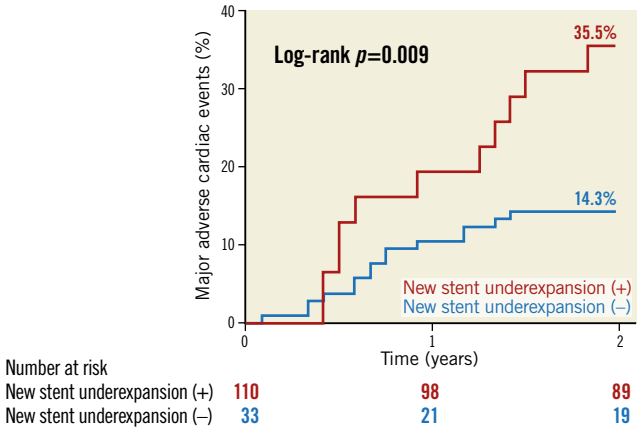


**Figure 4.** *MACE rates between patients with versus without new stent underexpansion. Patients with new stent underexpansion had more than twice the event rate versus those without new stent underexpansion (35.5% versus 14.3%, p=0.009) at two years. MACE: major adverse cardiac events*

layers of old stent struts were associated with new stent underexpansion when re-stenting the ISR lesion and that new stent underexpansion was associated with a higher event rate at follow-up.

Stent underexpansion, a main mechanism of ISR[8], contributed to new stent underexpansion in the present study even when higher pressures or larger balloons were used[13]. An intravascular ultrasound study showed that acute diameter gain decreased with increasing arc of calcification[14]. As expected, it was difficult to expand a new stent within an underexpanded old stent due to calcified plaque.

Severe calcification in *de novo* coronary arteries limits stent expansion[9-13]. Kobayashi et al[10] assessed the relationship between stent expansion and coronary calcification using OCT and demonstrated that a larger arc and area of calcium were associated with significantly worse stent expansion. Fujino et al[11] developed an OCT-based calcium scoring system to predict stent underexpansion: a maximum calcium angle >180°, maximum calcium thickness >0.5 mm, and calcium length >5 mm were risk factors, remarkably similar to the current study cut-offs. Thus, the current study expands our understanding of the effect of calcium on stent underexpansion from *de novo* coronary disease to ISR calcium (i.e., neoatherosclerotic or peri-stent calcium).

In an OCT study by Song et al[15], in-stent neointimal calcium was a dominant pattern of neoatherosclerosis, observed in 60% of ISR with neoatherosclerosis, consistent with our findings and previous autopsy studies[16]. A small OCT study evaluating the impact of neointimal calcification on stent-in-stent ISR treatment showed a trend for a smaller stent area and diameter at the site of neointimal calcification versus proximal to the neointimal calcification[17]. A recent study assessed the prevalence, predictors, and implications of calcified neoatherosclerosis as the cause of ISR; ISR lesions with calcified neoatherosclerosis were associated with poorer angiographic and OCT results[18].

We observed calcium fracture post re-stenting in six (14.6%) cases with good new stent expansion similar to *de novo* stenting[19]. Excimer laser coronary angioplasty or lithotripsy could disrupt calcium to facilitate full stent expansion, especially when treating an ISR lesion with a new stent[20,21].

Repeat stenting of a recurrent ISR lesion is associated with chronic stent underexpansion and a high rate of adverse events[22]. Stent-in-stent DES treatment of ISR is associated with recurrent restenosis rates between 20% and 40%[12]. In another OCT study[20], one third of ISR cases had multiple old stent layers associated with new stent underexpansion. A small study reported 11 recurrent ISR with two or three layers of metal after treatment using a drug-coated balloon with 13% MACE over 38 months[23]. Thus, although three meta-analyses have demonstrated that re-stenting should be the preferred treatment[3,24,25], a drug-coated balloon should be considered when there are more than two layers of old stents unless calcium modification is used before re-stenting. However, a recent study showed that a drug-coated balloon was also less effective for ISR lesions with more than three stent layers[26]. Hence, multiple metallic layers should be avoided, if possible. Finally, when re-stenting an ISR lesion, it is important to optimise the ISR

treatment just as it is important to optimise *de novo* stent implantation because new stent underexpansion is associated with a higher rate of events, as is *de novo* stent underexpansion.

## Limitations

This was a retrospective observational study in which we included only patients with pre- and post-re-stenting OCT. Second, >50% presented beyond five years from stent implantation, which may not be representative of daily practice. Third, there were no angiographic or OCT images of the original stent implantation. Fourth, only 50% of restenotic stents were newer-generation DES.

## Conclusions

When re-stenting an ISR lesion, old stent underexpansion, the amount of calcium, whether within the neointima or in peri-stent plaque, and multiple layers of old stent struts may be important determinants of new stent underexpansion which, in turn, may increase long-term events.

## Impact on daily practice

When re-stenting an ISR lesion, old stent underexpansion, the amount of coronary calcium, whether within the neointima or in peri-stent plaque, and multiple layers of old stent struts are important determinants of new stent underexpansion. New stent underexpansion is associated with adverse long-term outcome, and optimisation of ISR treatment is as important as *de novo* stent implantation.

## Appendix. Study collaborators

Fernando A. Sosa, MS, MBA; *Abbott Vascular, Santa Clara, CA, USA*. Elizabeth S. Haag, RN; *St. Francis Hospital, Roslyn, NY, USA*.

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## Conflict of interest statement

D. Yin reports grants from Boston Scientific during the conduct of the study. Z. Chen reports grants from Boston Scientific during the conduct of the study. A. Kirtane reports grants from Medtronic, Abbott Vascular, Boston Scientific, Abiomed, CathWorks, Siemens, Philips, ReCor Medical, and Spectranetics, outside the submitted work. M. Parikh reports personal fees from Abbott Vascular, personal fees from Medtronic, Boston Scientific, CDI, and Corsica, outside the submitted work. A. Jeremias reports a grant and personal fees from Abbott, outside the submitted work. F. Sosa is an employee of Abbott Vascular. Z. Ali reports grants and personal fees from Abbott, Medtronic, and Cardiovascular Systems Inc., other from Shockwave, and personal fees from Boston Scientific and Cardinal Health, outside the submitted work. A. Maehara reports institutional grants from Boston Scientific and Abbott Vascular. The other authors have no conflicts of interest to declare.

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## Supplementary data

**Supplementary Table 1.** Predictors of new stent underexpansion using different definitions of stent underexpansion.

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**Supplementary data**

**Supplementary Table 1. Predictors of new stent underexpansion using different definitions of stent underexpansion.**

Definition: MSA <4.5 $mm^2$ and stent expansion <70%

| **Predictive variables** | **Odds ratio (95% CI)** | ***p*-value** |
|---|---|---|
| Old stent underexpansion | 6.19 (1.82-7.61) | 0.006 |
| Double layers of old stent | 8.62 (2.15-13.30) | <0.001 |
| Maximum calcium arc $>180^0$ | 5.80 (1.76-7.84) | 0.005 |
| Maximum calcium thickness >0.5 mm | 4.83 (1.58–6.81) | 0.009 |

Definition: MSA <5.0 $mm^2$ and stent expansion <70%

| **Predictive variables** | **Odds ratio (95% CI)** | ***p*-value** |
|---|---|---|
| Old stent underexpansion | 5.45 (1.70-6.76) | 0.009 |
| Double layers of old stent | 6.03 (1.80-10.61) | 0.001 |
| Maximum calcium arc $>180^0$ | 6.48 (1.87-9.71) | 0.002 |
| Maximum calcium thickness >0.5 mm | 3.27 (1.19-4.30) | 0.04 |

Definition: MSA <4.0 $mm^2$ and stent expansion <70%

| **Predictive variables** | **Odds ratio (95% CI)** | ***p*-value** |
|---|---|---|
| Old stent underexpansion | 5.52 (1.71-6.65) | 0.01 |
| Double layers of old stent | 13.07 (2.57-14.47) | <0.001 |
| Maximum calcium arc $>180^0$ | 5.56 (1.72-6.55) | 0.01 |
| Maximum calcium thickness >0.5 mm | 9.43 (2.24-11.04) | 0.001 |

CI: confidence interval; MSA: minimum stent area