In-stent Restenosis

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KEYWORDS

• Percutaneous coronary intervention • In-stent restenosis • Neointimal hyperplasia
• Target vessel revascularization • Target lesion revascularization

KEY POINTS

- In-stent restenosis (ISR) typically presents as recurrent angina, but can also present as a myocardial infarction in some patients. ISR typically presents 6 to 12 months after percutaneous coronary intervention.
- Patient characteristics associated with ISR include age, female gender, diabetes, chronic kidney disease, and multivessel coronary artery disease. Lesion characteristics associated with ISR include smaller reference artery diameter, ostial lesion, and initial plaque burden.
- Anatomic assessment of ISR with intravascular imaging provides insight into the cause of ISR and true vessel sizing for appropriate stent size. Hemodynamic assessment with fractional flow reserve (FFR) is valuable to evaluate for functional ischemia because there is a poor correlation with estimated percent diameter stenosis and FFR in patients with diffuse restenosis.
- Treatment of ISR with drug-eluting stents has been shown to be superior to balloon angioplasty alone.
- Brachytherapy, excimer laser angioplasty, and routine angiographic surveillance are not recommended treatment and diagnostic options.

INTRODUCTION

In-stent restenosis (ISR) is the gradual renarrowing of a stented coronary artery lesion from arterial damage with subsequent neointimal tissue proliferation.[1] Binary angiographic restenosis is defined as greater than 50% luminal narrowing at follow-up angiography (**Figs. 1** and **2**). Clinical restenosis is defined as greater than 50% diameter stenosis and one of the following: positive history of recurrent angina, objective signs of ischemia (eg, electrocardiogram [ECG] changes), fractional flow reserve (FFR) less than 0.80, intravascular ultrasonography (IVUS) minimum cross-sectional area less than 4 mm^2 (<6 mm^2 for left main), or restenosis (>70% reduction in lumen diameter) even in the absence of clinical symptoms or signs (**Box 1**). Clinical restenosis is a requirement for target lesion revascularization (TLR). The Mehran system is a morphologic classification of ISR lesions: Pattern I includes focal ($\leq$10 mm in length) lesions, pattern II is ISR greater than 10 mm within the stent, pattern III includes ISR greater than 10 mm extending outside the stent, and pattern IV is totally occluded ISR. This classification system can predict the need for repeat revascularization after intervention (19%, 35%, 50%, and 98%, respectively).[2]

CLINICAL PRESENTATION

The mean time from percutaneous coronary intervention (PCI) with drug-eluting stents (DESs) to ISR was 12 months.[3] In bare-metal stents (BMSs), ISR was reported an average of 6 months post-PCI.[4] ISR typically presents as recurrent angina 25% to 50% of the time, but also presents as myocardial infarction (MI) in approximately 3.5% to 20% of patients.[1,3,5,6] In

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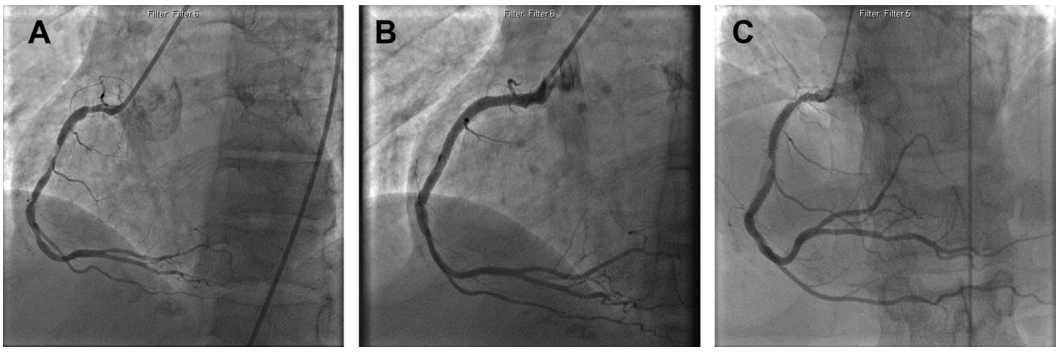

Fig. 1. (*A*) A 40-year-old man with history of lupus, end-stage renal disease secondary to lupus nephritis, and hypertension presented with stable angina. He was found to have a proximal right coronary artery (RCA) 45% lesion followed by a long eccentric 90% RCA lesion. (*B*) Percutaneous coronary intervention (PCI) of the proximal RCA with a 3.5 × 15 mm Xience Xpedition drug eluting stent and PCI of the mid RCA with a 3.0 × 38 mm Promus Premier drug eluting stent. (*C*) The patient presented 1 year later with chest pain and repeat angiogram showed severe ISR of the RCA stents. The patient also had coronary artery disease in the left anterior descending artery and was referred for coronary artery bypass surgery.

contrast, stent thrombosis is an abrupt thrombotic occlusion that presents as either MI or sudden cardiac death.[7]

It is also possible for neointimal hyperplasia plus focal thrombosis to be present inside the stent. Factors that are more suggestive of ISR, as opposed to thrombosis, are longer time from implantation, absence of angiographic factors such as thrombus, length of stent, IVUS findings showing neointimal hyperplasia, and findings during catheterization such as balloon slippage associated with hard neointimal tissue from ISR, in contrast with soft thrombi.[1]

INCIDENCE

Rates of ISR with DESs range from 3% to 20%. In the j-Cypher registry of 12,812 patients who received sirolimus-eluting stents (SESs), the TLR rate was 7.3% at 1 year, after which the rate was ~2.2% per year, and 15.9% at 5 years. The stent thrombosis rate was 0.3% at 30 days, 0.6% at 1 year, and 1.6% at 5 years (very late stent thrombosis continued to occur up 5 years after implantation).[8] In the Endeavor IV trial, 1548 patients were randomized to zotarolimus-eluting stent (ZES) or paclitaxel-eluting stent (PES).[9] At 3 years, rates of ischemia-driven TLR were similar. However, the rate of very late stent thrombosis (1–3 years) was significantly lower in ZES patients (0.1% vs 1.6%; hazard ratio [HR], 0.09; confidence interval [CI], 0.01–0.71; $P = .004$). In the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) LATE study study, 1012 patients were randomly assigned to SES or PES. Of 444 patients who had repeat angiography, 5-year rates of TLR were 13.1% and 15.1% respectively ($P = .29$).[10]

The use of DESs has significantly reduced the rate of restenosis and TLR compared with BMSs. A meta-analysis of 38 randomized controlled trials with more than 18,000 patients showed that there was significant reduction in TLR with both SESs and PESs compared with BMSs.[11] SESs were associated with the lowest risk of MI (HR 0.81, 95% CI 0.66-0.97, $P = .030$ vs BMS; HR 0.83, 95% CI 0.71–1.00, $P = .045$ vs PES). The reduction in TLR seen with DES compared with BMS was more pronounced with SES than with PES (HR 0.70; 95% CI, 0.56–0.84; $P = .0021$). Although there was no significant difference in definite stent thrombosis from 0 to 4 years, the risk of late stent thrombosis (>30 days) was increased for PESs.

There is also late catch-up in neointimal hyperplasia in DESs, shown in both first-generation and second-generation stents.[12] BMSs show a late decrease in neointimal hyperplasia. Nevertheless, the overall neointimal hyperplasia is still significantly less in DESs than in BMSs.[12–14]

PREDICTORS OF IN-STENT RESTENOSIS

The predictors of ISR include patient, lesion, and procedural characteristics (Table 1). Patient characteristics associated with ISR include age, female gender, diabetes, chronic kidney disease, and multivessel coronary artery disease.[1,15,16] Lesion characteristics associated with ISR include smaller reference artery diameter, ostial lesion, initial plaque burden, and residual plaque after implantation. In contrast with BMSs, DESs tend