Optimal Approach for Treating In-Stent Restenosis

Customizing therapy in a new era.

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The advent of drug-eluting stents (DESs) has dramatically reduced the incidence of in-stent restenosis (ISR). Angiographic restenosis, defined as a percent diameter stenosis ≥ 50% at follow-up, occurred with an incidence of 20% to 30% with bare-metal stents (BMSs) at 6 months, with a target lesion revascularization (TLR) rate of approximately half of that.[1-3] Of course, the restenosis rates for more complex disease were much higher (50%–60% in bifurcations and saphenous vein grafts).[4,5] Restenosis rates of current second-generation DESs are < 10%[6-8]; however, restenosis can still be a major clinical issue in some patients, as it is associated with an increased risk of myocardial infarction and death.[9,10]

RISK FACTORS FOR RESTENOSIS

There are many predictors of ISR, and they are categorized as patient related, lesion related, and procedure related (Table 1). Stent underexpansion, long stenting, small reference diameter, and residual plaque at the stent edge are all major procedure-related factors of ISR.[11-14] Imaging guidance at the time of treatment for de novo lesions may reduce the occurrence of procedure-related factors, especially when treating complex lesions. Hong et al randomly assigned 1,400 patients with long coronary lesions to either intravascular ultrasound (IVUS)- or angiography-guided percutaneous coronary intervention (PCI) and found that IVUS-guided PCI reduced ischemia-driven TLR (2.5% vs 5.0%; $P = .02$).[15] ISR itself is also a risk factor for ISR[11]; thus, optimized stenting is necessary when treating de novo lesions to avoid reintervention.

CLINICAL APPROACH

Current evidence shows that there is no clinical benefit to routine angiographic follow-up.[16] In most cases, ISR is diagnosed with recurrent cardiac symptoms. In other cases, ischemia may need to be proven by either invasive or noninvasive testing to distinguish the need to perform intervention. Even if there are angiographically significant restenoses, fractional flow reserve for ISR would not be decreased compared to similarly narrowed de novo lesions. One possible reason for this is the morphologic difference between ISR and de novo lesions.[17] Moreover, neither angiography nor IVUS accurately predicts cardiac ischemia.[18] After ischemia is proven, either by symptomatology or precatheterization testing, the next step is to decide how to treat the lesion. We have many options: conventional balloon angioplasty, cutting or scoring balloon angioplasty,

TABLE 1. RISK FACTORS FOR RESTENOSIS

Patient-related factors	• Diabetes mellitus • Chronic renal failure • Resistance to stent drug • Hypersensitivity to stent components
Lesion-related factors	• Chronic occlusion • In-stent restenosis • Stent fracture • Bifurcation • Ostial lesion • Small vessel diameter • Long lesion • Severe calcification • Saphenous vein graft
Procedure-related factors	• Stent underexpansion • Long stenting • Small reference diameter • Residual plaque at the stent edge

rotational atherectomy, excimer laser coronary atherectomy (ELCA), balloon angioplasty with a drug-coated balloon (DCB), DES implantation, vascular brachytherapy, bypass surgery, and/or any combination of these.

HISTORY OF TREATING ISR

During most of the BMS era, ISR was mostly treated with conventional balloon angioplasty or repeated BMS implantation. Recurrent event rates after balloon angioplasty were approximately 20% by 1 to 2 years.[19] The RIBS trial compared BMS implantation and balloon angioplasty and randomized 450 patients with BMS-ISR to either group. After 4 years of follow-up, target vessel revascularization (TVR) was as high as 25% and 29% ($P = .35$) and the major adverse cardiac event (MACE) rate was 31% and 37% for the BMS implantation and balloon angioplasty groups, respectively.[20,21] Cutting balloon angioplasty was expected to reduce TLR, and initial observational studies showed promising results, but a randomized trial of 482 patients did not detect a clinical advantage of using cutting balloon compared with balloon angioplasty.[22,23] Rotational atherectomy and ELCA have not showed any major advantage in treating BMS-ISR.[24,25] Brachytherapy showed the most promising outcomes and was the standard therapy for ISR in the later BMS era.[26,27]

Currently, BMSs have been replaced by DESs, and BMSs are only used in specific situations (eg, patients with extremely high bleeding risk, necessity of short duration of antiplatelet therapy, economic reasons). As a result, BMS-ISR is now less common, but if encountered, DCB or DES implantation should be the first choice. The RIBS V trial randomized 189 BMS-ISR patients either an everolimus-eluting stent (EES) or a DCB arm. Both groups showed acceptable outcomes in terms of binary restenosis (4.7% vs 9.5%; $P = .22$) and TVR (2% vs 6%; $P = .17$).[28]

Importantly, there is a fundamental morphologic difference between BMS-ISR and DES-ISR. BMS-ISR tends to exhibit a diffuse pattern (> 10 mm), whereas DES-ISR tends to be focal.[29] The recurrent restenosis rate in BMS was > 60% when diffuse ISR was treated with balloon angioplasty.[30]

DES-ISR

What is the best treatment for DES-ISR? Siontis et al reported the results of a meta-analysis of 27 randomized controlled trials comparing the use of conventional balloon angioplasty, BMS, DCB, sirolimus-eluting stent, paclitaxel-eluting stent, EES, vascular brachytherapy, and rotational atherectomy. They found that EES was the most effective strategy for treating ISR, with the lowest risk of restenosis and repeat revascularization. DCB ranked second, with a difference of 9% in percent diameter stenosis.[31] The recent DARE trial randomized 278 patients (56% had DES-ISR) to either a DCB or EES treatment group. The primary endpoint of in-segment minimal luminal diameter at 6 months (1.71 vs 1.74 mm; P for noninferiority < .0001) and secondary endpoint of TVR at 12 months (8.8% vs 7.1%; $P = .65$) were similar in both groups.[32] Second-generation DESs perform similarly; therefore, any current DES may be reasonable for treating DES-ISR. In the RESTENT-ISR trial, 304 DES-ISR patients were randomly assigned to undergo either EES or zotarolimus-eluting stent therapy. The 9-month angiographic and IVUS follow-up showed no significant differences in late lumen loss (0.40 vs 0.45 mm; $P = .57$) and neointimal volume. Three-year MACE rates were comparable between the two groups (15.8% vs 22.6%; $P = .28$).[33]

When treating DES-ISR, the use of a DES that releases a different drug may improve outcomes compared with using a DES with the same drug. A meta-analysis of 10 controlled trials and observational studies compared the use of a different drug group and the same drug group. Use of a DES with a different drug reduced the odds of TLR or TVR (odds ratio [OR], 0.73; 95% confidence interval [CI], 0.55–0.96) and MACE (OR, 0.72; 95% CI, 0.54–0.96).[34]

The primary advantage of DCBs is the ability to deliver antiproliferative drugs without leaving another layer of metallic strut, but the main disadvantage is that they do not add any radial force. Therefore, DESs would be preferred if there is any tissue reintrusion or elastic recoil, and DCBs may be preferred if there are two or more layers of previously deployed struts. It could be unfavorable to deploy another layer of metal in an existing lumen that is already restricted by multiple layers of stent.

In general, adequate lesion preparation of a restenotic stent is imperative prior to DCB inflation. Neointimal modification with a scoring or cutting balloon may have possible advantages over standard balloon predilatation. The randomized ISAR-DESIRE 4 clinical trial demonstrated a significantly lower rate of in-segment percentage diameter stenosis on follow-up angiography in the scoring balloon group compared to the standard balloon group (35% vs 40.4%; $P = .047$). TLR at 1 year was lower with the scoring balloon strategy, but the differences did not reach statistical significance (16.2% vs 21.8%; $P = .26$). The investigators speculated that use of a scoring balloon enhanced local tissue drug distribution and improved the efficacy of subsequent DCB use.[35]

Morphologic stratification with optical coherence tomography (OCT) may enhance the potential value of standard balloon dilatation. In a retrospective observational study, Arikawa et al classified DES-ISR into two groups, heterogeneous and homogeneous layered patterns, according to neointimal tissue characteristics as assessed by OCT. Minimal lumen diameter at follow-up angiography was greater in the heterogeneous group (1.01 vs 1.75 mm; *P* = .04). They concluded that the heterogeneous pattern generally consisted of cell-poor tissue and acquired larger acute gain, and this led to a better outcome.[36]

ROTATIONAL ATHERECTOMY

In the BMS era, rotational atherectomy with adjunctive low-pressure ballooning was compared with balloon angioplasty for treatment of BMS-ISR. The ARTIST trial, a multicenter randomized study of 298 patients with diffuse ISR, failed to show a benefit of rotational atherectomy compared with balloon angioplasty in both angiographic and clinical outcomes.[24] Thus, rotational atherectomy was not and is not routinely used for ISR treatment. However, it still may be required in specific cases, such as for lesion preparation with underexpanded stents.

Some case reports have shown successful treatment of ISR that was resistant to use of a noncompliant balloon due to surrounding severe calcification. Rotational atherectomy facilitated stent-calcium complex expansion.[37-39] Because DES-ISR can often be associated with stent underexpansion, adequate lesion modification is critical.[13] Rotational atherectomy and ELCA can facilitate proper stent expansion, even in those noncompliant balloons that failed to expand.

EXCIMER LASER CORONARY ATHERECTOMY

ELCA is a strong alternative for preparation of noncompliant balloon-resistant de novo and ISR lesions. The LARS prospective observational study reported safety and efficacy of ELCA for treatment of BMS-ISR.[40] Mehran et al reported outcomes of consecutive patients with BMS-ISR who underwent either ELCA or rotational atherectomy. ELCA reduced intimal hyperplasia volume less than rotational atherectomy, but 1-year TLR was similar between the two groups (26% vs 28%; *P* = nonsignificant).[41] We previously reported the usefulness of ELCA for DES-ISR treatment. Even though ELCA was used for more complex lesions, ELCA provided a larger acute luminal gain than the non-ELCA group.[42] The underlying mechanisms were visualized by OCT. Pre- and postprocedural OCT images showed that ELCA reduced in-stent neointimal tissue and pulverized surrounding calcium.[43,44]

In current practice, the laser is activated during continuous serum perfusion, as the activation in the presence of a contrast medium will lead to the formation of larger vapor bubbles and may lead to vessel injury with dissection or perforation. Turning this disadvantage into am advantage, a contrast medium has been utilized within the area of underexpanded stents. A case series demonstrated the feasibility of this technique.[45] This contrast-enhanced laser therapy may be considered with caution to avoid serious complications.

VASCULAR BRACHYTHERAPY

For BMS-ISR, vascular brachytherapy demonstrated superiority compared with conventional balloon angioplasty. The START trial randomized 476 patients with BMS-ISR to brachytherapy or placebo. The primary endpoint of clinically driven TVR at 8 months was significantly lower in the brachytherapy arm (17% vs 26.8%; *P* = .02) and remained significant after 2 years.[26,27] Thereafter, two pivotal randomized trials compared first-generation DESs with vascular brachytherapy in patients with BMS-ISR. The SISR trial randomized 384 patients to brachytherapy or sirolimus-eluting stenting. target vessel failure at 9 months was higher in the brachytherapy group (21.6% vs 12.4%; *P* = .02).[46] The TAXUS-V ISR trial assigned 396 patients either brachytherapy or paclitaxel-eluting stent implantation. Similarly, TVR at 9 months was greater in the brachytherapy group (17.5% vs 10.5%; *P* = .046).[47] New concerns about late catch-up, edge restenosis related to geographic miss, and late stent thrombosis related to delayed re-endothelialization were raised.[48-50] Thus, brachytherapy has mostly been removed as first-line therapy for ISR, and there are no further randomized studies planned for brachytherapy as a treatment for ISR.

As mentioned, evidence has shown the clinical benefits of DESs and DCBs for DES-ISR therapy; however, DCBs are unavailable in the United States. In cases in which additional DES therapy is unfavorable, brachytherapy may be considered for recurrent DES-ISR. Negi et al evaluated 186 patients treated with brachytherapy; 95% of patients had more than two episodes of TLR. The incidence of TLR was acceptable, as lesions were highly complex (12.1% at 1 year and 20.7% at 3 years). All patients received dual antiplatelet therapy for a minimum of 12 months, and there was only one patient who had late thrombosis during the 3-year period.[51]

CONCLUSION

Although ISR is much less common now than during the BMS era, it does still occur and can be a challenge to manage. Many cases of ISR in the modern era are focal in nature and can be treated in a simple fashion; however, the optimal approach for treating ISR must be determined on a case-by-case basis. We need to customize the strategy of treating the individual patient with consideration of lesion characteristics, such as proper stent deployment, lesion location, bifurcation, hinge motion, bypass graft, previous stent layer, and vessel size. Intracoronary imaging may suggest the underlying mechanism of ISR, which can also help with clinical decision-making. ■

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