Management of patients with in-stent restenosis (ISR) remains an important clinical problem. Although drug-eluting stents (DES) have drastically reduced the incidence of ISR, treatment of DES-ISR is particularly challenging. ISR mainly results from aggressive neointimal proliferation, but recent data also suggest that neoatherosclerosis may play an important pathophysiological role. Intracoronary imaging provides unique insights to unravel the underlying substrate of ISR and may be used to guide repeated interventions. In this paper, we systematically reviewed clinical trial data with currently available therapeutic modalities, including DES and drug-coated balloons, in patients presenting with ISR within bare-metal stents or DES.}

**Current Treatment of In-Stent Restenosis**

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**Madrid, Spain; and Munich, Germany**

Treatment of patients with in-stent restenosis (ISR) remains a challenge (1). Bare-metal stents (BMS) are still frequently used during percutaneous coronary intervention, although they are associated with relatively high restenosis rates, especially when used in complex clinical and anatomic scenarios (2). Factors associated with the current use of BMS include the unaffordable price of drug-eluting stents (DES) in certain geographic areas, concerns about a high risk of bleeding in relation to a requirement for prolonged dual antiplatelet therapy after DES, and a perceived low restenosis risk in large coronary vessels. Accordingly, treatment of patients with BMS-ISR continues to represent a significant therapeutic burden in routine clinical practice in many catheterization laboratories around the world (1,2).

The introduction of DES has drastically reduced the occurrence of severe neointimal proliferation, the dominant cause of restenosis after stent implantation (3). This decrease translated into important reductions in clinical need for subsequent repeat revascularization (4,5). However, first-generation DES were plagued by safety concerns related to a small, but clinically relevant, increase in the risk of very-late stent thrombosis (6). Recently, however, the adoption of newer-generation DES and their unrestricted use in clinical practice has proven that these devices are not only more effective (7) but also safer (8,9) compared with first-generation DES. Nevertheless, DES are not immune to restenosis. In fact, routine angiographic surveillance after unrestricted use of newer-generation devices demonstrates rates of angiographic restenosis of approximately 12% (7). Of additional concern, the treatment of patients with DES-ISR has proven to be particularly challenging (1,10).

In the present review, we discuss currently available therapeutic strategies for the management of patients with ISR. We performed a systematic review to identify all randomized clinical trials published on this subject (11–39). Results of the most recent trials, especially those assessing novel modalities, are critically discussed in the light of previous evidence. In addition, we review recent developments relating to delineation of the underlying substrate accounting for late stent failure. Notably, recent pathological studies demonstrated that “neoatherosclerosis” represents a common substrate in patients with late stent failure (40). In this regard, progress in intracoronary imaging techniques was able to unravel the underlying pathological substrate of ISR in vivo (1). This information may be used to select and tailor interventions to tackle the underlying putative mechanisms and also to optimize results of these repeated interventions.

**Methods**

A search in MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials was performed (without language restrictions) from 1995 through November 30, 2013. In addition, abstract lists and conference proceedings from the 2013 scientific meetings of the American College of Cardiology, the European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, the American Heart Association, and the World Congress on Cardiology were searched. We used, as search limits, the following: humans, randomized controlled trial, “coronary restenosis” and “in-stent restenosis” (Medical Subject Headings). Reference lists from these papers were also reviewed for additional studies.

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Only randomized clinical trials comparing therapeutic modalities in patients with ISR were included (29 randomized studies in total [11–39]).

**Relevant Clinical and Anatomic Issues**

**Definition.** The definition of ISR remains an angiographic one: namely, recurrent diameter stenosis >50% at the stent segment or its edges (5-mm segments adjacent to the stent) (41,42). Angiography not only allows determination of ISR severity but also its morphological pattern. The Mehran system permits a morphological classification of BMS-ISR lesions (pattern I, focal; pattern II, diffuse; pattern III, proliferative; and pattern IV, occlusion) and can predict the need for repeat revascularization after intervention (19%, 35%, 50%, and 98%, respectively) (42). This classification scheme also has prognostic value in patients with DES-ISR (43). In addition, the American College of Cardiology/American Heart Association classification has been validated in patients with ISR: B2-C lesions are not only more frequently associated with suboptimal acute results, but also with a higher restenosis rate and poorer long-term clinical outcomes (44).

**Clinical presentation.** In terms of clinical presentation, ISR had traditionally been thought to represent a relatively benign clinical entity, with predominantly stable clinical presentation and largely satisfactory acute results with repeat interventions (1,45). This was in keeping with the prevailing etiologic paradigm suggesting that the progressive homogeneous smooth muscle cell proliferation constituted the universal substrate of ISR. More recent studies, however, suggest that patients with ISR frequently present with unstable symptoms and, in fact, many of them exhibit elevations of cardiac markers fulfilling diagnostic criteria for myocardial infarction (7,46).

Whether acute coronary syndrome presentations are more common with DES-ISR remains unknown. However, a shift in the underlying pathological substrate toward restenotic lesions with a higher proportion of in-stent atherosclerotic plaque, the so-called neoatherosclerosis (40), means that this hypothesis deserves further investigation (Fig. 1). Conversely, the natural history of “asymptomatic” patients with angiographic restenosis seems favorable (47). Therefore, treatment of asymptomatic patients (the so-called “oculostenotic reflex”) should be avoided whenever possible (48,49). In some cases, however, very severe ISR (>75% diameter stenosis according to quantitative coronary angiography) has also been considered a clinical indication for repeat revascularization. Currently, the functional significance of ISR may be readily evaluated in the catheterization laboratory by using the pressure wire, and prospective studies have validated the use of fractional flow reserve for clinical decision making in these patients (50). Notably, the clinical outcome of patients with ISR with deferred interventions based on a fractional flow reserve >0.75 is excellent (51). This diagnostic strategy is especially attractive in patients with angiographically moderate or ambiguous ISR.

**Type of underlying stent: BMS-ISR versus DES-ISR.** Accumulating evidence strongly suggests that there are significant differences between ISR that occur after BMS compared with those seen after DES (1,10,52). Time of presentation, morphological patterns, underlying substrate, and response to interventions largely differ in patients with BMS-ISR and DES-ISR (1,52). This finding is consistent with observations that the time course of neointimal accumulation differs considerably after DES compared with after BMS (53,54), which reflects a manifestation of delayed arterial healing that seems to characterize the vascular response after DES implantation (55). Moreover, compared with BMS-ISR, DES-ISR tends to exhibit a focal pattern, often affecting the stent edges. This outcome may be because the overall high suppression of neointimal growth by DES means that technical problems, including geographic miss phenomenon or strut fractures, are relatively more important contributing factors in patients with DES-ISR (1,45). In addition, neoatherosclerosis occurs not only more frequently, but also earlier in patients with DES-ISR compared with those with BMS-ISR (40) (Table 1).

**Underlying substrate.** Assessing the main underlying cause of ISR may be critical for guidance and optimization of these repeated interventions (1,45). In many patients, underlying mechanical problems explain the subsequent development of ISR. These tend to be preventable and, more importantly, if adequately recognized, they may be corrected during reinterventions. Underexpansion is considered a major factor triggering ISR after either BMS or DES implantation (56,57). This problem may be due to stent underdeployment as a result of undersizing or due to the use of low deployment pressures (57). Conversely, resistant underexpansion may be caused by the presence of underlying heavily calcified lesions that prevent adequate stent expansion despite high dilation pressures. In other patients, however, ISR is detected in well-expanded stents. In selected patients, stent misplacement or stents not fully covering the underlying lesion may explain the appearance of focal ISR. “Candy wrapper” angiographic appearance is typical of geographic miss, particularly in patients treated with DES or brachytherapy (58). In this scenario, the sharp contrast between the excellent appearance in the stent lumen (effective suppression of neointimal growth) and the focal-edge restenosis (negative remodeling, plaque growth, or both) accounts for this distinctive angiographic pattern.

Stent fractures may also trigger focal ISR or even stent thrombosis. Fractures are more frequent in the right coronary artery and occur more frequently in some DES types (1,59). Repeat stent implantation is frequently advocated.
in this setting. Finally, the adoption of DES brought to light some new etiological factors, including drug resistance or local hypersensitivity reactions, which have also been associated with DES failure (52,59).

**Table 1** Comparison of Principal Features of Restenotic Tissue After Bare-Metal and Drug-Eluting Stent Implantation

<table>
<thead>
<tr>
<th>Imaging features</th>
<th>Bare-Metal Stent Restenosis</th>
<th>Drug-Eluting Stent Restenosis</th>
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<tr>
<td>Angiographic morphology</td>
<td>Diffuse pattern more common</td>
<td>Focal pattern more common</td>
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<tr>
<td>Optical coherence</td>
<td>Homogeneous, high-</td>
<td>Layered structure or</td>
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<tr>
<td></td>
<td>signal band most</td>
<td>heterogeneous most</td>
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<tr>
<td></td>
<td>common</td>
<td>common</td>
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<tr>
<td>Time course of late luminal loss</td>
<td>Late loss maximal by 6-8 months</td>
<td>Ongoing late loss out to 5 years</td>
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<tr>
<td>Histopathological features</td>
<td></td>
<td></td>
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<tr>
<td>Smooth muscle cellularity</td>
<td>Rich</td>
<td>Hypocellular</td>
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<tr>
<td>Proteoglycan content</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Peri-strut fibrin and inflammation</td>
<td>Occasional</td>
<td>Frequent</td>
</tr>
<tr>
<td>Complete endothelialization</td>
<td>3-6 months</td>
<td>Up to 48 months</td>
</tr>
<tr>
<td>Thrombus present</td>
<td>Occasional</td>
<td>Occasional</td>
</tr>
<tr>
<td>Neatherosclerosis</td>
<td>Relatively infrequent, late</td>
<td>Relatively frequent, accelerated course</td>
</tr>
</tbody>
</table>

**Figure 1** Pathological Images of In-Stent Restenosis

Low-power (A and B, 4×) and high-power (C and D, 10×) magnification images of restenosis within (A and C) a bare-metal stent (BMS) and (B and D) a drug-eluting stent (DES), both implanted 5 years antemortem. In the BMS, the dominant pathology is smooth muscle cell-rich neointimal hyperplasia. There is also some chronic inflammation with neovascularization around stent struts (green arrowhead). In the DES, there is presence of neatherosclerosis with formation of a necrotic core (black arrowheads) and calcification (grey arrowheads). Courtesy of Dr. Michael Joner, CVPath Inc., Gaithersburg, Maryland.

Other therapeutic considerations. Antiplatelet drugs should be used before intervention for ISR, consistent with recommendations after any coronary intervention. A 6- to 12-month duration of therapy has been recommended in patients treated with DES or drug-coated balloons (DCB) depending on the clinical presentation (60,61). Although in some early studies, abciximab was considered to be of particular value in patients with ISR, subsequent experience failed to confirm this clinical benefit (62,63). Likewise, oral sirolimus was initially considered to be of potential value in patients with ISR (17). However, data supporting the long-term efficacy of this strategy are lacking, and the higher incidence of adverse drug effects seen with this therapy indicates that its use in the treatment of patients with ISR cannot be recommended (64). Last, but not least, coronary surgery should always be considered in patients with recalcitrant ISR, particularly in those with a diffuse ISR pattern or associated significant disease in other major vessels (45). However, the relatively scant information currently available on the acute and long-term results of coronary surgery in patients with ISR remains surprising. Most surgical series describe good results in patients with previous interventions, but dedicated studies focused on the results of coronary surgery for patients with ISR remain very limited. Some investigators suggest that saphenous vein grafts have an
unacceptably high incidence of failure among patients treated for ISR (65). To improve the long-term angiographic and clinical results in these patients, the use of arterial conduits should be always considered.

**Role of Intravascular Imaging**

Intracoronary imaging may play an important role in evaluation of underlying mechanical factors that contribute to ISR (56,57). For example, intravascular ultrasound readily detects the presence of neointimal hyperplasia obstructing the stent, device underexpansion, or edge problems (56). In addition, the external elastic lamina is usually well delineated behind the stent struts, and this information provides potentially valuable insights on vessel sizing for optimization of stent expansion. However, due to its limited axial resolution (150 μm), the lumen–neointimal interface may be difficult to delineate in some areas. In this respect, optical coherence tomography (OCT) provides a much better axial resolution (15 μm), yielding detailed images of the vessel–lumen interface, the neointimal tissue, and the strut distribution (52,57). Against this setting, residual plaque behind the stent is poorly visualized as a result of lower tissue penetration compared with ultrasound. Moreover, in patients with ISR, the detailed visualization of intrastent tissue opens new avenues for tissue characterization (66) and may permit establishment of new classification systems for ISR, potentially with important clinical implications.

ISR after BMS typically shows a homogeneous high-signal tissue band according to OCT, which is characteristic of neointimal hyperplasia rich in smooth muscle cells (Fig. 2) (52). Alternatively, ISR after DES is typically characterized by a layered or heterogeneous intrastent tissue band. Such a tissue appearance may represent hypocellular neointima with high proteoglycan or fibrin content or may be part of the spectrum of in-stent neoatherosclerotic changes. Indeed, some investigators suggested that in patients with DES-ISR, OCT imaging may exhibit presence of neoatherosclerotic tissue within the stent in up to 50% of cases (67). Specific findings observed include presence of neointimal disruptions, lipid-laden neointima, lipid pools, thin-cap fibroatheroma, and macrophage accumulation. Notably, OCT allows not only evaluation of the presence of neoatherosclerotic tissue per se but also of the presence of unstable features (e.g., plaque rupture, nonocclusive intracoronary thrombus), which may play a strong role in prognostic assessment and clinical decision making.

![Figure 2 Patterns of In-Stent Restenosis as Depicted by Optical Coherence Tomography](image)

(A) Homogeneous bright neointimal proliferation. (B) Uniform neointimal proliferation with microvessels (arrows). (C) Layered pattern with multiple microvessels (arrows) in the dark layer overlying the stent struts. (D) Multilayered pattern. *Wire artifact.
A further implication of the availability of high-resolution intravascular imaging is that it challenges the paradigm that ISR and stent thrombosis are distinct pathological entities. Recent studies suggest that in-stent neoatherosclerosis may be identified as the underlying pathological substrate in a substantial proportion of cases of both ISR and stent thrombosis (40,67). Indeed, patients with complicated neoatherosclerosis may present as unstable angina or myocardial infarction and a characteristic clinical picture of either ISR or of very late stent thrombosis (Figs. 3 and 4) (68). Interestingly, thrombus aspirates from patients with stent thrombosis frequently contain plaque remnants diagnostic of neoatherosclerosis (69). These observations present evidence to suggest that a continuous pathological spectrum of vessel healing and disease recurrence or progression may underlie a range of causes of late stent failure. ISR caused by severe homogeneous smooth muscle cell proliferation represents just one end of the spectrum. At the other extreme are patients experiencing stent thrombosis in a widely patent but uncovered stent. In the middle, neoatherosclerosis manifests clinically as a multifaceted and elusive condition causing both ISR and stent thrombosis (40,68). Hopefully, the ongoing European Project PRESTIGE (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort) will provide new insights in this regard.

### Conventional Balloon Angioplasty

Balloon angioplasty (BA) was one of the earliest strategies used in patients experiencing ISR (70). The procedure is technically straightforward and consistently associated with satisfactory acute results and a very low incidence of complications. Lumen enlargement results from both tissue extrusion (axial and longitudinal) and additional stent expansion (71). Results are particularly favorable in patients with “focal” patterns of ISR (42). However, the long-term results of patients with diffuse ISR are frequently shadowed by high recurrent restenosis rates. In patients with ISR treated with BA, clinical predictors of recurrences are similar to those seen in de novo lesions; in particular, patients with diabetic status and those with early recurrences are at higher risk (72). Although evidence supporting the value of...

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**Figure 3** OCT Images of a Patient Who Presented With Prolonged Chest Pain 3 Years After the Implantation of an Everolimus-Eluting Stent in the Left Anterior Descending Coronary Artery

Angiography demonstrated in-stent restenosis (ISR), but the patient developed a significant enzymatic rise, diagnostic of a myocardial infarction. (A) Homogeneous neointimal hyperplasia. (B) Bright neointima completely shadowing the stent struts (consistent with lipid-laden or infiltrated neointima). (C and D) Images of a ruptured thin cap (arrows) with underlying cavities (+), together with large protruding red thrombi (T) causing major distal shadowing of the stent. *Wire artifact. OCT = optical coherence tomography.

particular technical approaches (relative balloon length, balloon size, or final pressures) remains limited, most investigators try to optimize the results of the repeated procedures (45,59,72). In general, a balloon-to-artery ratio of 1.1:1 is selected. In the case of important underexpansion of the underlying stent, high-pressure balloon dilation is used. Of note, BA should target the narrowing rather than the entire stented segment. Observed “dog bone” effects during balloon dilation should promote a shift to aggressive dilations with a noncompliant balloon or occasionally with a super-high-pressure noncompliant balloon (73). Actually, some groups systematically use noncompliant balloons in patients with ISR. A detailed review of the angiogram showing the results of initial stent implantation provides important technical clues to guide reinterventions (45). One of the limitations of BA is that subacute tissue re-intrusion back to the lumen tends to occur within minutes after the last balloon inflation (23). This explains the “early lumen loss” phenomenon detected in BA studies in this setting, a finding also associated with subsequent recurrent restenosis.

Edge-related complications should be carefully avoided during aggressive balloon dilations. Special care should be paid to prevent balloon slippage outside the stent (“watermelon seeding” phenomenon) (74). This problem, typical of ISR lesions, occurs more often in severe and diffuse narrowing, especially when balloons are oversized. This is not just a time-consuming nuisance resulting in more cumbersome procedures, but it is also associated with suboptimal acute results and adverse clinical and angiographic outcomes that might be related to geographic miss. Occasionally, despite dedicated maneuvers, anchoring the balloon at the target site during inflation may be challenging. Some investigators propose the use of a buddy-wire technique to stabilize the balloon (45). The use of progressive balloon inflations and the selection of relatively small and short balloons have also been advocated to prevent complications should balloon slippage occur. Side branches emerging from ISR lesions rarely cause problems during reinterventions. These branches may experience clinically silent transient occlusion, but they are systematically patent at late follow-up (75).

Available information supporting the value of BA in patients with DES-ISR is more limited than that obtained in patients with BMS-ISR. Moreover, although a BA-alone strategy has been frequently used in patients with ISR and a high bleeding risk, the advent of DCB has rapidly gained ground to become the dominant strategy in this patient cohort.

**Cutting and Scoring Balloon Therapy**

The cutting balloon is an attractive and simple technique for treatment of patients with ISR. It offers protection against the problems of “watermelon seeding.” The lateral blades of this device anchor the balloon within the target lesion, preventing balloon slippage–related problems. Moreover, from a mechanistic standpoint, the device deeply incises neointimal tissue and, at least theoretically, may favor its
Debulking Techniques

The rationale for plaque debulking was based on the hypothesis that removing the tissue obstructing a well-expanded stent was the only action required to regain vessel lumen. Intravascular ultrasound studies suggested that lumen gain was larger and residual neointima smaller when ablative techniques were used in patients with ISR compared with use of standard therapies (80,81). Once again, early observational studies suggested that the use of laser or rotational atherectomy, followed by a "conservative" balloon postdilation, was superior to conventional BA alone in these patients. It was believed that after an adequate ablation, just a gentle balloon postdilation was required to avoid additional vessel wall injury potentially able to elicit a severe recurrent proliferative response. Directional atherectomy was also used in some small early studies, but this relatively bulky device was soon abandoned because it was not well suited for small or distal vessels, which are frequent locations of ISR (82). Excimer laser showed good results in selected cases but eventually proved to have poorer ablation capability compared with rotational atherectomy (81).

The value of rotational atherectomy in patients with BMS-ISR was analyzed in 2 randomized studies (Table 2). ROSTER (Randomized Trial of Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-Stent Restenosis) was a small single-center study in patients with diffuse ISR in whom intravascular ultrasound was systematically used to exclude cases with severe stent underexpansion (21). In this trial, rotational atherectomy reduced the amount of residual tissue within the stent and the rate of target lesion revascularization at follow-up, compared with BA alone. Conversely, ARTIST (Angioplasty Versus Rotational Atherectomy for Treatment of Diffuse In-Stent RestenosisTrial), a larger multicenter randomized study (298 patients with diffuse ISR) comparing rotational atherectomy with BA alone, failed to show benefit with rotational atherectomy (14). In fact, the restenosis rate, as well as the rates of acute complications and long-term clinical events, were higher in the rotational atherectomy arm. Although some argued that the low-pressure final balloon inflations may have been unable to effectively treat potentially underexpanded stents (intravascular guidance was not mandated), the unfavorable clinical and angiographic results of this large study eventually led to abandonment of this form of therapy. However, in rare cases, rotational atherectomy may still be required as a bailout strategy in patients with undilatable ISR lesions as a result of severely underexpanded stents (83,84) or calcified intrastent neoatherosclerosis (85). The value of ablative techniques in patients with DES-ISR has not been evaluated.

Vascular Brachytherapy

The treatment of patients with ISR represents the most successful application of vascular brachytherapy. Brachytherapy effectively suppressed the proliferative response and significantly reduced clinical and angiographic restenosis rates. Randomized clinical trials in patients with ISR demonstrated the superiority of brachytherapy compared with conventional BA or atheroablative techniques (11–13,16,28) (Table 2). Early balloons filled with radioactive fluids showed experimental promise but never demonstrated clinical efficacy. However, both beta and gamma radiation sources were able to achieve major reductions in the angiographic restenosis rates. Gamma emitters had profound tissue penetration, whereas beta emitters had less tissue penetration. Radioprotection was a major problem with gamma emitters; dosimetry problems frequently arose with beta emitters.

Experience with brachytherapy provided many lessons about the adverse effects of treatment with intracoronary antiproliferative therapies. Indeed, the issues of geographic miss and edge restenosis, as well as delayed arterial healing and its sequelae (late stent thrombosis and late catch-up), have been well described with this therapy (86). Intravascular ultrasound provided important insights into many of these complications, including documentation that late thrombotic occlusion was often secondary to delayed endothelialization and vessel remodeling leading to late acquired stent malapposition (87). These findings led to
<table>
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<th>First Author/Trial (Ref. #) Year</th>
<th>Stent Therapy</th>
<th>Time (months)</th>
<th>RE</th>
<th>ISGLL</th>
<th>MACE</th>
<th>TVR</th>
<th>Clinical Follow-Up</th>
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<tr>
<td>ARTIST (14) 2002 BMS BA 146</td>
<td>61 25.0 13.6 2.65 0.53</td>
<td>6</td>
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Details of the literature search are given in the Methods. The primary endpoint of each trial is highlighted in bold. *Only 62% bare-metal stent (BMS)-in-stent restenosis (ISR): p < 0.05.

ARTIST — Angioplasty Versus Rotational Atherectomy for Treatment of Diffuse In-Stent Restenosis Trial; BA — balloon angioplasty; BT — intracoronary brachytherapy; CB — cutting balloon; DCB — drug-coated balloon; DES — drug-eluting stent(s); DES-P — paclitaxel drug-eluting stent(s); DES-S — sirolimus drug-eluting stent(s); DM — diabetes mellitus; ISAR-DESIRE — Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2; ISAR-DESIRE 3 — Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 3; STILL — In-stent late loss; ISG LL — in-segment late loss; LL — lesion length; Long WRIST — Washington Radiation for In-Stent Restenosis Trial for Long Lesions; MACE — major adverse cardiac events (including death or cardiac death, myocardial infarction [MI], and target lesion revascularization [TLR] or target vessel revascularization [TVR] as considered in each trial for the combined outcome measure); MLD — minimal lumen diameter; OSIS - Oral Sirolimus to Inhibit Recurrent In-stent Stenosis; PCI — percutaneous coronary intervention (BA, rotational atherectomy [RA], laser, BMS); RE — binary restenosis; RIBS I — Restenosis Intra-stent Balloon Angioplasty Versus Elective Stenting; RIBS II — Restenosis Intravascular: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting; RIBS V — Restenosis Intra-stent: Drug-eluting Balloon vs. Everolimus-eluting Stent; ROSTER — Randomized Trial of Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-Stent Restenosis; ROTA — rotational atherectomy; RVD — reference vessel diameter; S-DES — sirolimus-eluting stent for diffuse restenosis; SIR — sirolimus-eluting stent for diffuse in-stent restenosis; SIRhd — high-dose oral sirolimus; SISR — Sirolimus-Eluting Stent vs. Brachytherapy in Patients With Bare Metal In-Stent Restenosis; TAXUS V EBP — A Prospective, Randomized Trial Evaluating Slow-Release Formulation TAXUS Paclitaxel-Eluting Coronary Stent in the Treatment of In-Stent Restenosis; WRIST — Washington Radiation for In-stent Restenosis Trial.
recommendations for extended durations of dual antiplatelet therapy (61), mirroring many of the issues subsequently encountered with first-generation DES therapy.

In many respects, the advent of DES was the end of brachytherapy. Two large randomized clinical trials compared the efficacy of brachytherapy versus DES in patients with BMS-ISR (Table 2). The SISR (Sirolimus-Eluting Stent vs. Brachytherapy in Patients With Bare Metal In-Stent Restenosis) trial allocated 384 patients with BMS-ISR to undergo brachytherapy or sirolimus-eluting stent implantation (26). At follow-up, the rates of target vessel failure were 2-fold higher after brachytherapy. The TAXUS V ISR (A Prospective, Randomized Trial Evaluating Slow-Release Formulation TAXUS Paclitaxel-Eluting Coronary Stent in the Treatment of In-Stent Restenosis) trial randomized 396 patients with BMS-ISR to receive either brachytherapy or paclitaxel-eluting stents (27). At 9-month follow-up, paclitaxel-eluting stents significantly reduced angiographic restenosis rates and the need for target vessel revascularization. Subsequent reports from these 2 trials confirmed that the advantage of DES over brachytherapy was maintained up to 5 years of follow-up.

In patients with DES-ISR, observational studies suggest that brachytherapy was of clinical utility (88). However, randomized trials against repeat DES or DCB therapy were never conducted. Overall, the inherent complexity of the technique, together with a reduced commercial interest, led to the virtual abandonment of this strategy.

Repeat Stenting for Patients With ISR

Bare-metal stents. Despite increasing vessel wall injury and subsequent neointimal proliferation compared with BA in de novo lesions, BMS reduce the risk of restenosis due in large part to higher acute gain. In patients with BMS-ISR, intravascular ultrasound studies also demonstrated that repeat stenting was the best strategy to obtain a larger acute lumen gain and better results immediately after the procedure (80). In addition, mechanistic studies demonstrated that the early lumen loss phenomenon seen after BA was virtually abolished after repeat stenting (23). Such observations partially allayed the initial resistance from many physicians to repeat stenting (the so-called “sandwich technique”), although repeat stenting was initially reserved for patients with suboptimal results or complications during treatment of ISR (89,90).

The RIBS I (Restenosis Intra-stent Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting) trial randomized 450 patients with BMS-ISR to receive either BA or repeat BMS implantation (15). Acute angiographic results were significantly better after stent implantation due to a larger acute gain. However, at 6-month follow-up, the late loss was also significantly larger in the stent group. As a result, final minimal lumen diameter and percent diameter stenosis were similar in both arms. Likewise, recurrent restenosis rates were high and similar in the 2 groups (15). Although this trial failed to demonstrate the benefit of systematic BMS implantation in patients with ISR, there was some evidence of clinical benefit in 2 relevant pre-specified lesion subsets. First, patients with large vessels (≥3 mm in diameter on quantitative coronary angiography) obtained better long-term clinical and angiographic outcomes after repeat stenting compared with BA. Second, patients with ISR affecting the stent edge and the adjacent vessel also exhibited better results after stenting (91). Studies assessing the value of BMS in patients with DES-ISR are lacking and unlikely to be undertaken.

Drug-eluting stents. The development of DES has revolutionized the field of interventional cardiology. In de novo lesions, DES produce a profound inhibition of neointimal proliferation (3–5). This characteristic is particularly attractive for patients with complex lesions and off-label indications, including ISR. Early observational studies suggested that first-generation DES were very effective and safe in patients with ISR and provided excellent clinical outcomes (92). Although thorough lesion pre-dilation with or without noncompliant balloons remains important to treat potential underlying stent underexpansion (assuming intravascular imaging is not performed), adjunctive DES implantation offers durable preservation of acute gain. At the same time, because stent fracture and mechanical issues may be more prevalent in patients with DES-ISR than in those with BMS-ISR, routine guidance with intracoronary imaging is recommended by some (57). Finally, edge problems should be carefully prevented (as previously discussed).

The ISAR-DESIRE (Intracoronary Stenting or Angioplasty for Restenosis Reduction–Drug-Eluting Stents for In-Stent Restenosis) trial was the first randomized study assessing the value of DES in patients with BMS-ISR (22) (Table 2). In this 2-center German trial, 300 patients were randomly allocated to treatment with sirolimus-DES, paclitaxel-DES, or BA. The rate of recurrent restenosis was significantly reduced with sirolimus-DES (14.3%) and paclitaxel-DES (21.7%) compared with BA (44.6%). Patients treated with sirolimus-DES tended to have lower rates of angiographic restenosis and target vessel revascularization compared with those receiving paclitaxel-DES. This treatment effect was also shown in a subsequent meta-analysis comparing these 2 DES for BMS-ISR (93). The RIBS II (Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting) trial was a multicenter Spanish study that compared sirolimus-DES versus BA in patients with BMS-ISR (25). Compared with the BA arm, patients treated with sirolimus-DES had a significantly lower restenosis rate (11%) and superior long-term clinical outcome, mainly as a result of a reduced need for reinterventions (Fig. 5). Interestingly, the superiority of sirolimus-DES over BA was consistent across 10 pre-specified patient and lesion subsets. In addition, a mechanistic intravascular ultrasound study confirmed the dramatic reduction of neointimal proliferation seen after use of sirolimus-DES (25). The long-term (4-year) follow-up of this study was reassuring, because a sustained clinical benefit was
demonstrated (94). Importantly, long-term adverse safety issues have not been observed, at least with contemporary dual antiplatelet treatment regimens.

Treatment of DES-ISR is especially challenging (1,10,59). Overall, treatment of DES-ISR is associated with poorer late outcomes than those obtained after treatment for BMS-ISR (1,10,59). Although repeat stenting with DES was quickly established as safe and effective, this problem persists even when repeat stenting with DES is used. Initial observational studies suggested that DES provided superior results compared with other strategies such as BA or cutting balloon angioplasty (95). Even in patients with focal patterns of DES-ISR, repeat stenting with DES is superior to BA (1,59).

Repeat stenting with DES rapidly became established as the treatment of choice in DES-ISR. However, the issue of whether a DES eluting the same or a similar type of drug (homo-DES approach) versus a switch to a different type of drug (hetero-DES approach) should be selected has continued to attract considerable debate (96). The benefits of a switch strategy are based on the hypothesis that it might overcome drug resistance or specific polymer-related problems. Most studies focused on assessing the relative value of different drugs (mainly limus versus non-limus). Overall, results remain inconclusive, and the evidence favoring a switch strategy is weak. The ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) trial randomly allocated 450 patients with sirolimus-DES-ISR to undergo repeat stenting with sirolimus-DES versus switching to stenting with paclitaxel-DES (30). Regarding antirestenotic efficacy, there were no differences between the 2 arms in late loss (0.40 vs. 0.38 mm), binary restenosis (19.6% vs. 20.6%), or target lesion revascularization (16.6% vs. 14.6%). Safety was also comparable. These observations argue against a clear benefit from a switch DES strategy. However, it is important to keep in mind that same-drug versus switch-drug is an oversimplification because the study DES differed not just in drug but in many device components, which may influence efficacy.

In the RIBS III (Restenosis Intra-Stent: Balloon Angioplasty Versus Drug-Eluting Stent) trial, a prospective multicenter registry including 363 patients with DES-ISR, the use of a hetero-DES approach was recommended, and outcomes were compared between patients who were treated according to this recommendation versus those who were not (97). The main finding was that the hetero-DES approach (or switch DES strategy) was associated with better clinical outcomes. Of note, the control group actually included diverse therapeutic modalities, including BA, BMS, and repeat stenting with a homo-DES approach. However, when the results of the hetero-DES strategy were compared directly with those of repeat stenting with a homo-DES approach, the findings were broadly consistent. Interestingly, in RIBS III, there was a suggestion that the use of second-generation DES was superior to first-generation DES and also that guidance with intracoronary imaging was associated with better long-term results.

Bioresorbable vascular scaffolds have also been proposed as treatment for patients with ISR, although only anecdotal cases of ISR treated with these devices have been reported to

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**Figure 5** Diameter Stenosis at Follow-up in the RIBS II Study

*BA = balloon angioplasty; FU = follow-up (broken lines); RE = binary restenosis rate; RIBS II = Restenosis Intra-Stent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting; SES = sirolimus-eluting stent(s). Modified with permission from Alfonso et al. (25).*
date (98). The chief advantage is that the device should eventually disappear from the vessel wall, avoiding the presence of multiple stent layers ("onion-skin" phenomena) (99). Potential limitations of bioresorbable vascular scaffolds in this setting include lumen crowding due to strut thickness (particularly in small vessels), device flexibility that may affect access to restenotic lesions, and questions regarding radial strength and recoil, which may be particularly important in treating cases of ISR.

Finally, the best approach to patients presenting with “recurrent” DES-ISR remains unsettled (99). Many of these patients had resistant underexpandable stents despite the use of high pressures. When severe resistant underexpansion is confirmed (which may require intracoronary imaging), some investigators support the use of highly aggressive strategies, including rotational atherectomy, to correct this underlying problem (stent ablation). However, the risk/benefit of this approach remains unknown, and the problem of publication bias (selective reporting of successful cases) seems likely (83,84). In patients with recurrent ISR, implantation of new DES would result in a vessel with multiple metal layers (99). This patient cohort seems to be at a high risk for additional recurrences, and coronary surgery should always be contemplated for these “frequent flyer” patients, although this will usually be dictated by the prognostic relevance of the restenotic lesion (45).

**DCB Angioplasty**

Although the value of DCB in de novo lesions remains controversial, they have been proven to be very effective in patients with both BMS-ISR and DES-ISR (100) (Table 2). The pioneering study of Scheller et al. (24) in 52 patients with BMS-ISR demonstrated that DCB were superior to BA alone. Six-month angiographic results were significantly improved in the DCB arm (late loss of 0.03 mm vs. 0.74 mm; p < 0.002). The main limitation was that the control group therapy (BA) has now been superseded by repeat stenting with DES. Accordingly, a subsequent randomized trial by the same investigators compared DCB with paclitaxel-DES in 130 patients with BMS-ISR (29). At follow-up, DCB significantly reduced the primary endpoint of the study (angiographic late loss: 0.17 mm vs. 0.38 mm; p = 0.03), although minimal lumen diameter and diameter stenosis (more acceptable angiographic endpoints in trials comparing balloons and stents) were similar in both groups. Recently, the RIBS V (Retrostent Intra-stent: Drug-eluting Balloon vs. Everolimus-eluting Stent) trial reported the first data from a randomized comparison of DCB with second-generation everolimus-DES in 189 patients with BMS-ISR (38). In this study, the minimal lumen diameter at follow-up was better after everolimus-DES (2.01 mm vs. 2.36 mm; p < 0.001), although binary restenosis (4.7% vs. 9.5%; p = 0.22) and clinical events at 1 year were low and similar in both groups. The study suggested that second-generation DES exhibit some evidence of superiority in terms of angiographic endpoints but without a clear signal of clinical benefit. Therefore, additional studies with a larger number of patients and a longer follow-up are required to address this important question.

The value of DCB in patients with DES-ISR has also been well tested (Table 2). Initially, a 50-patient, single-center, randomized study demonstrated that in patients with limus DES-ISR, DCB provided superior clinical and angiographic results compared with BA (31). The angiographic late loss was significantly better in the DCB arm (0.18 mm). The efficacy of DCB in patients with DES-ISR was subsequently confirmed in a multicenter, randomized trial including 110 patients with any type of DES-ISR (33). Moreover, results of a controlled study suggested that DCB are equivalent to paclitaxel-DES in patients with DES-ISR (39). Interestingly, another randomized study suggested that DCB are more effective in patients with BMS-ISR than in those with DES-ISR (37), confirming the consistent pattern observed with all available therapeutic modalities. Recently, the larger ISAR-DESIRE 3 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis) multicenter randomized trial (36) investigated the efficacy of DCB versus paclitaxel-DES versus conventional BA in patients with limus DES-ISR. The use of these 3 arms is very interesting from an academic standpoint, because BA provides the classical comparator, whereas the 2 active arms used the same drug. This study demonstrated that DCB were noninferior to paclitaxel-DES and that both DCB and paclitaxel-DES were superior to BA alone (Fig. 6). It was suggested that by obviating the need of an additional stent layer, DCB might emerge as the treatment strategy of choice for patients with DES-ISR (36). In summary, data from the available randomized clinical trials suggest that DCB are superior to BA and similar to first-generation DES in patients with BMS-ISR or DES-ISR. This evidence is also supported by some meta-analyses (101).
A number of open issues in relation to DCB remain. First, a class effect for these devices cannot be assumed. A single specific DCB using iopromide as a hydrophilic spacer was used in all these trials. Further studies are required to confirm the efficacy of different DCB technologies in this setting. Long-term results of DCB seem to be largely maintained over time (102). However, anecdotal reports suggest that neoatherosclerosis may also occur in some patients treated with DCB (103). In addition, whether DCB proves comparable to repeat stenting with a second-generation DES in patients with DES-ISR remains unsettled. The ongoing RIBS IV (Restenosis Intra-stent of Drug-eluting Stents: Paclitaxel-eluting Balloon vs Everolimus-eluting Stent) randomized trial will address this issue. Finally, whether the efficacy of DCB can be further improved by lesion preparation with a scoring or cutting balloon (104) remains unknown and is the subject of the on-going ISAR-DESIRE-4 randomized trial. Although largely speculative, currently DCB may be preferred over DES in patients with ISR and multiple metal layers, in those with large side branches, and in those at high bleeding risk undergoing prolonged dual antiplatelet therapy. Alternatively, DES may be preferred over DCB in patients with stent fracture or restenosis extending outside the stent edge and also in patients with suboptimal results after lesion predilation.

Conclusions

Although the advent of DES has reduced the incidence of ISR, treatment of this clinical entity remains a prevailing clinical problem. The substrate of ISR encompasses a pathological spectrum ranging from smooth muscle cell proliferation to neoatherosclerosis. Intracoronary imaging provides unique insights into the underlying etiology of ISR, but its role in optimizing the clinical results of these reinterventions still remains unsettled. Evidence stemming from controlled clinical studies suggests that among currently available therapeutic modalities, DES and DCB provide the best clinical and angiographic results in patients with ISR. However, the field is rapidly evolving. Further studies are required to identify clinical and anatomic characteristics that may help to refine selection and tailor available therapeutic strategies to improve clinical outcomes.

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