Effective and Efficient Strategies for Coronary Revascularization in the Drug-Eluting Stent Era

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We now have at our disposal a variety of new technologies for percutaneous coronary revascularization, including drug-eluting stents (DES), intracoronary radiation therapy, and glycoprotein IIb/IIIa inhibitors. Coronary stents have improved both early and late outcomes following percutaneous coronary intervention. Stent characteristics including design, stent strut thickness, and stent metal alloy are associated with different rates of restenosis. This article reviews recent findings pertaining to the use of DES and other technologies for the treatment of coronary artery disease in diabetics and small vessel disease. The causes and treatment of in-stent restenosis are discussed. The optimal approach to coronary revascularization remains to be determined as brachytherapy, improvements in stent design, and new drug-eluting stents become available.
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With the new millennium, we have at our disposal a variety of methods for coronary revascularization that allow the tailoring of a particular approach to a specific clinical situation. The breakthrough technologies including drug-eluting stents (DES), intracoronary radiation therapy (IRT), and glycoprotein IIb/IIIa inhibitors have significant price tags. We therefore will be expected to use these new technologies based on an approach that can be thought of as "reasoned rationing" that is based on the thoughtful application of clinical data to your specific patient, not merely on impulse. The primary purpose of this section of this very important medical educational initiative will be to provide context to many of the recent important developments affecting our approach to patients in the cardiac catheterization laboratory.

Coronary Artery Stents and Restenosis

Coronary stents have improved both early and late clinical outcomes following percutaneous coronary intervention (PCI). In the era prior to coronary stenting, abrupt coronary closure complicated 4%–8% of PCI procedures, occurred unpredictably, and was the cause of appreciable morbidity and mortality for the patient.[1–3] By providing a circumferential scaffold to "tack up" intimal flaps and dissections, stents effectively reduced the incidence of abrupt coronary closure. We have come a long way from "bigger is better" to "the more you gain, the more you lose." The interventional cardiologist's approach to battling restenosis has passed through several phases of change and even contradiction, from debulking to stenting and from shaving to scaffolding. Finally, intimal hyperplasia, the ultimate enemy, may be close to being defeated.

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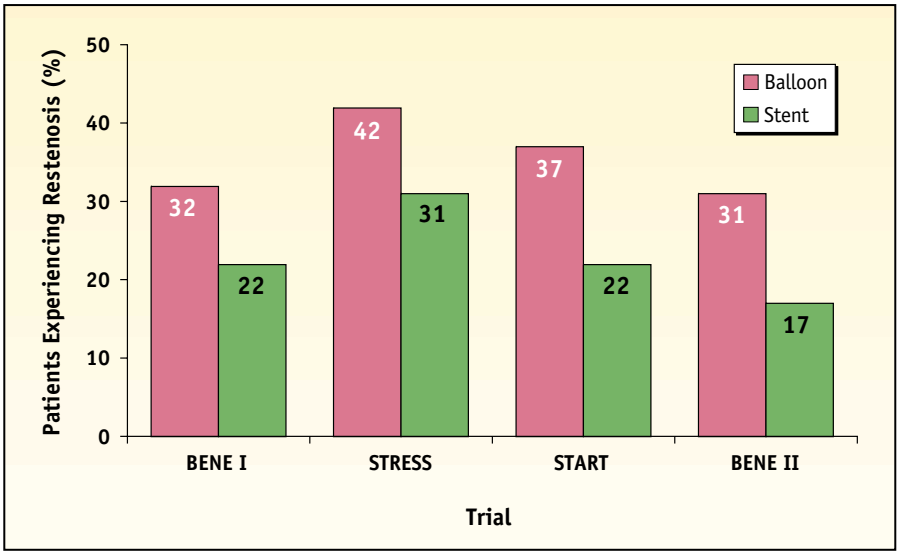
In the late 1980s and 1990s, advances in both procedural pharmacotherapy with adjunctive platelet glycoprotein IIb/IIIa receptor blockade and post-procedural combination antiplatelet therapy enhanced the relative benefit of stents versus standard balloon angioplasty by reducing the occurrence of subacute stent thrombosis, periprocedural myocardial infarction, the need for urgent repeat revascularization, and mortality. In randomized trials comparing stent versus balloon PCI in patients with target vessel diameters > 3.0 mm, coronary stent deployment reduced the occurrence of late (6-month) coronary closure, defined as at least 50% lumen diameter restenosis on quantitative coronary angiography (Figure 1). These trials primarily enrolled patients with single-vessel, single-lesion coronary disease whose offending target stenosis could be effectively covered by a single 15-mm–long Palmaz-Schatz® (Cordis Corporation, Miami, FL) coronary stent. Yet, despite the relatively simple disease process under study, binary (> 50%) in-stent restenosis (ISR) at 6 months was still observed in 20%–30% of patients. Furthermore, the prevalence of adverse early and late clinical outcomes following coronary stent deployment was proportional to the complexity of coronary target lesion morphology and the performance of multi-vessel PCI.[4] Thus, the clinical limitations of first-generation coronary stent devices prompted evolution in coronary stent design.

Gaining a clearer understanding of restenosis pathophysiology will allow us to develop improved prevention and treatment strategies. The earlier discussion by Schwartz and Henry in this supplement provides a comprehensive discussion of this subject. It is accepted that angiographic factors associated with restenosis include small-diameter reference coronary arteries, longer lesion length, and longer stent length. What seems less appreciated are the morphologic parameters that correlate with restenosis. The recent study by Farb and colleagues provided detailed histologic evaluation of human stent implants.[5] Greater neointimal growth associated with deep medial injury and increased medial fracture length occurs more often with improper oversizing of stents and implantation at excessive pressures. Plaques with large lipid cores are at higher risk for lipid core penetration by struts and for a more intense inflammatory reaction. This inflammatory response further amplifies the intimal proliferative response. This data runs counter to the "bigger is better" theory.

The importance of inflammation in the restenotic process is high-

Figure 1. *Restenosis (≥ 50%) at 6 months in randomized trials comparing stent versus balloon percutaneous coronary intervention. BENE indicates BElgian NEtherlands STENT Study; STRESS, STent REStenosis Study; and START, STents And Radiation Therapy.*



lighted by the finding that elevated levels of C-reactive protein (CRP > 0.3 mg/dL) is associated with clinical restenosis rates at 1-year follow-up.[6] Patients with elevated CRP levels had restenosis rates of 63% versus 27% in patients with normal CRP levels. Modifying or "cooling off" this inflammatory process and reducing CRP levels prior to and around the time of stent implantation with the use of agents such as statins or the IIb/IIIa receptor inhibitor abciximab may be useful adjuncts in modifying the contribution of inflammation to restenosis.

Treatment of Small Vessel Disease

Interventions in small vessels (< 3.0 mm) constitute up to 40% of coronary artery-based procedures in the United States.[7] It is clear that an inverse relationship exists between vessel size and restenosis risk following PCI.[8,9] Studies with intravascular ultrasound (IVUS) support the notion that smaller vessels do not have the lumen volumes to accommodate the intimal hyperplasia following stent implantation or the negative remodeling following angioplasty.[10,11] Restenosis rates also depend on other clinical variables, including diabetic status and lesion complexity. In one study, restenosis rates in patients undergoing small vessel stent implantation ranged from 30% in lower-risk lesions to 53.5% in higher-risk lesions.[12]

The BElgian NEtherlands STENT (BENESTENT) Study investigators analyzed the outcome of elective stent implantation compared to balloon angioplasty in both large and small vessels.[13] In the stented group, smaller vessels (< 3 mm) were associated with a greater acute relative gain and subsequent greater loss index and a higher risk of adverse cardiac events, including subacute thrombosis, myocardial infarction, and procedural failure. In the group undergoing angioplasty there was no difference between large and small vessels in abrupt closure or myocardial infarction. For both balloon angioplasty and stent procedures, reintervention was more common in the small vessel group than in the large vessel group.

A series of randomized trials have compared coronary stenting with balloon angioplasty. The ISAR-SMART investigators evaluated the MULTI-LINK® stent (Guidant Corporation, Indianapolis, IN) in native coronary arteries between 2.0 mm and 2.8 mm in size with mean vessel diameter of 2.4 mm with a high prevalence of complex lesions.[14] Despite a larger acute lumen gain following stenting versus percutaneous transluminal angioplasty (PTCA) (1.77 mm vs 1.47 mm, $P = .001$), 6-month follow-up angiography revealed a greater loss index for stenting (0.59 vs 0.44, $P = .006$) resulting in no difference in restenosis (36% vs 37%). There was no difference in adverse events (death, myocardial infarction, coronary artery bypass grafting, and repeat PTCA) during the first 30 days.

The STent REStenosis Study (STRESS) investigators who evaluated the Palmaz-Schatz stent in smaller vessels found a restenosis rate of 34% in patients assigned to stenting and 55% in those assigned to angioplasty ($P < .001$). The study included coronary artery luminal diameters less than 3.0 mm with the mean dimension of 2.7 mm, larger than that evaluated in the ISAR-SMART study and perhaps responsible for the lower restenosis rates in vessels undergoing PTCA.

The clinical and angiographic outcome of the NIR® stent (Boston Scientific Corporation, Natick, MA) was assessed in a consecutive series of patients with type C lesions and vessels less than 3 mm diameter.[15] Vessel reference diameter was 2.5 mm, and the mean length of implanted stents was 28 mm. The restenosis rate at 6-month follow-up was 43%. In a randomized comparison of coronary stenting for small coronary arteries (*de novo*, non-ostial lesions with mean reference diameter of 2.5 mm) with the seven-cell NIR stent versus PTCA, no significant difference in 6-month restenosis was observed.[16] A 20% crossover rate from the angioplasty group to stenting was observed and was related to an inadequate PTCA primary result. These investigators concluded that optimal balloon angioplasty with provisional stenting "may be a reasonable approach to the treatment of lesions in small coronary arteries."

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The Stenting in Small Coronary Arteries (SISCA) trial was a randomized comparison of PTCA and the heparin-coated BeStent™ (Medtronic AVE, Santa Rosa, CA).[17] Angiographic inclusion criteria included a *de novo* lesion stenosis greater than 50% in a vessel with a reference diameter between 2.1 and 3.0 mm suitable for treatment with a single 15-mm stent. After 6 months, nonsignificant trends toward a reduced rate of restenosis (9.7% vs 18.8%) and larger minimal lumen diameter (MLD) (1.69 mm vs 1.57 mm) were observed with stenting. The low restenosis rates

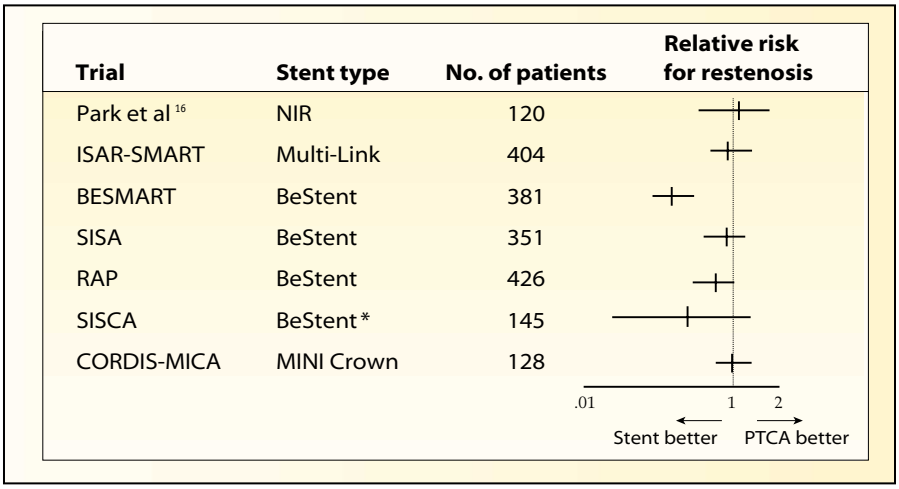

Figure 2. *Relative risk for restenosis following stenting vs percutaneous transluminal coronary angioplasty (PTCA) for small coronary vessels. ISAR-SMART indicates Intracoronary Stenting or Angioplasty for Restenosis Reduction in SMall ARTeries; BESMART, BEstent in SMall ARTeries; SISA, Stenting in Small Arteries; RAP, Restenosis en Arterias Pequeñas; SISCA, Stenting In Small Coronary Arteries; CORDIS-MICA, MINI Crown Stent in Small Coronary Arteries. Reprinted from Kastrati et al.[20]*

observed in both arms of this study are probably related to the low risk characteristics of the lesions treated. In an editorial to this study, Kastrati reviewed the findings of the Restenosis en Arterias Pequeñas (RAP)[18] and the BeStent and MINI Crown Stent in Small Coronary Arteries (CORDIS-MICA) trial[19] finding no significant difference in restenosis rates between a stent and PTCA strategy[20] (Figure 2).

In a recent three-way, randomized comparison, the bare metal JoStent® (JOMED, Helsingborg, Sweden), a heparin-coated JoStent, and PTCA demonstrated similar rates of binary (> 50%) restenosis at 6 months (25%, 30%, and 32% respectively) and similar event-free survival to 250 days post-PCI (88%, 88%, and 84%, respectively).[21] Interestingly, acute lumen gain and post-procedural MLD were significantly larger following stenting. In an analysis of the BENESTENT trial comparing stent and angioplasty results, in vessels < 3.00 mm the net gain was only 1.01 mm in the stented group and 0.77 mm in the PTCA group. This compares to a net gain in larger vessels > 3.00 mm of 1.32 mm in the stented group and 0.93 mm in the PTCA group.[22] It appears that, in small vessels, the superior post-procedural MLD obtained with stenting cannot overcome the obligatorily greater late loss seen with stenting than with balloon angioplasty. Thus, net gain (acute gain − late loss) achieved at 6 months with stent versus balloon is more similar in small vessels than in large vessels.

Efforts have focused on the development of stents with thinner struts ("less metal"), with the intent of provoking a lesser degree of arterial deep-wall injury and of enhancing flexibility for the purpose of small-vessel stenting. In a retrospective analysis of small vessel stenting (vessels < 3.0 mm), restenosis rates were significantly lower in patients treated with thin struts (< 0.10 mm thick) than those treated with thick struts (> 0.10 mm thick) (28.5% vs 36.6%, $P = .009$).[23] For the preceding analysis, thin strut stents included the MULTI-LINK® (Guidant Corporation, Indianapolis, IN), Palmaz-Schatz, BiodivYsio® (Abbott Laboratories, Abbott Park, IL), BeStent, JoStent Flex®, V-Flex™ (Cook Group Incorporated, Bloomington, IN), and Carbostent™ (Sorin Biomedica Cardio S.p.A., Via Crescentino, Italy). The thick strut group included the NIR, Bx Velocity™ (Cordis Corporation, Miami, FL), AVEII™ (Medtronic AVE, Santa Rosa, CA), Crossflex™ (Cordis Corporation, Miami, FL), ACS MULTI-LINK® DUET™ (Guidant Corporation, Indianapolis, IN), and Bard XT® (Bard Limited, Galloway, Ireland). Indeed, even in the initial experience using DES, although the incidence of in-stent restenosis was not influenced by the tertile of coronary target-vessel size, in-segment restenosis (in-stent plus 5-mm margins adjacent to the stent) correlated inversely with vessel size in a manner similar to that observed for non-DES.[24] Thus, proportionally higher rates of in-segment restenosis were observed for tertiles of smaller vessel size, although no differences for ISR by vessel size were observed. This observation likely reflects the non-specific arterial response to balloon injury outside the margins of the drug-eluting stent. The importance of developing an optimal stent delivery platform and strategy that minimize arterial trauma outside the confines of the drug delivery system (stent) is evident.

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Without being able to improve the restenosis rates in small vessels with plain old stents (POS) and little randomized data available evaluating the use of brachytherapy in these patients, we are left with limited data available on the use of coated stents. A recent study evaluated the safety of a biocompatible phosphorylcholine coating on the BiodivYsio stent in very small coronary vessels with MLD < 2 mm.[25] Phosphorylcholine is a component of cell membranes and has the advantage of decreasing the thrombogenicity of the stent surface. The target vessel revascularization rate at 6 months was 10.3%. This study was limited by being a three-center registry, lack of a control group, and lack of systematic angiographic follow-up. As mentioned above, coatings with heparin have had no effect on restenosis.

A 6-month report of the randomized, double-blind study with the sirolimus-eluting Bx Velocity™ balloon expandable stent in the treatment of patients with *de novo* native coronary lesions (RAVEL) was reported by Morice and colleagues.[26] In the tertile of smallest vessels treated in this study with a reference vessel diameter of 2.1 mm, a restenosis rate of 0% was seen in the sirolimus-treated group versus 37% in the control group. There was no significant late loss in these lesions. However, by virtue of the trial inclusion/exclusion criteria that mandated exclusion of long lesions, ostial target lesions, significant calcium, and angiographic evidence of thrombus make these lesions relatively low risk. In the initial data from the SIRIUS 400 experience using the sirolimus DES in more "real-world" lesions, although the incidence of *in-stent* restenosis was not influenced by the tertile of coronary target-vessel size, *in-segment* restenosis (in-stent plus 5-mm margins adjacent to the stent) correlated inversely with vessel size in a manner similar to that observed for non-DES.[24] Thus, proportionally higher rates of *in-segment* restenosis were observed for tertiles of smaller vessel size, although no differences for *in-stent* restenosis by vessel size were observed. This observation likely reflects the nonspecific arterial response to balloon injury outside the margins of the drug-eluting stent. The importance of developing an optimal stent-delivery platform and strategy that minimize arterial trauma outside the confines of the drug-delivery system (stent) is evident, particularly in small vessels.

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Diabetics

Diabetic patients with coronary artery disease have significantly worse long-term outcomes than nondiabetics.[27] Restenosis rates after balloon angioplasty in diabetic patients can be as high as 63%.[28] The Bypass Angioplasty Revascularization Investigation (BARI) found better outcomes at 7 years in diabetic patients with symptomatic multi-vessel disease treated surgically than in those treated with PTCA.[29] This benefit was confined to patients who had a left internal mammary arterial graft and who had more severe disease. This study was done in the "pre-stent" era and does not reflect contemporary percutaneous treatment algorithms. A much more up-to-date comparison is derived from the Arterial Revascularization Therapy Study (ARTS), which compared 1205 patients with multi-vessel disease randomized to either stent placement or bypass surgery.[30] Of these patients, 208 had diabetes and had an average of 2.7 lesions treated. There was no significant difference in in-hospital events or 1-year rates of death or myocardial infarction. The rate of repeat revascularization was significantly lower in the surgical group (3.1% vs 22%, $P < .001$). A criticism of the ARTS trial was the infrequent use of the glycoprotein receptor inhibitor abciximab, which had demonstrated both a restenosis and mortality benefit in the diabetic population from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT).[31]

At this time, there have been no clinical trials dedicated to evaluating the safety and efficacy of IRT or DES as treatments to prevent restenosis in diabetic patients. In the 6-month evaluation of the RAVEL trial, more late loss was seen in the diabetic patients than in nondiabetics. The binary restenosis rate was 0% for the diabetics treated with sirolimus versus 42% for the control population. This evaluation was based on only 19 patients treated with sirolimus with focal disease (lesion length of

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9 mm).[26] The results of RAVEL cannot be generalized to the universe of diabetic patients cared for routinely in the catheterization laboratory as it excluded from consideration treatment of multi-vessel disease, lesions < 2.5 mm, and lesion length > 18 mm.

In the Cook-sponsored Evaluation of Paclitaxel-Eluting Stent (ELUTES) and Asian Paclitaxel-Eluting Stent Clinical Trial (ASPECT) studies, the use of paclitaxel resulted in 3.1% and 4% restenosis rates, respectively.[32,33] In these two studies involving a total of 370 patients, paclitaxel was shown to reduce the incidence of restenosis at the site of stent placement. In the ELUTES trial, restenosis rates in diabetics were reduced from 65% to the 25% range. These promising results have laid the foundation for the Guidant-sponsored DELIVER trial that has completed enrollment of 1043 patients in this single-blinded, randomized study comparing the paclitaxel-coated ACHIEVE™ (Guidant Corporation, Indianapolis, IN) Drug-Eluting Coronary Stent to an uncoated stent.

Intracoronary radiation therapy was shown to be effective for the treatment of ISR in diabetics in a consecutive series of 749 patients with ISR treated with IRT (gamma or beta) or placebo.[34] The IRT group included 252 diabetics and the placebo group 51 with a mean lesion length of 24 mm and mean reference vessel diameter of 2.6 mm. This patient population is closer to a real-world diabetic population. A significant reduction of restenosis was observed in the diabetic patients treated with IRT (16% vs 64%, $P < .0001$). Comparing the effectiveness of IRT plus angioplasty to DES would certainly be valuable in terms of identifying the optimal strategy for the diabetic patient. It is anticipated that one or both of these strategies should reduce restenosis rates and leave us with revascularization rates similar to those for bypass surgery. This should further increase the volume of primary interventions performed by cardiologists and lead to net cost savings by reducing the incidence of restenosis and referrals for coronary artery bypass surgery.

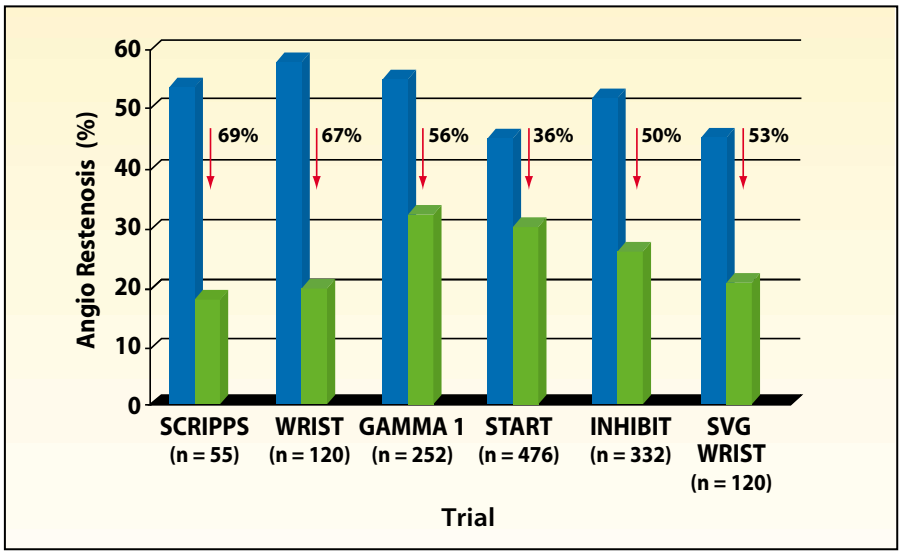

Figure 3. *Six randomized trials comparing intravascular radiation (green bars) to placebo (blue bars) in patients with in-stent restenosis. See text for full names of trials. SCRIPPS indicates Scripps Coronary Radiation to Inhibit Proliferation Post Stenting; WRIST, Washington Radiation for In-Stent Restenosis Trial; START, STents And Radiation Therapy; INHIBIT, INtimal Hyperplasia Inhibition with Beta In-Stent Trial; and SVG, Saphenous Vein Graft.*

In-Stent Restenosis

Multiple factors have been identified that contribute to the development of ISR. Clinical and angiographic predictors include target lesion length, target vessel reference diameter, proximal left anterior descending coronary target lesion location, diabetes, unstable (vs stable) angina, post-procedural in-stent MLD, and smoking.[35] Procedural variables associated with ISR have included stent length, length of stented coronary segment, and multiple stents with "stent overlap." Mechanical problems, including stent underexpansion, have contributed to approximately 25% of ISR.[35] Only recently has the role played by plaque inflammation prior to coronary stent deployment for promoting neointimal tissue formation been appreciated. Plaque inflammation, as reflected by a mononuclear white cell infiltrate composed largely of macrophages and T lymphocytes, predicts symptomatic restenosis in the year following PCI. Ongoing plaque inflammation is suggested by, and has been correlated with, elevation in serum CRP. Furthermore, the degree of stent-induced coronary arterial injury, and thus the subsequent degree of stent-PCI–provoked inflammatory response, has been directly correlated with the magnitude of neointimal tissue proliferation. Factors related

Based on current clinical trial data, IRT is the only proven approach to treat in-stent restenosis.

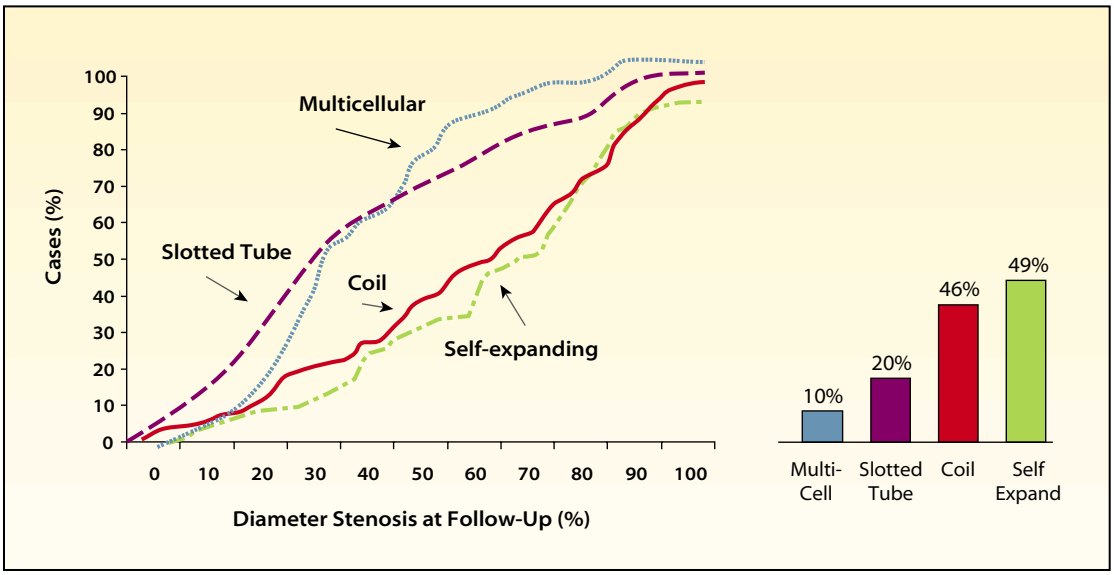

Figure 4. *Left, Cumulative frequency distribution of stenosis diameter following deployment of various stent designs. Right, Frequency of binary stenosis (≥ 50%) for various stent designs. Reprinted from Escaned J, Goicolea J, Alfonso F, et al. Propensity and mechanisms of restenosis in different coronary stent designs: complementary value of the analysis of the luminal gain-loss relationship.* J Am Coll Cardiol. *1999:34:1490–1497.*

to the physico-chemical properties of the stent and its delivery system that may influence the arterial response to injury have attracted great interest.

In-stent restenosis has been classified into four different categories: (1) focal, less than 10 mm confined within the stent border; (2) intrastent, over 10 mm in length but still confined within the stent border; (3) proliferative, over 10 mm in length extending beyond the stent border; and (4) complete occlusion. The target lesion revascularization rate at 1 year with PCI is predicated on the type of restenosis pattern, ranging from 19% for the focal pattern, 35% with the intrastent pattern, 50% with the proliferative pattern, and 83% with occlusion.[37] Besides the focal pattern, which can be treated with angioplasty, the higher restenosis rates seen with the other patterns demand an alternative approach. Both gamma and beta radiation sources have reduced rates of recurrent ISR between 36% to 69% (Figure 3). It appears that a recurrent restenosis rate of 20% represents the best that IRT will be able to provide. A DES approach to ISR will depend on the ability to effectively treat very diffusely diseased arteries. As of this writing, DES trials have excluded such patients from evaluation. A potential benefit of a DES over an IRT approach would be to reduce the incidence of late vessel closure by allowing more rapid normalization of endothelial function. With new technological breakthroughs, including the use of new metallurgical agents and DES, and optimization of deployment strategies, the incidence of ISR should become less common but will not disappear. Based on current clinical trial data, IRT is the only proven approach to treat ISR.

Stent Characteristics and Restenosis

Stent Design

Differences in stent design are associated with differences in restenosis. In a large and unselected population of patients in whom a variety of stents were used to treat coronary lesions, restenosis rates ranged from 20% with the MULTI-LINK®

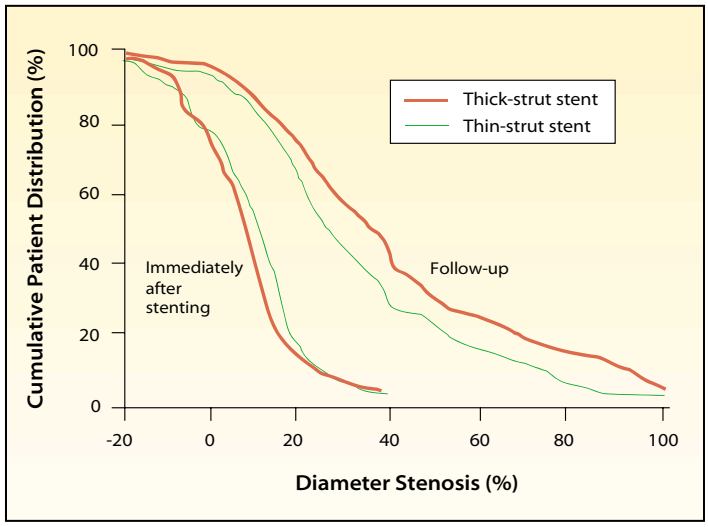

Figure 5. *Cumulative distribution of stenosis diameter following deployment of thick-strut vs thin-strut stents.*

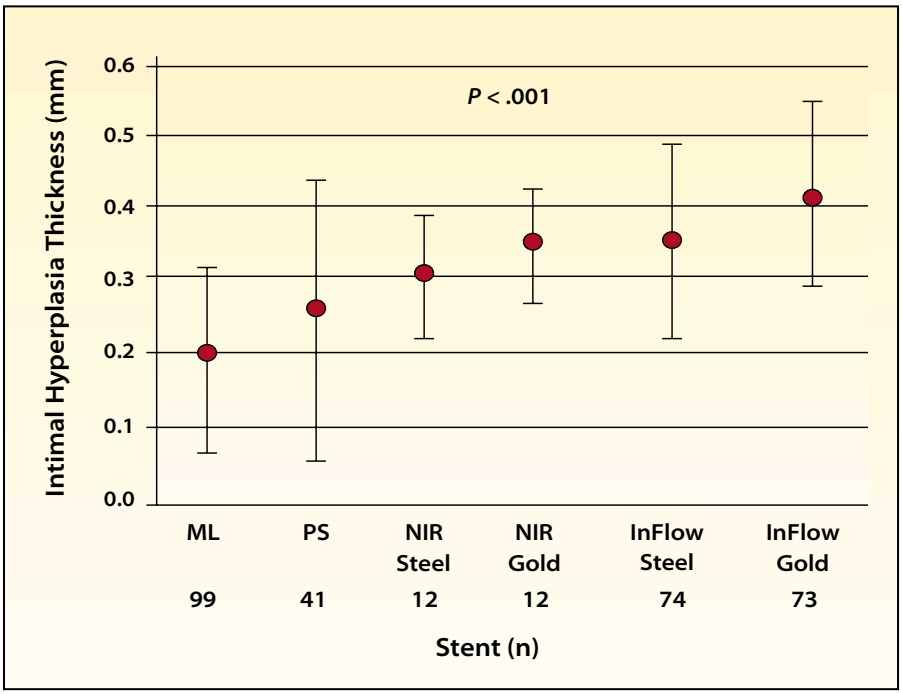

Figure 6. *Influence of stent design and composition on intimal hyperplasia measured by intravascular ultrasound. ML indicates MULTI-LINK®; PS, Palmaz-Schatz. Reprinted from Hoffmann et al.*[49]

to 50% with the Inflow Gold™ (Invatec Inflow Dynamics, Munich, Germany).[38] Observational data suggest a greater proliferative response following deployment of self-expanding and coil stents than of stents with multicellular design (Figure 4). Furthermore, even for stents of similar design, stent strut thickness is directly related to angiographic restenosis. In a randomized comparison of a multilink thin-strut (MULTI-LINK®) versus a multilink thick-strut (DUET™) stent, immediate angiographic results favored the thick-strut device. However, late restenosis was significantly less with the thin-strut stent (Figure 5).[39] Stent strut thickness was also directly correlated with restenosis in a randomized comparative trial of the thin-strut MULTI-LINK® versus the thicker-strut Bx Velocity™ stent. Angiographic binary restenosis at 6 months was greater in patients treated with the thick-strut Bx Velocity™ than with the thin-strut stent MULTI-LINK® (31.4% vs 17.9%, respectively; $P = .001$), as was late (1-year) target-vessel revascularization (21.9% vs 12.3%, respectively; $P = .002$).[40] In a randomized comparison between the MULTI-LINK® and GFX stents (Medtronic AVE, Santa Rosa, CA), a higher restenosis rate was seen with the GFX (26% vs 4%, $P = .003$) due to greater intimal hyperplasia.[41] These stents differ in that the GFX has greater strut thickness, has greater metallic surface area, and consists of connected stainless steel segments.

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Stent Metal Alloy

Multiple small, randomized comparisons have suggested that gold stent coatings promote neointimal proliferation and late angiographic restenosis for both the InFlow and NIR coronary stents. These angiographic observations are substantiated by IVUS measurements of increased in-stent obstruction and intimal-hyperplasia thickness and area in gold-coated versus stainless-steel stents (Figure 6). A multivariable regression analysis identified non–multilink stent design and gold coating as independent predictors of intimal hyperplasia by IVUS (Table 1).

In Search of a "Better Mousetrap"

Recent efforts toward improving stent features have focused on thinner struts, non–stainless-steel metal alloys, and focal-tapered balloon delivery systems. The aim of these efforts has been to reduce the degree of stent-vessel injury and enhance stent flexibility while maintaining radial strength and visibility. One example for which preliminary data are available is the VISION™ multilink stent manufactured by Guidant Corporation.[42] This novel, thin-strut (0.0032-inch), multilink stent is composed of cobalt chrome metal alloy with less nickel content (~7%) than prior multilink, 316L stainless steel stents, which are about 15% nickel. As part of a multicenter, international registry, 294 VISION™ stents were deployed in 267 patients (average age 64 years, 68% male, 23% diabetic). Stent lengths of 8, 12, 15, 18, 23, and 28 mm and diameters of 3, 3.5, and 4 mm were

used. The average target-vessel reference diameter was 2.94 mm and lesion length was 10.6 mm. To 30 days after stent deployment, major adverse cardiovascular events (defined as death, myocardial infarction, or target-site revascularization) were observed in 1.9% of patients. At 6 months, quantitative coronary angiography demonstrated a binary ISR rate of 15.7% (for all stent lengths combined) and a late lumen loss of 0.83 mm.

These results compare quite favorably with the results observed in the randomized, MULTI-LINK® versus Palmaz-Schatz, ACS MULTI-LINK® Stent Clinical Equivalence in De Novo Lesions Trial (ASCENT), in which 518 patients were treated with the thin-strut (0.0022-inch) ACS MULTI-LINK® stent.[43] Despite reference vessel diameter (2.96 mm) and lesion length (10.9 mm) similar to those treated with VISION™ stents, major adverse cardiovascular events to 30 days were observed in 5% of ASCENT multilink patients. In addition, although the MULTI-LINK® stent length was limited to 15 mm in the ASCENT trial, the 6-month binary restenosis was 16%, and late loss averaged 0.78 mm. Thus, the VISION™ stent demonstrated improved procedural performance and enhanced radial strength and visibility while achieving late angiographic outcomes comparable to those of the thinner-strut, multilink stent. It should be noted that the late angiographic outcomes achieved by the VISION™ stent appeared better than those observed in prior MULTI-LINK® stent design (PENTA™, TETRA™, DUET™) registries (Table 2). Furthermore, the incorporation of focal STEP balloon technology into the MULTI-LINK® delivery system has resulted in a reduced incidence of stent margin dissection and adjacent coronary-vessel trauma. This observation may have future implications for devising an optimal platform for delivering a drug-eluting stent.

Table 1
Independent Predictors of Intimal-Hyperplasia (IH) Thickness Measured by Intravascular Ultrasound

	OR (95% CI)	*P*	R^2	*P*
Non–MULTI-LINK® stent design	3.45 (1.13 – 11.11)	.034	0.019	.014
Gold coating	3.78 (1.88 – 7.54)	< .001	0.144	< .001

OR indicates odds ratio; CI, confidence interval.
Data from Hoffmann et al.[49]

Data are available to suggest that combining IRT with stent deployment is associated with a higher late adverse-event rate.

Brachytherapy Plus PTCA

One approach that has not received much play in the catheterization laboratory is combining IRT with PTCA for the treatment of *de novo* obstructions. Data are available to suggest that combining IRT with stent deployment is associated with a higher late adverse-event rate. This does not seem to be the case when combining IRT with PTCA (without stent). The BETA-CATH trial was the first and largest prospective, randomized, blinded, placebo-controlled multicenter study that evaluated the use of brachytherapy in *de novo* lesions with PTCA alone or combined with stent placement.[44] Target-vessel failure, the primary endpoint, was not significantly reduced in the radiation arm (stent or PTCA) compared with placebo (stent or placebo). However, in the group of patients who received IRT plus PTCA alone, a 35% reduction of target-vessel failure/MACE was observed versus the IRT plus stent group with a 30%

Table 2
The Guidant Family of Stents: Quantitative Angiographic Evaluation

	VISION	PENTA	TETRA	DUET	MULTI-LINK*
Stent strut width	0.0032	0.0036-0.0049	0.0036-0.0049	0.0055	0.022
Patients, n	267	200	202	270	518
Reference vessel diameter, mm		2.94	2.91	2.93	3.03 2.96
Lesion length, mm	10.6	12.9	10.8	11.8	10.9
Binary restenosis, %	15.7	17.5	23.6	19.7	16.0
Late loss	0.83	0.90	1.05	1.01	0.78

*From ACS Multi-Link Stent Clinical Equivalence in De Novo Lesions Trial (ASCENT).

increase in target-vessel failure/MACE. The poor results in the IRT plus stent treatment arm were attributed to the phenomenon of "geographic miss," ie, arterial intimal injury outside of the radiated arterial segment.

The Proliferation REduction with Vascular ENergy Trial (PREVENT) used the GALILEO® system, which incorporates the use of a 32P source wire with a centering catheter.[45] This novel design allows for more uniform distribution of radiation energy within the exposed vessel wall and for antegrade blood flow during radiotherapy. This trial evaluated the use of beta-radiation as an adjunct to PTCA in patients presenting with *de novo* lesions or restenosis following PTCA. A significant reduction of restenosis occurred in the IRT group versus the control group, which received no radiation (8% vs 39%, P = .012). How an IRT plus PTCA approach will compare to one with DES from both efficacy and cost standpoints awaits the test of time.

The Future of DES

Has DES has succeeded as a cure for restenosis? The U.S. Multicenter, Randomized, Double-Blind Study of the Sirolimus-Eluting Stent in De-novo Coronary Lesions—Preliminary Analysis of the First 400 Patients (SIRIUS 400) trial investigated DES use in a more "real-world" population than in the RAVEL trial or any other trial of DES to date.[24] Single *de novo* lesions with target lesion diameter between 2.5 and 3.5 mm and target lesion length between 15 and 30 mm were studied. There was a high prevalence of diabetes (28%), hypertension (70%), and multivessel disease. Quantitative coronary angiography revealed a surprisingly high 9.2% in-segment restenosis rate compared to 32.3% in the control arm. Over half of the restenosis in the sirolimus-treated patients occurred in the segment just proximal to the stent. Of concern was a trend toward an increase of in-hospital major adverse cardiac events in the sirolimus-treated group compared to placebo (3.7% vs 1.0%, P = .092) that manifested by an increase in Q-wave and non–Q-wave myocardial infarctions. This may mandate the need for glycoprotein IIb/IIIa therapy with DES placement so that there will not be a need to trade off a higher incidence of myocardial infarction for decreased restenosis. Target-vessel failure at 270 days was more similar than many would have thought in the sirolimus-treated group than placebo (10.5% vs 19.5%, P = .017). The lesson learned from this trial so far is that restenosis or complications with DES does not equal zero. The overall restenosis rate of 9% in SIRIUS 400 is higher than the 0% seen in RAVEL. Whether the more real-world application of sirolimus in SIRIUS 400 leading to a higher restenosis rate than in RAVEL is related to lack of meticulous operator technique or the more complex nature of the coronary obstructions treated is open to question and may be explained after evaluation of the entire SIRIUS database and the DELIVER trial.

Of concern was a trend toward an increase of in-hospital major adverse cardiac events in the sirolimus-treated group than placebo.

Main Points

- Drug-eluting stents represent a quantum leap in our ability to prevent coronary artery restenosis; however, a thoughtful and meticulous approach to maximize their positive impact will be mandatory.
- The VISION™ stent demonstrated improved procedural performance and enhanced radial strength and visibility while achieving late angiographic outcomes comparable to those of the thinner-strut, multilink stent.
- Restenosis is a particular problem in small vessels following percutaneous coronary intervention; DES is a reasonable approach in vessels between 2.26 and 3 mm in diameter, though in-segment restenosis remains a problem.
- Though most stents leave a pleasing acute angiographic result, they are not commodities and have many important characteristics that distinguish them, including design, stent strut thickness, and stent metal alloy, and that are associated with different rates of restenosis.
- With new technological breakthroughs, including the use of new metallurgical agents, DES, and optimization of deployment strategies, in-stent restenosis should become much less common.
- The optimal approach to coronary revascularization remains to be determined, and interventional cardiologists need to become thoroughly familiar with technological developments in brachytherapy, stent design, and drug-eluting stents.

Therefore, consideration and development of other modalities to treat *de novo* lesions and reduce restenosis rates seems reasonable. Important questions that remain to be answered include the incidence of late major adverse clinical events such as late thrombosis and the "catch-up" phenomenon of late restenosis in patients treated with DES. Improvements needed in stenting technique include limiting the balloon injury zone to match the stented treatment zone, the use of longer stents to cover reference segment disease, avoidance of gaps between stents, and the use of intravascular ultrasound to insure complete stent-wall apposition and full lesion coverage. Avoiding pre- and post-dilation outside of the stent treatment zone will be mandatory to avoid collateral balloon injury.

Whether other drug-eluting agents have qualities that enhance DES will be decided as the results of the DELIVER trial with paclitaxel are presented.

Whether other drug-eluting agents have qualities that enhance DES will be decided as the results of the DELIVER trial with paclitaxel are presented. Additional clinical studies are ongoing or planned to evaluate the efficacy of DES in bifurcation lesions, unprotected left main lesions, and saphenous vein graft disease. In addition, interventional cardiologists need to consider other technological innovations, including the new-generation VISION™ stent, on its own or as a drug delivery device, in addition to "older" technologies such as IRT. An exciting, potentially valuable development is the emergence of photophoresis to reduce restenosis. An aliquot of a patient's peripheral blood is removed, separating the leukocyte-depleted blood and returning it to the patient. The leukocyte-enriched plasma is then exposed to ultraviolet light and to the photoactive substance methoxsalen. These cells are then returned to the patient where they modulate the inflammatory T-cell response to injury. A pilot trial has shown a significant reduction of restenosis.[46]

The costs of DES highlight the need to objectively identify those lesions that are hemodynamically significant, and physiologic assessments can help do so. This evaluation can be performed in the catheterization laboratory by measuring coronary blood flow reserve. In a study by Chamuleau and associates in which PTCA in lesions of intermediate severity was deferred, if coronary flow reserve was at least 2 or single photon emission computed tomography (SPECT) was negative, coronary flow reserve allowed for better risk stratification than did SPECT.[47] Assessments of coronary flow reserve can also be estimated prior to cardiac catheterization using contrast-enhanced magnetic resonance imaging and positron emission tomography.[48] These last technologies are currently being studied in clinical trials. We are also witnessing the evolution of technologies that will identify those plaques that are truly vulnerable and may be eligible for "passivation therapies."

The optimal approach to patients in the catheterization laboratory remains a moving target as brachytherapy, improvements in stent design, and new drug-eluting stents become available.

Conclusion

For the treatment of obstructive coronary disease, some data-based recommendations can be made for the treatment of physiologically significant coronary obstructions:

- *Diabetics:* The benefits of DES versus other technologies support the use of DES even in the presence of multivessel disease.
- *Small-vessel disease:* In vessels between 2.26 and 3 mm in diameter, use of DES seems reasonable; however, proximal-edge restenosis needs to be avoided by meticulous coverage of the balloon injury zone by the DES.
- *Bifurcation disease:* Available data on the subset of patients with this condition are inadequate to make any strong recommendations at the present time.
- *In-stent restenosis:* Even though the results of DES in general have been encouraging, the benefits are not as clear as those seen in the treatment of *de novo* lesions. A clinical trial comparing the ability of IRT and DES to treat ISR is needed to determine the most optimal therapy. A reasonable approach would be to consider IRT when the alternative DES approach would mandate multiple stent implantations of which the costs are prohibitive and the results unclear.
- De novo *very long lesions (> 30 mm):* No data have been released evaluating IRT or DES.
- De novo *large vessel focal stenosis:* In vessels > 3.0 mm MLD and lesion length < 15 mm a DES approach seems preferred.

The optimal approach to patients in the catheterization laboratory remains a moving target as brachytherapy, improvements in stent design, and new drug-eluting stents become available. What is clear is the need for interventional cardiologists to become intimately familiar with these evolving technologies as our approach to obstructive disease becomes lesion specific. The costs of drug-eluting stent technology will mandate its thoughtful and meticulous application in order to attain the results so far seen in clinical trials. ■

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