The Approach to Small Vessels in the Era of Drug-Eluting Stents

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The treatment of small-vessel disease will occupy an increasingly important part of interventional cardiology practice and this raises several issues. The definition of "small vessels" has great implications for device size selection, and knowledge of "normal" small-vessel dimensions is important. Stents have been applied in the setting of smaller-vessel disease and future iterations of small-vessel stents will need to address several design factors. Stent strut thickness might impact on subsequent restenosis as well as late lumen loss. There has been great interest in the use of drug-eluting stents for small vessels. Randomized clinical trials of sirolimus-eluting versus bare metal stents in the treatment of small-vessel disease have shown significant improvements in the rates of target lesion revascularization and restenosis with sirolimus-eluting stents. These improvements in restenosis rates are attributable to the low levels of late loss with the drug-eluting stent.
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The treatment of patients with "small-vessel" disease is expected to become more important as high-risk patients (particularly diabetics) and lesions are considered for percutaneous coronary interventions. There are several considerations in this setting.

Table 1
Coronary Dimensions (in Millimeters) in Men and Women with Angiographically Normal Coronary Arteries

Vessel	Normal Men	Normal Women
Proximal RCA	3.9 ± 0.6	3.3 ± 0.6
Mid RCA	3.5 ± 0.6	3.3 ± 0.6
LMCA	4.5 ± 0.5	3.9 ± 0.4
Proximal LAD	3.6 ± 0.5	3.2 ± 0.5
Mid-LAD	2.9 ± 0.5	2.8 ± 0.5
Proximal circumflex	3.4 ± 0.5	2.9 ± 0.5
Mid-circumflex	2.8 ± 0.5	3.1 ± 0.4

RCA, right coronary artery; LMCA, left main coronary artery; LAD, left anterior descending artery. Data from Dodge et al.[1]

Definition and Documentation of Small Vessel Disease

The definition of "small vessels" has great implications for device size selection. Because the angiographic findings represent only the vessel lumen, it might not be possible to determine whether a vessel that is small angiographically is actually small or small because of diffuse disease. Alternatively, a vessel might appear small because it is underfilled by virtue of a subtotal or a completely occluded upstream vessel. Assessment with intravascular ultrasound (IVUS) allows better understanding of the true vessel size unless there has been significant negative remodeling. It must be remembered that if there is a great disparity between the vessel size by angiography and intravascular ultrasound, sometimes because of marked positive remodeling, it might be hard to select the optimal device size; for example, a mid-right coronary artery that by angiography is only a 2.5-mm vessel but by IVUS is a 3.5- or 3.75-mm vessel presents a dilemma for selection of the optimal device size.

Table 2
Predicted Angiographic Restenosis Rates Based on Stent Minimal Lumen Diameter (MLD), Lesion Length, and Presence or Absence of Diabetes Mellitus

	Lesion Length (mm)			
In-stent MLD (mm)	10	15	20	25
Diabetics				
2.5	35%	39%	43%	46%
3.0	23%	26%	30%	33%
3.5	15%	17%	19%	22%
4.0	9%	10%	12%	14%
Nondiabetics				
2.5	27%	30%	33%	37%
3.0	17%	19%	22%	25%
3.5	10%	12%	14%	16%
4.0	6%	7%	8%	10%

Angiographic data are available on vessel size. Dodge and colleagues[1] evaluated coronary artery size in a series of consecutive patients undergoing coronary angiography. They found that men had larger vessels than women but that the proximal vessels, which are typically treated with stent implantation, are larger than often appreciated (Table 1). For example, in men, the proximal left anterior descending and proximal right coronary arteries, respectively, are 3.6 mm and 3.9 mm in diameter. In women, they are 3.2 mm and 3.3 mm, respectively. These dimensions are larger than usually appreciated by interventional cardiologists. These investigators also found that the lumen diameter was not affected by age or vessel tortuosity but was increased with left ventricular hypertrophy or left ventricular dilatation. Knowledge of these "normal" dimensions is important. For example, from a practical standpoint, selection of a 3.0-mm stent in a proximal right coronary artery might mean that the stent is too small. In addition, vessels taper over their course, depending in part on the length of the vessel and the presence of side branches. A stent of ideal diameter for a proximal vessel might be oversized for the more distal vessel if the stent is too long.

Pathologic Substrate

Inappropriately small vessels are typically a marker of diffuse disease. In these vessels, with conventional percutaneous transluminal coronary angioplasty (PTCA), the results of treatment have been characterized

by decreased initial success rates with increased dissection, acute or threatened closure, increased no reflow either because of the heavily diseased distal vessel with poor runoff or embolization of the increased volume of plaque, increased late subacute closure rates, and finally increased rates of restenosis.[2,3] The relationship between vessel size and particular vessel size, lesion length, and diabetes has been well studied (Table 2).[4] This relationship has been evaluated for studies of both conventional PTCA and stent implantation.

Stent Implantation

Because of the strength of relationship in terms of restenosis between vessel size and subsequent development of restenosis, stents have been applied in the setting of smaller-vessel disease. It must be remembered that the stents used in the earlier experiences were not specifically designed for small vessels—they were larger stents crimped on smaller balloons. This might have impacted the results. Moreno and colleagues[5] performed a recent meta-analysis of 11 trials that randomized a total of 2971 patients to either conventional PTCA or to a variety of stents. There was variability in both the specific stent evaluated and the definition of small vessels, which might have led in part to the variability in the results among the studies. In addition, the amount of acute gain varied among the studies. As can be seen in Figure 1, the restenosis rate was improved by stent implantation, with a relative risk of 0.77 (95% confidence interval [CI] 0.65, 0.92).

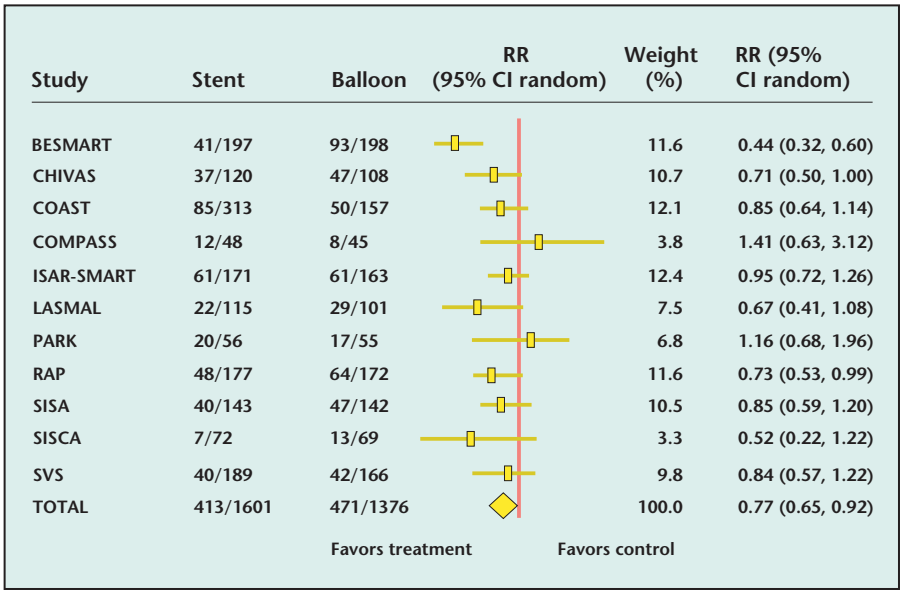

Figure 1. *Data from a recent meta-analysis of 11 trials that randomized a total of 2971 patients to either conventional percutaneous transluminal coronary angioplasty or to a variety of stents for small coronary vessels. Test for heterogeneity: $\chi^2(10) = 21.32$, P = .019; test for overall effect z = 2.93, P = .003. Reproduced with permission from Moreno et al.*[5]

Prediction of Early Cardiac Events

The relationship between early cardiac events after stent placement and vessel size in coronary arteries with reference vessel less than 3.0 mm has been studied in 3156 patients.[6] This group included patients with unstable angina and patients with acute myocardial infarction. The 30-day cumulative early thrombotic outcome was 4.2%, which included mortality in 85 patients (2.7%), nonfatal myocardial infarction in 0.9%, and stent thrombosis in 19 patients (0.6%). Eight variables were identified by logistic regression analysis as being associated with thrombotic events; these included clinical, lesion, and procedural variables (Table 3).

Table 3
Independent Predictors of Thrombotic Events Within 30 Days in Patients Treated With Stents for Small Vessels

	χ^2 Statistic	*P*	Adjusted OR (95% CI)
Clinical variables			
Female	6.5	.011	1.64 (1.12, 2.38)
Abnormal LV function	38.4	<.001	3.08 (2.16, 4.40)
Acute coronary syndrome	22.6	<.001	2.53 (1.73, 3.72)
No hypertension	13.2	<.001	1.92 (1.35, 2.70)
Lesion-related variables			
Complex lesions (B2/C)	6.9	.009	2.09 (1.21, 3.63)
Primary lesion	8.4	.005	2.86 (1.41, 5.89)
Procedural variables			
Length stented segment	7.6	.006	1.21 (1.06, 1.39)
Residual dissection	29.2	<.001	5.38 (2.92, 9.92)

OR, odds ratio; CI, confidence interval; LV, left ventricular. Adapted with permission from Hausleiter et al.[6]

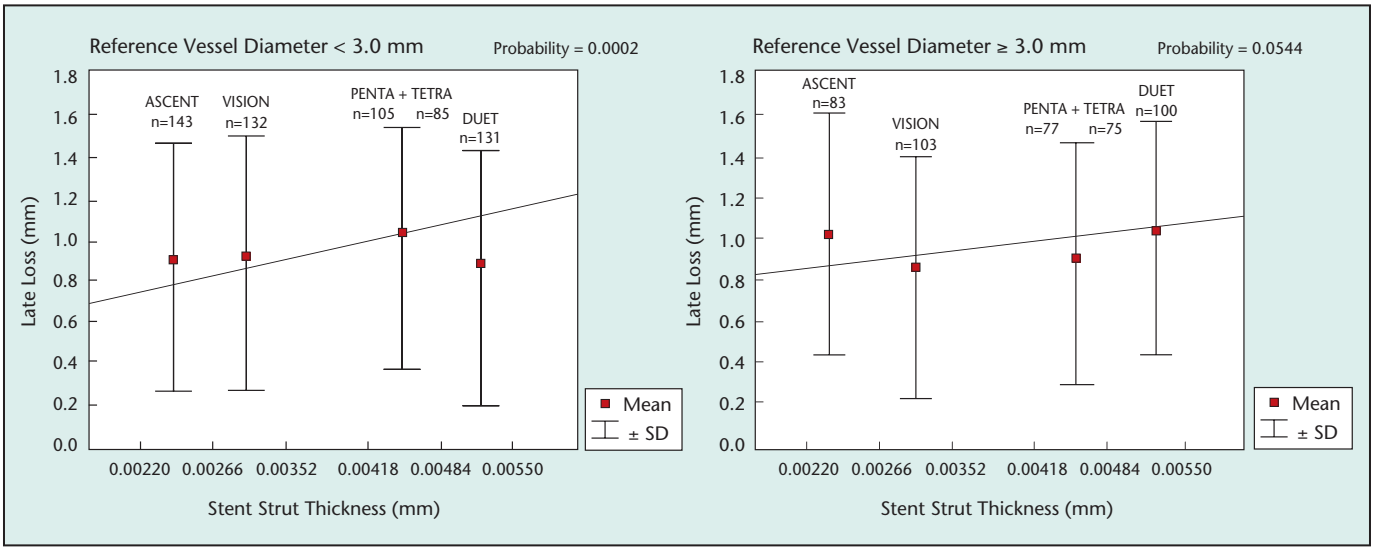

Figure 2. *Relationship of stent strut thickness to coronary late lumen loss, by reference diameter. Reproduced from Kereiakes.*[9]

Specific Bare Metal Stent Device Used

There is great variability in stent configuration and design. Strut thickness might impact on subsequent restenosis as well as late lumen loss.[7,8] In a clinical trial of 611 patients undergoing stent implantation, there was random assignment to either a stent with a 50-µm-thick strut or a stent with a 140-µm-thick strut. Angiographic restenosis in the thin-strut group was only 17.9%, compared with 31.4% in the thick strut group.[7] In smaller vessels, there is some suggestion that thinner struts might even be more important than in larger vessels (Figure 2).[9]

Drug-Eluting Stents in Small Vessels

There has been great interest in the use of drug-eluting stents for small vessels.[10-14] There is an expanding body of knowledge about this group, from subset analyses of larger multicenter randomized clinical trials and registries and from randomized clinical trials specifically aimed at evaluating small vessels. The majority of the information relates to the more robust data set of sirolimus-eluting stents (SES). In the multicenter randomized clinical trial SIRIUS (Sirolimus-Coated Bx Velocity Balloon-Expandable Stent), vessel size was broken down into terciles: small (approximately 2.3 mm), medium (approximately 2.8 mm), and large (approximately 3.3 mm).[13] As can be seen in Figure 3, in the bare metal stent group (control), there was a dramatic relationship between vessel size in terciles and restenosis, ranging from 42.9% in the smallest vessels to 30.2% in the largest vessels. There was also a relationship in the SES-treated patients: the larger vessels had an in-segment restenosis rate of 1.9%, whereas in small vessels it was 18.6%. Although the latter rate remains elevated, it is still significantly improved when compared with that seen with bare metal stents.

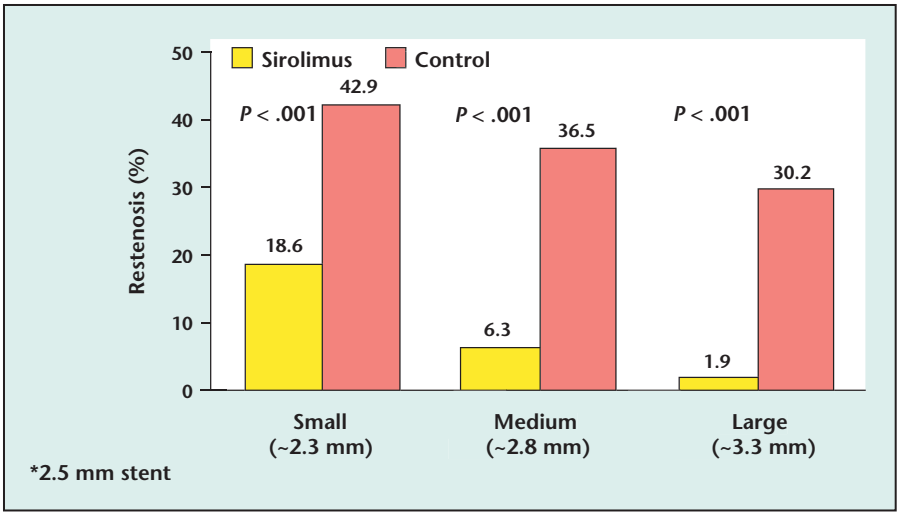

Figure 3. *CYPHER® vs Bx Velocity™ stent (both Cordis Cardiology, Miami Lakes, FL): in-segment restenosis by vessel size tercile in the SIRIUS trial, as assessed by late quantitative coronary angiography.*

There have been two specific randomized clinical trials of SES in the treatment of small-vessel disease. Schofer and colleagues[11] randomly assigned 352 patients undergoing treatment of de novo lesions 15 mm to 32 mm in length and 2.5 mm to 3.0 mm in diameter to either an SES or a bare metal stent (mean vessel diameter was 2.55 mm). There was no difference in initial procedural success rates, which were 100% and 99.4%, respectively, for SES and bare metal stents. There was also no difference in follow-up events of death or myocardial infarction. There was, however, a dramatic reduction in target lesion revascularization (4.0% vs 20.9%; 95% CI –23.6, –10.2; $P < .0001$), a dramatic reduction in binary restenosis (5.9% vs 42.3%; $P = .0001$) (Figure 4), and at 8 months, the minimal lumen diameter (MLD) was significantly larger with the SES compared with the bare metal stent (2.22 mm vs. 1.33 mm; $P < .0001$). This larger follow-up MLD was accompanied by a marked improvement in the major adverse cardiac event rate (Figure 5).

In a smaller randomized trial, Schampaert and coworkers[10] randomized 100 patients with a vessel size of 2.5 mm to 3.5 mm to either an SES or a bare metal stent. As was true with the experience of Schofer and colleagues, at 270 days there was no difference in the hard endpoints of death or myocardial infarction, but a dramatic reduction in clinically driven target lesion revascularization (4.0% vs 18.0%; 95% CI –26.0, –2.0) and angiographic restenosis (2.3% vs 52.3%; $P < .0001$) was observed. Late lumen loss both within the stent and within the treated segment were also both dramatically improved with SES compared with bare metal stents.

A third trial[14] has also been reported with even smaller vessels (reference vessel diameter 2.22 mm), which were randomly assigned to either SES or bare metal stent. Dramatic reductions in binary restenosis (9.8% vs 53.1%; $P < .001$) and in target lesion revascularization (7.0% vs 21.1%; $a = .0021$) were observed with SES.

Finally, in a registry experience of 91 patients with 112 lesions with a reference diameter of 1.88 ± 0.34 mm treated with a 2.25-mm SES, the outcome was also excellent.[12] The binary restenosis rate was only 10.7%, target lesion revascularization at 12 months was 5.5%, and late lumen loss was only 0.07 ± 0.48 mm.

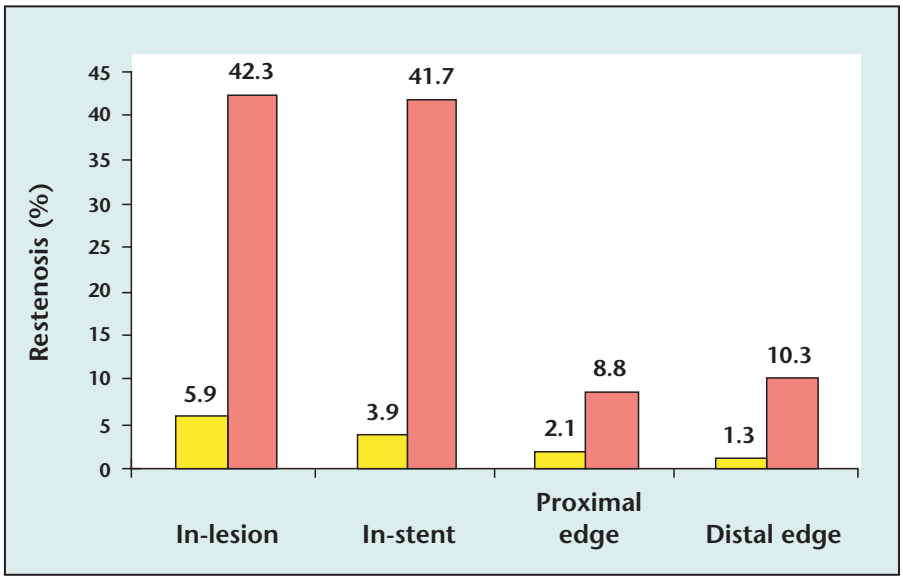

Figure 4. *Restenosis rates in 352 patients with small-vessel lesions treated with either a sirolimus-eluting stent (SES) (yellow bars) or a bare metal stent (orange bars). Data from Schofer et al.[11]*

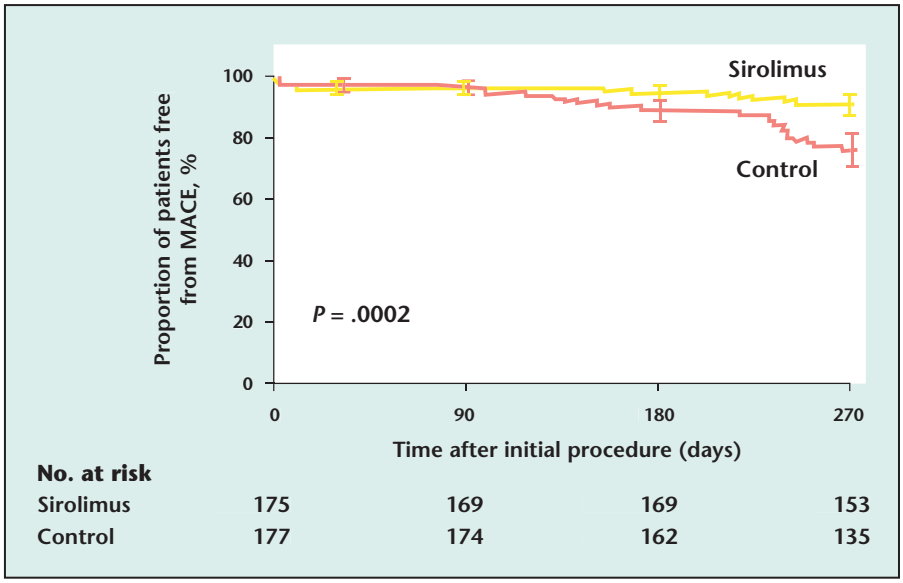

Figure 5. *Kaplan-Meier estimates of survival free from major adverse cardiac events (MACE) in patients with small-vessel lesions treated with either a sirolimus-eluting stent or a bare metal stent (control). Reproduced with permission from Schofer et al.[11]*

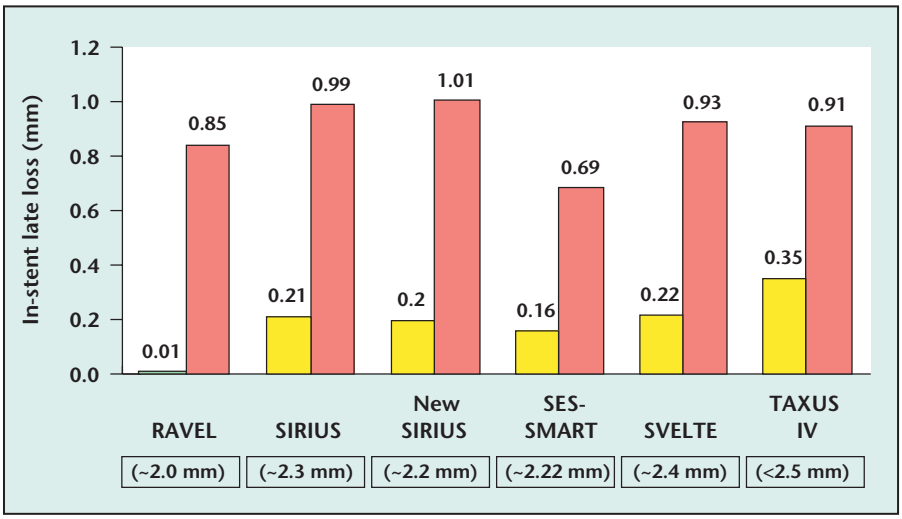

Figure 6. *In-stent late loss in 6 different trials comparing drug-eluting stents (yellow bars) and bare metal stents (orange bars).*

Late Loss

Late loss has been used as a surrogate endpoint in an increasing number of interventional trials. It is defined as the difference between the final MLD at the time of follow-up angiography and the MLD immediately after the index procedure. With bare metal stents, in a variety of studies, the late loss ranges from 0.8 mm to 1.0 mm. This variable has great implications for small vessel disease.

Table 4
Considerations for Development of Small Vessel (<2.99 mm) Drug-Eluting Stents

Component	Attribute	Objective
Stent	Thin strut	↑ Flexibility
		↓ Profile
		↑ Distensibility (low pressure deployment)
	Non-316L SS alloy	↑ Visibility
		↑ Radial strength
Delivery system	"Focal" balloon	↓ (No) Extension beyond stent margin
		↓ Barotrauma/Geographic miss
	Self-expandable	↓ Pressure deployment
Polymer	Viscoelastic properties	↓ Flexibility
		↑ Recoil/Foreshortening
	Drug release kinetics	? Need for protracted delivery
Drug	Specific efficacy in women/diabetics	↑ Prevalence in small target vessel cohorts

Reproduced from Kereiakes.[9]

For example, if the final MLD in a 2.5-mm vessel is 2.10 mm, and then the late loss is 1.0 mm, a significant restenosis issue will exist. The same 1.0-mm late loss would obviously be much better tolerated in a 4.5-mm vessel. There is information on late loss in the drug-eluting stent era (Figure 6). As can be seen with SES, the late loss typically averages 0.15 mm to 0.20 mm. This low level of late loss accounts for the remarkable improvement in restenosis rates compared with bare metal stents.

Ideal Stent Design

As stated previously, stents used for small vessels have typically been similar to larger stents but mounted on smaller balloons. There are some unique considerations that will be incorporated into subsequent small vessel stent iterations (Table 4). Flexibility and low profile will be extremely important for vessel access; thin struts will probably be helpful in this regard. Radial strength might have to be enhanced because of the presence of calcification and diffuse disease. The delivery balloon itself will have to be capable of high pressures with low compliance but also should have a very low overhang segment beyond the stent margins. This latter feature is essential to avoid endoluminal barotrauma to the vessel outside of the stent margins. There is considerable room for improvement both in the polymer and the specific drug used, as well as in the kinetics of the drug delivery. Given the fact that there is still a relationship between vessel size and restenosis, with increased restenosis in small vessels, it might be that more drugs or a combination of drugs will be needed to achieve optimal outcomes. In addition, the drug or drugs might require sustained release over a longer period of time for optimal results.

Conclusion

Treatment of small-vessel disease will occupy an increasingly important part of interventional cardiology practice. The issues are complex, ranging from the definition of small vessels to risk stratification to restenosis (both with and without drug-eluting stents) and finally to new stent designs. Tremendous advances have been made in the field, but work still needs to be done to optimize outcome. ■

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Main Points

- A recent meta-analysis of 11 trials that randomized a total of 2971 patients to either conventional percutaneous transluminal coronary angioplasty or to a variety of stents for small coronary vessels found that the restenosis rate was improved by stent implantation, with a relative risk of 0.77.
- The definition of "small vessels" has great implications for device size selection. Assessment with intravascular ultrasound allows better understanding of the true vessel size than angiography, unless there has been significant negative remodeling.
- Eight variables have been identified as being associated with thrombotic events after placement of stents in small vessels: female, abnormal left ventricular function, acute coronary syndrome, no hypertension, complex lesions, primary lesion, length of stented segment, and residual resection.
- There has been great interest in the use of drug-eluting stents for small vessels; the majority of the available information relates to the more robust data set of sirolimus-eluting stents (SES).
- In the SIRIUS trial, SES-treated patients were shown to have an in-segment restenosis rate of 1.9% in larger vessels, whereas in small vessels it was 18.6%. Although the latter rate remains elevated, it was still significantly improved when compared with that seen with bare metal stents.
- A randomized clinical trial of 352 patients undergoing treatment of de novo lesions in small vessels with either an SES or a bare metal stent demonstrated dramatic reductions in target lesion revascularization and binary restenosis with the SES; at 8 months, the minimal lumen diameter (MLD) was significantly larger with the SES compared with the bare metal stent.
- "Late loss" is defined as the difference between the final MLD at the time of follow-up angiography and the MLD immediately after the index procedure. With SES, the late loss typically averages 0.15 mm to 0.20 mm, which accounts for the remarkable improvement in restenosis rates compared with bare metal stents.