Coronary Small-Vessel Stenting in the Era of Drug Elution

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Stent therapy (versus balloon angioplasty alone) provides predictable outcomes following percutaneous coronary intervention (PCI), in both the immediate, periprocedural setting and in durable (6-12 month) follow-up, in patients with target vessel reference diameters greater than or equal to 3.0 mm. The rate of positive outcomes for stenting, versus balloon angioplasty, is less robust for smaller (< 3.0 mm) coronary vessels. Specific attributes of stent design, including strut thickness and metal alloy composition, influence stent performance characteristics, particularly in smaller coronary vessels. Polymer-based drug elution from stents may reduce or eliminate the inflammatory-neointimal proliferative response provoked by stent deployment but the drug delivery platform remains critically important. The best drug-eluting stent (DES) platform for small coronary vessel applications is one incorporating low profile, enhanced flexibility, and ease of deployment (balloon expandability), as well as providing adequate endoluminal surface coverage for scaffolding and uniform drug delivery. DES specifically designed for small-vessel application will become the standard for small vessel PCI.

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Percutaneous coronary intervention (PCI), particularly stent deployment, elicits an inflammatory response to trauma proportional to the degree of arterial media injury.[1,2] Monocyte-macrophage infiltration is prevalent both early (≤ 3 days) and late (> 30 days) following coronary stent deployment and is integral to the processes of neointimal proliferation and late in-stent restenosis

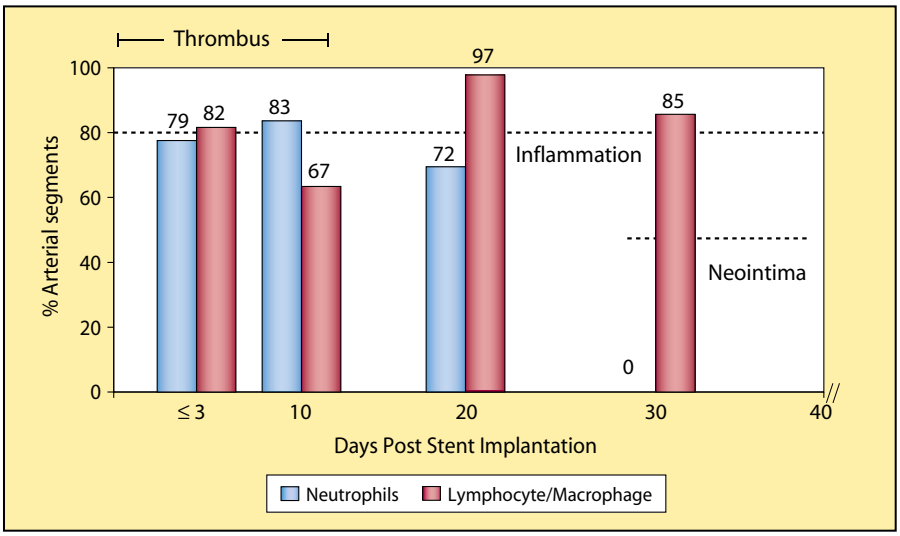


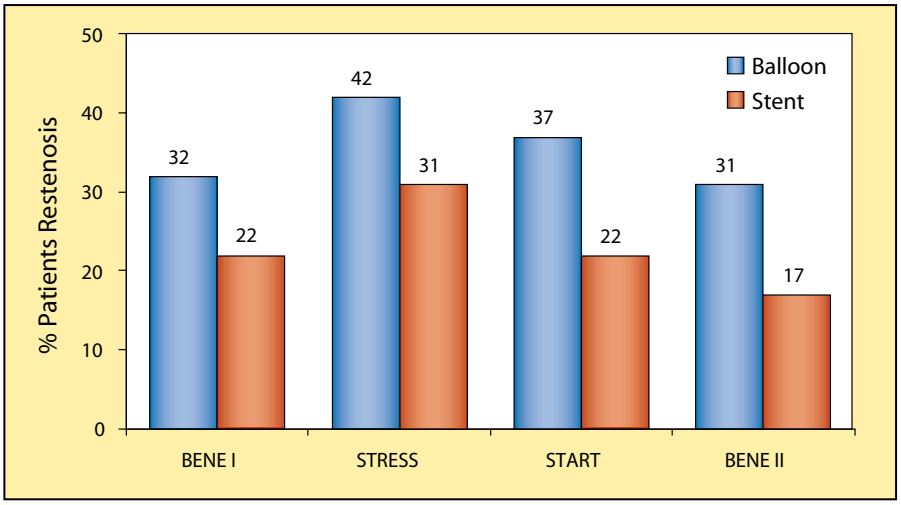
Figure 1. *Histology of the inflammatory response to coronary stent deployment in human studies, illustrated over time. Lymphocyte/macrophage infiltration is prevalent both early (< 3 days) and late (> 30 days) following stent deployment. Data from Farb et al.*[1]

(Figure 1). Coronary restenosis following balloon angioplasty involves the complex interplay of elastic recoil, vessel remodeling (transmural shrinkage or adventitial scarring), and neointimal proliferation.[3] Although stent deployment provides a metal alloy scaffold, which negates elastic recoil and remodeling, it actually increases the magnitude of neointimal proliferation in comparison to that observed following balloon angioplasty.[4] Early randomized, comparative trials of balloon angioplasty versus stenting for the treatment of atherosclerotic coronary obstructions demonstrated a reduction in late clinical and angiographic restenosis and a correlative reduction in the need for repeat target vessel revascularization in patients who were randomly allocated to stent deployment[5-8] (Figure 2). Sequential postprocedural and late (6-month) angiographic and intravascular ultrasound (IVUS) evaluations demonstrated that although the volume of late neointimal tissue response was greater following stent deployment, the stent-metal scaffold provided a much larger postprocedural lumen diameter (vs balloon angioplasty) and, accordingly, net lumen gain (acute gain–late loss) was enhanced by stenting.

An important caveat to the ensuing "stent-is-better-than-balloon" interpretation of these trials is that the enrollment criteria for trial participation included only patients with target vessel diameters of greater than or equal to 3.0 mm. Indeed, the high profile and rigidity of early coronary stent prostheses precluded reliable access to smaller, more distal segments of the coronary tree. Subsequent improvements in stent technology, particularly reduced profile and enhanced flexibility and stent retention, facilitated successful stent deployment in smaller (< 3.0 mm) diameter coronary vessels and led to additional randomized comparative trials of stent versus balloon angioplasty in small coronary vessels.[9-15] Of note, the previously documented salutary benefit of stent over balloon therapy in larger caliber (> 3.0 mm) coronary vessels was less evident and inconsistent in smaller vessels (Figure 3).[16,17] Indeed, despite the number of coronary stent prostheses currently available, no bare-metal stent has yet received U.S. Food and Drug Administration approval for elective deployment in coronary vessels less than or equal to 2.5 mm in diameter.

The more recent availability of polymer-based, drug-eluting coronary stent devices for the treatment

Figure 2. *Binary angiographic restenosis (> 50 %) at 6 months by quantitative coronary angiography in randomized trials of balloon versus stent for percutaneous coronary intervention. These trials enrolled patients with reference vessel diameters > 3.0 mm and were limited by stent availability in lengths of only 15 mm. BENE, BENESTENT (Belgium Netherlands Stent Trial); STRESS, Stent Restenosis Study; START, Stent versus Angioplasty Restenosis Trial. Data from Serruys et al,*[5] *Fischman et al,*[6] *Serruys et al,*[7] *Massotti et al.*[8]



of target vessels 2.5 to 3.5 mm in diameter has prompted a reassessment of our understanding of both the restenosis process and the role of stenting in the treatment of smaller (<3.0 mm) diameter coronary vessels.

The Problem With Small Vessels

Since the advent of PCI, it has been evident that small target-vessel size was a predictor of risk for restenosis. Indeed, multivariate analysis identified preprocedural reference vessel diameter and post-procedural minimum (in-stent) lumen diameter as the most powerful determinants of both late binary (> 50%) angiographic and clinical (target site revascularization) restenosis (Figure 4, Table 1).[5,18-21] Other key determinants of restenosis included lesion or stent length and the presence of diabetes mellitus.[22,23] Although lesion and stent length are collinear, stent length appears to supersede lesion length in importance as it may appreciably exceed lesion length and better reflect the extent of vessel wall injury. The relationships of postprocedural in-stent minimum lumen diameter (MLD) and stent length to angiographic binary restenosis have been correlated for patients with or without diabetes mellitus and show the presence of diabetes as an independent predictor of late lumen loss (Table 2).[23,24] Data from randomized comparative trials of stent versus balloon for PCI, as well as experience from interventional registries, provide insights into the specific attributes of bare-metal stent design that contribute to restenosis and thus to the challenge of stenting in small coronary vessels.

Although a pooled analysis of early, randomized trials comparing stent versus balloon therapy for PCI in small vessels demonstrated no clear advantage for stenting (Figure 3),[16] the influence of both stent design and stent-strut thickness in determining the degree of neointimal proliferative response to deployment are evident.[25-27] Observations from studies utilizing either animal or human models are consistent with the premise that stent design influences the vascular response to stent deployment.[25-28] Stent strut orientation[25] as well as cell (open vs. closed)[29] and stent type (multicellular, slotted tube, coil, self-expanding)[28] influence the degree of stent-induced platelet activation, as well as the magnitude of subsequent inflammatory-neointi-

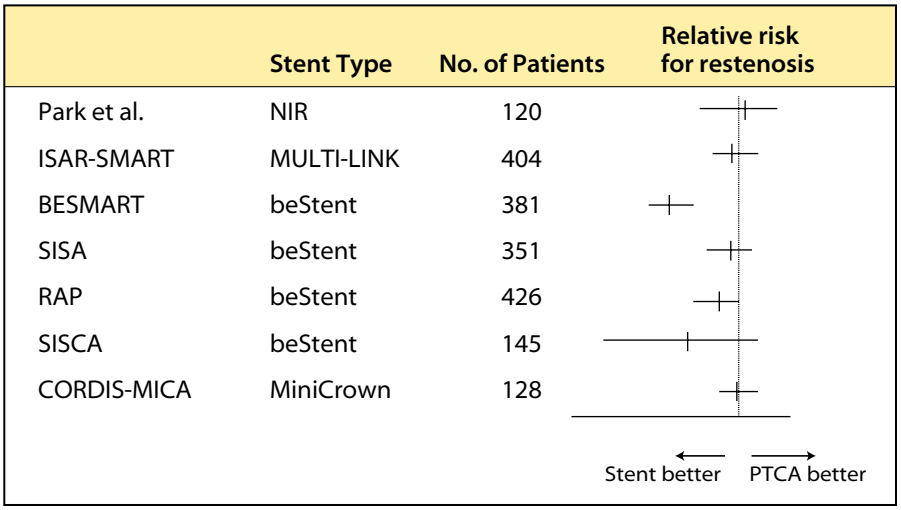
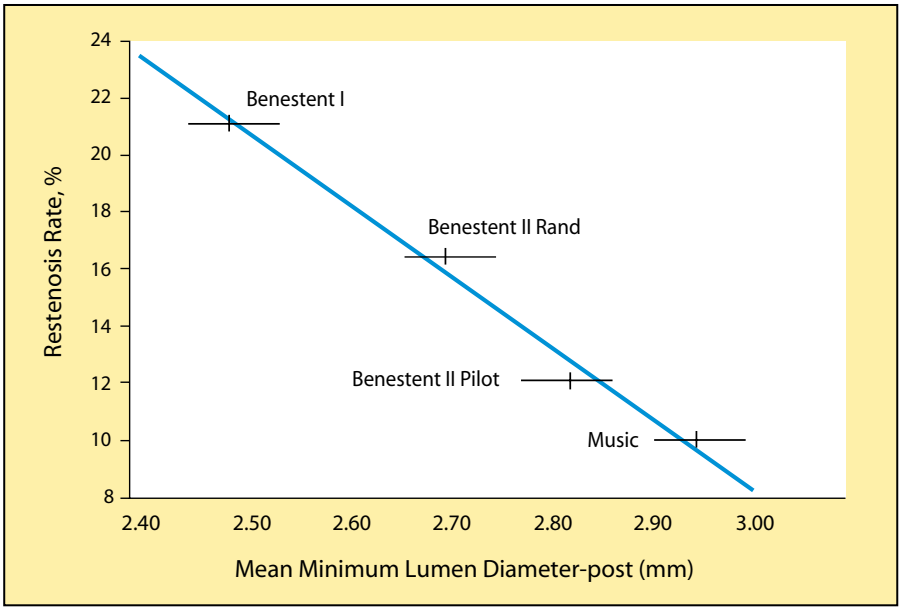


Figure 3. *Pooled analysis of stenting versus balloon angioplasty for small coronary vessels from randomized, comparative trials. ISAR-SMART, Intracoronary Stenting or Angioplasty for Restenosis Reduction in Small Arteries; BESMART, BeStent in Small Arteries; SISA, Stenting in Small Arteries; RAP, Restenosis en Arterias Pequenas; SISCA, Stenting in Small Coronary Arteries; CORDIS-MICA, MiniCrown Stent In Small Coronary Arteries. Reproduced with permission from Kastrati et al.*[16]

Figure 4. *Angiographic binary restenosis is inversely related to minimum lumen diameter (in-stent) postprocedure. Data from individual trials are shown. MUSIC, Multicenter Ultrasound Stenting In Coronaries, BENESTENT, Belgium Netherlands Stent. Reproduced with permission from Serruys et al.*[18]



mal response.[28] Stent strut thickness appears to be a determinant of the degree of stent-vessel injury and, hence, directly relates to subsequent late lumen loss.[23,26,27] Of note, in the pooled analysis of multiple randomized stent versus balloon trials in small-coronary-vessel PCI,[16] those trials which employed stents with thinner struts (i.e. BeStent™, Medtronic, Inc., Minneapolis, MN; 0.0030" strut thickness) demonstrated relative benefit for stent therapy over balloon (Figure 3). In separate, multivariate analyses, stent strut thickness, stent length, and the presence of diabetes were significant correlates with late in-stent restenosis in small (≤ 2.99 mm) coronary vessels.[22,23] In randomized comparative trials of thick versus thin strut stents of either the same (MULTI-LINK,™ Guidant Corporation, Indianapolis, IN)[26] or different (MULTI-LINK™ vs Bx Velocity,™ Cordis Corporation, Miami, FL) stent design,[27] rates of late lumen loss and clinical and angiographic restenosis were increased following deployment of the thicker strut device (Figure 5). Although variability across trials and registry reports exists, in general, the relationship between stent strut thickness and late restenosis remains evident (Figure 6).[30,31] Furthermore, the direct relationship between stent strut thickness and late lumen loss is most apparent for smaller (< 3.0 mm) reference vessel diameters (Figure 7). This observation suggests that stent strut thickness has greater importance in determining late outcomes in smaller caliber vessels.

Others have suggested that although stent strut thickness may correlate statistically with late lumen loss and angiographic restenosis, this relationship pales in importance compared to other variables, such as reference vessel diameter, lesion/stent length, and diabetes mellitus, and

Table 1
Multivariate Analyses from Multiple Stent Trials

Variable	Odds Ratio	*P*
Angiographic Binary (> 50%) Restenosis		
Postprocedural in-stent MLD (per mm)	0.32	<0.001
Lesion length (per mm)	1.03	0.005
Stent length (per mm)	1.02	0.020
Diabetes mellitus	1.48	0.033
Target Lesion Restenosis		
Final MLD (per mm)	0.31	0.0001
Stent length (per mm)	1.02	0.0001
Prior myocardial infarction	0.64	0.0001
Diabetes mellitus	1.40	0.0005
Unstable angina	1.33	0.008
Cigarette smoking	0.80	0.047

MLD, minimum lumen diameter.

Table 2
Prediction of Angiographic Binary (>50%) Restenosis

Stent Length (mm)	Post-Procedure In-Stent MLD (mm)					
	2.50	2.75	3.00	3.25	3.50	3.75
8	16.4	12.3	9.2	6.8	5.0	3.6
15	21.5	16.5	12.4	9.3	6.8	5.0
18	24.0	18.5	14.1	10.5	7.8	5.8
25	30.7	24.2	18.7	14.2	10.6	7.9
28	33.9	26.9	21.0	16.0	12.1	9.0
35	41.8	34.0	27.1	21.1	16.1	12.1
All Patients						
8	16.4	12.3	9.2	6.8	5.0	3.6
15	21.5	16.5	12.4	9.3	6.8	5.0
18	24.0	18.5	14.1	10.5	7.8	5.8
25	30.7	24.2	18.7	14.2	10.6	7.9
28	33.9	26.9	21.0	16.0	12.1	9.0
35	41.8	34.0	27.1	21.1	16.1	12.1
Diabetic Patients						
8	24.7	19.9	15.8	12.4	9.6	7.5
15	30.3	24.7	19.9	15.8	12.4	9.6
18	32.9	27.0	21.8	17.4	13.7	10.7
25	39.3	32.9	27.0	21.8	17.4	13.7
28	42.2	35.6	29.4	23.9	19.2	15.2
35	49.2	42.2	35.5	29.4	23.9	19.2

Binary restenosis (%) at 6-months follow-up is shown as function of stent length deployed and post-procedural in-stent minimum lumen diameter (MLD).
Data from Kereiakes et al.[24] and Mauri et al.[31]

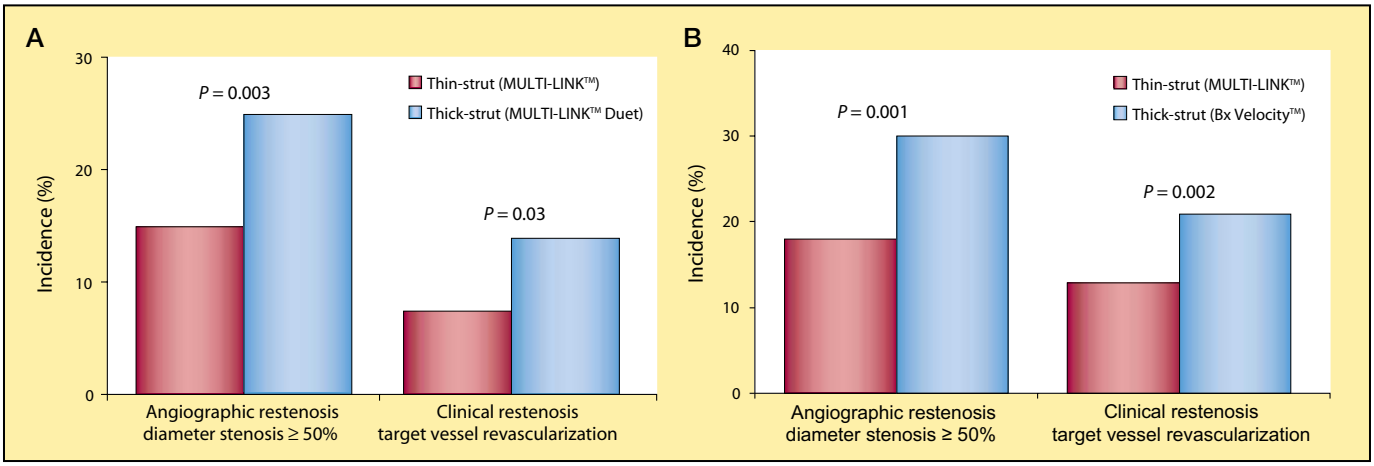
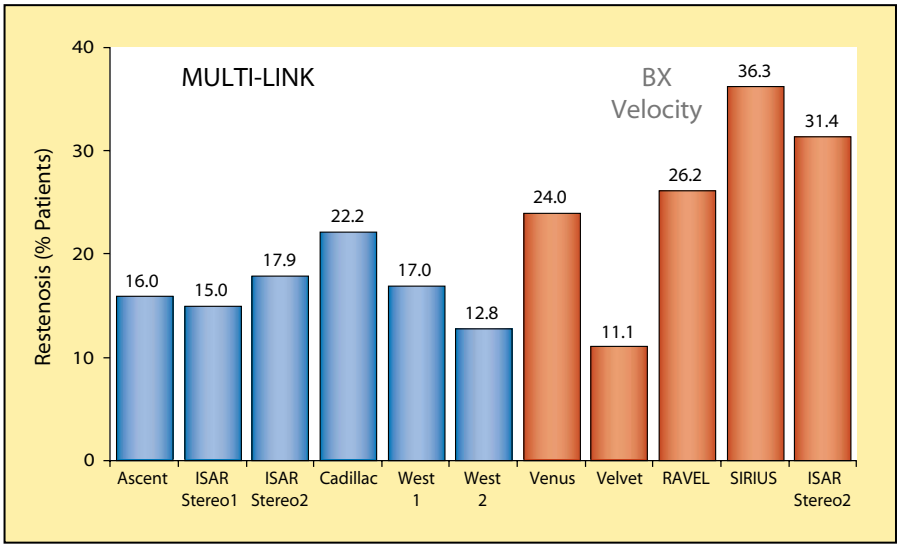


Figure 5. (A) *The ISAR-STEREO 1 trial randomly compared the thin-strut MULTI-LINK™ stent with the thick-strut MULTI-LINK™ DUET stent of otherwise similar design. Both angiographic and clinical restenosis were increased in patients who were randomly assigned to the thick strut MULTI-LINK™ DUET stent.* **(B)** *The ISAR-STEREO 2 trial randomly compared the thin strut MULTI-LINK™ stent with the thicker strut Bx Velocity™ stent. Both angiographic and clinical restenosis were increased in patients randomly assigned to receive the thicker strut stent. ISAR-STEREO, Intracoronary Stenting and Angiographic Results: Strut Thickness Effect on Restenosis Outcome.* **(A)** *Reproduced with permission from Kastrati et al.[26]* **(B)** *Reproduced with permission from Pache et al.[27]*

may not be demonstrable for clinical restenosis (target lesion revascularization).[32] Another interesting observation is that "luminal recovery" (ie, loss of neointimal volume), or regression of the restenotic process, is demonstrable between 6 and 12 months following deployment of either thick- or thin-strut stent devices.[33,34] More recent data suggest that the degree of stent vessel injury may be better described by the multidimensional parameters of either stent cross sectional area or stent metal volume. Stent metal volume may provide a better index of stent vessel injury, particularly in smaller caliber vessels, as it reflects the volume of traumatic tissue displacement.

Metal alloy is yet another determinant of the neointimal response to stent deployment and late restenosis. Multiple randomized comparative trials, utilizing both quantitative coronary angiographic and IVUS evaluation techniques, have demonstrated increased neointimal proliferation and late lumen loss following the deployment of gold versus 316L stainless steel coronary stents, regardless of specific stent design.[35-38] By multivariate analysis, gold metal alloy composition and stent design, as well as the presence of diabetes, were independent predictors of intimal hyperplasia thickness in response to stenting.[38] Similar observations have been made for stents composed of martensitic nitinol.[39] Conversely, cobalt-chromium metal alloy has no detrimental effects on vessel-injury response and has facilitated the development of thinner strut stents with enhanced visibility, flexibility, and radial strength.[40] Although the cobalt-chromium alloys currently employed in stent construction vary considerably in nickel content compared with 316L stainless steel (Table 3), no correlation between percent nickel content and late lumen loss/restenosis has been

Figure 6. *Binary angiographic restenosis by quantitative coronary angiography from randomized trials which employed the thin-strut MULTI-LINK™ stent are compared graphically to the restenosis rates observed in trials which employed the thicker-strut Bx Velocity™ stent. In general, the frequency of binary angiographic restenosis is increased following deployment of the thicker-strut stent. Data derived from Berger.[30]*



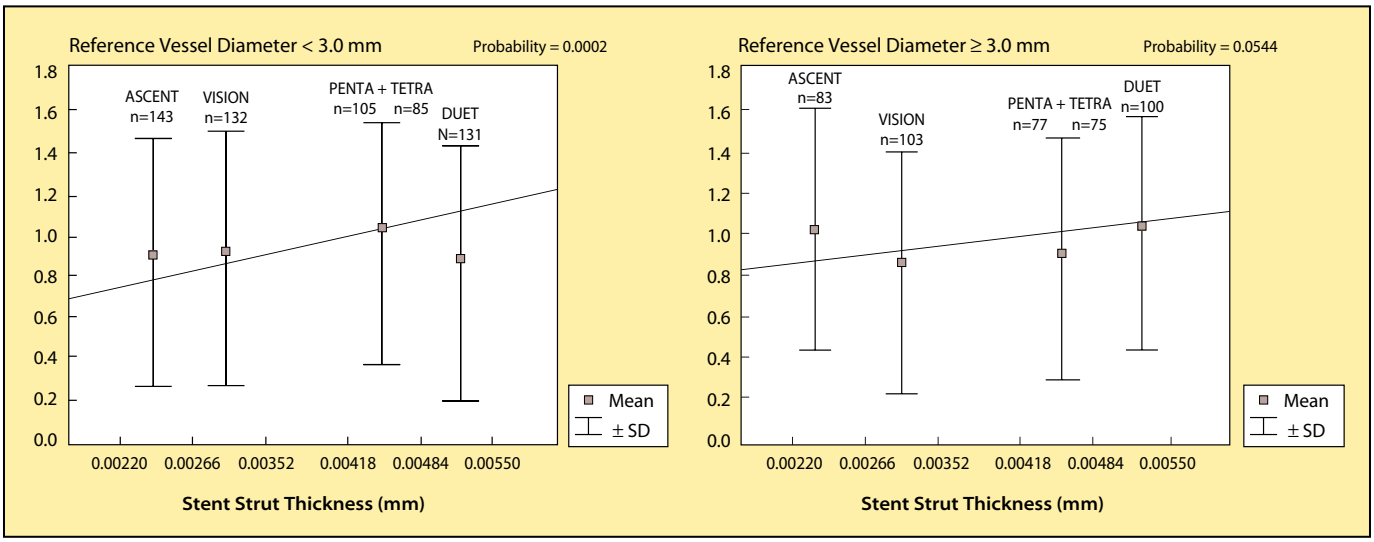


Figure 7. *Relationship of stent-strut thickness to coronary late lumen loss by reference vessel diameter (> 3.0 vs < 3.0 mm). Stent-strut thickness is a powerful determinant of late lumen loss in smaller (< 3.0 mm) vessels. Data derived from the randomized ACS Multi-Link Stent Equivalence in De Novo Lesion Trial (ASCENT), as well as the VISION, PENTA, TETRA and DUET registries. Analyses and graphics provided by Stan Fink, PhD, Guidant Corporation.*

established.[40,41] The availability of thinner strut, lower profile stents with enhanced flexibility has facilitated access to more tortuous, small-caliber, coronary vessels. Cobalt-chromium stents currently available and approved for coronary use include the MULTI-LINK VISION,™ (Guidant Corporation) and DRIVER (Medtronic, Inc.) stents in diameters of 3.0 mm to 4.0 mm. These stents have strut thicknesses of 0.0032" and 0.0036" respectively with crossing profiles for the stent/balloon delivery system (3.0 mm diameter stent) of 0.039" and 0.043," respectively. Despite the obvious attraction of these devices for use in small caliber vessels, they are not yet available, in the United States, in diameters less than 3.0 mm.[41]

The Current Standard for Small Vessel Platforms

The MULTI-LINK PIXEL® (Guidant Corporation) coronary stent combines 5 crest circumferential coverage (compared with the standard 6 crest Multi-Link stent design) with thinner (0.0039") strut thickness to optimize scaffolding while reducing metal thickness/strut-induced injury during small-vessel stenting. The Pixel stent was evaluated in 150 patients with abrupt or threatened coronary closure following balloon angioplasty. Stent sizes deployed included 2.5 mm (62.7%), 2.25 mm (20.5%) and 2.0 mm (16.9%) and rates of

Table 3
Chemical Requirements for Stent Composition

Element	316L SS* Min/Max %	VISION™ ** Min/Max %	DRIVER™ # Min/Max %
Carbon	/0.030	0.05/0.15	-/0.025
Manganese	/2.00	1.00/2.00	-/0.15
Silicon	/0.75	-/0.40	-/0.15
Phosphorus	/0.025	-/0.040	-/0.015
Sulfur	/0.010	-/0.030	-/0.010
Chromium	-- /17.00-19.00	19.00/21.00	19.00/21.00
Nickel	-- /13.00-15.00	9.00/11.00	33.00/37.00
Molybdenum	-- /3.00	--	9.0/10.5
Tungsten	--	14.00/16.00	--
Iron	Balance	-/3.00	-/1.0
Cobalt	--	Balance	Balance
Titanium	--	--	-/1.0
Boron	--	--	-/0.015
Nitrogen	-- /0.010	--	--
Copper	-- /0.50	--	--

*ASTMF 138-00
**ASTMF 90-97
ASTMF 562-02
SS, Stainless Steel

both device and procedural success were high (97.3% and 100%, respectively). Clinical outcomes to 30 days and 180 days following Pixel stent deployment were quite favorable (Table 4).

Table 4
Clinical Outcomes to 30 and 180 Days Following PIXEL® Coronary Stent Deployment

		30 Day (n=150)	180 Day (n=147)
Event	Number	%	%
TVF (MI, TLR, TVR)	2	1.3	13.6
Any MACE (Death, MI, CABG, TLR)	1	0.7	10.2
Target Vessel Revascularization (TVR) not at the Target Lesions	1	0.7	3.4
Target Lesion Revascularization (TLR)	0	0.0	6.1
• CABG	0	0.0	1.40
• PTCA	0	0.0	4.8
Stent Thrombosis	1	0.7	0.7
Death	0	0.0	0.0
Myocardial Infarction	1	0.7	4.1
• Q-Wave MI	0	0	0.7
• Non-Q-Wave MI	1	0.7	3.4

TVF, target vessel failure; TLR, target lesion revascularization; TVR, target vessel revascularization; MI, myocardial infarction; MACE, major adverse cardiovascular events; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.

The Era of Drug-Eluting Stents

With the advent of drug-eluting stent (DES) technology, renewed interest and enthusiasm has been generated in stenting small coronary vessels. Multivariate analysis of A Multicenter, Randomized, Double Blind Study of the Sirolimus-Coated BX Veolicty™ Balloon-Expandable Stent in the Treatment of Patients With De Novo Coronary Artery Lesions (SIRIUS) trial angiographic data identified reference vessel diameter (RVD) as a significant independent predictor of binary angiographic restenosis (Table 5) with an odds ratio of 0.42 per mm vessel diameter ($P < 0.0001$).[42] A similar relationship of RVD to target lesion revascularization (TLR) was observed as well. As would be expected, RVD was not independently correlated with late lumen loss (odds ratio 0.96 per mm vessel diameter; $P = 0.37$), which remained relatively constant and device-dependent (CYPHER,™ Cordis Corporation, vs Bx Velocity™) regardless of vessel size. The relationship between late loss and postprocedural MLD determines binary angiographic restenosis. In-stent late loss and binary restenosis by tertile of target-vessel size and randomly assigned treatment allocation (CYPHER™ vs. Bx Velocity™) in the SIRIUS trial (Figure 8) demonstrates little difference in late loss or restenosis in the lowest versus highest vessel tertiles. Conversely, in-segment analysis, which includes 5 mm vessel margins proximal and distal to the deployed stent, demonstrates an increase in late loss and restenosis in the smallest (versus largest) tertile vessels (Figure 9). Thus, the inverse relationship between vessel size and restenosis observed with bare metal

Table 5
Multivariate Analysis of the SIRIUS Trial: Angiographic and Clinical Restenosis

Predictor	Binary (>50%) Angiographic Restenosis		Target Lesion Revascularization		Late Loss (in-segment)	
	Odds ratio	*P* value	Odds ratio	*P* value	Odds ratio	*P* value
Treatment (CYPHER™ vs control)	0.21	<0.0001	0.15	<0.0001	1.76	<0.0001
RVD (per mm)	0.42	<0.0001	0.42	<0.0001	0.96	<0.37
Lesion length (per 10 mm)	1.58	0.032	1.41	0.032	1.08	0.044
Diabetes mellitus	1.72	<0.0001	2.39	0.0001	1.26	0.0001

RVD, reference vessel diameter.

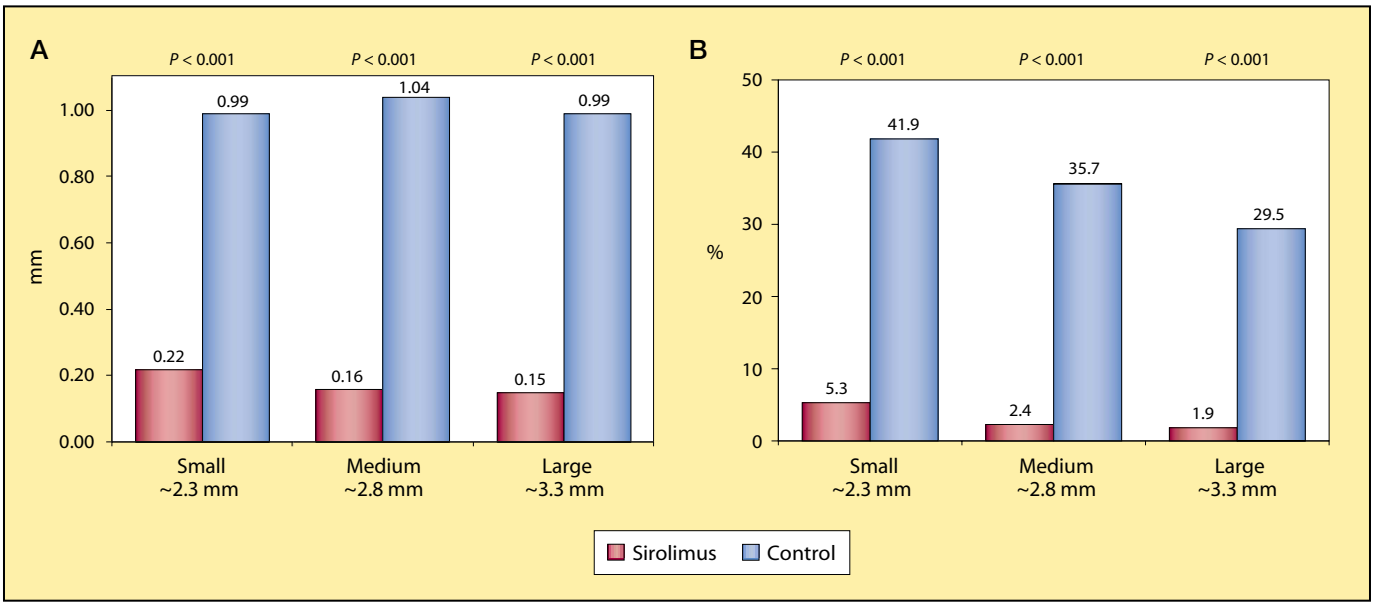
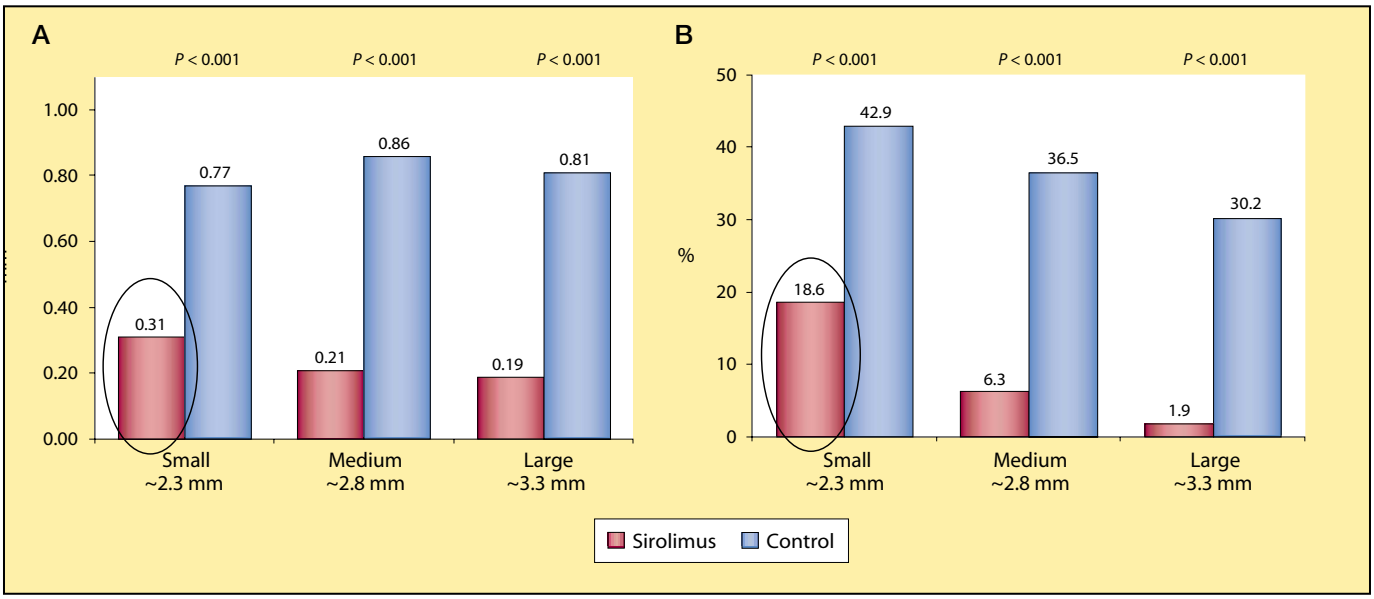


Figure 8. (A) *In-stent late loss and* **(B)** *in-stent restenosis, grouped by vessel size tertile, following deployment of the sirolimus-eluting (CYPHER™) stent versus control (Bx Velocity™) stent in the SIRIUS trial angiographic cohort at 8-month follow-up.*

stents is maintained following CYPHER™ DES deployment. Furthermore, the differential between in-stent and in-segment restenosis points to the importance of the stent delivery system and the propensity for inducing vessel injury outside the confines of the stent drug-delivery platform. This phenomenon is the conceptual equivalent of "geographic miss" as observed in trials of brachytherapy.

Thus, it appears that even in the era of DES, vessel injury at the margins of the stent must be minimized or eliminated, or treated pharmacologically. The extent of balloon extension beyond the stent margins ("balloon hangout") and maximum pressure required for stent deployment may influence the extent of

Figure 9. (A) *In-segment late loss and* **(B)** *in-stent restenosis for patients randomly assigned to receive the sirolimus-eluting (CYPHER™) versus control (Bx Velocity™) stents in the SIRIUS trial angiographic cohort at 8-month follow-up. Patients grouped by vessel-size tertile.*



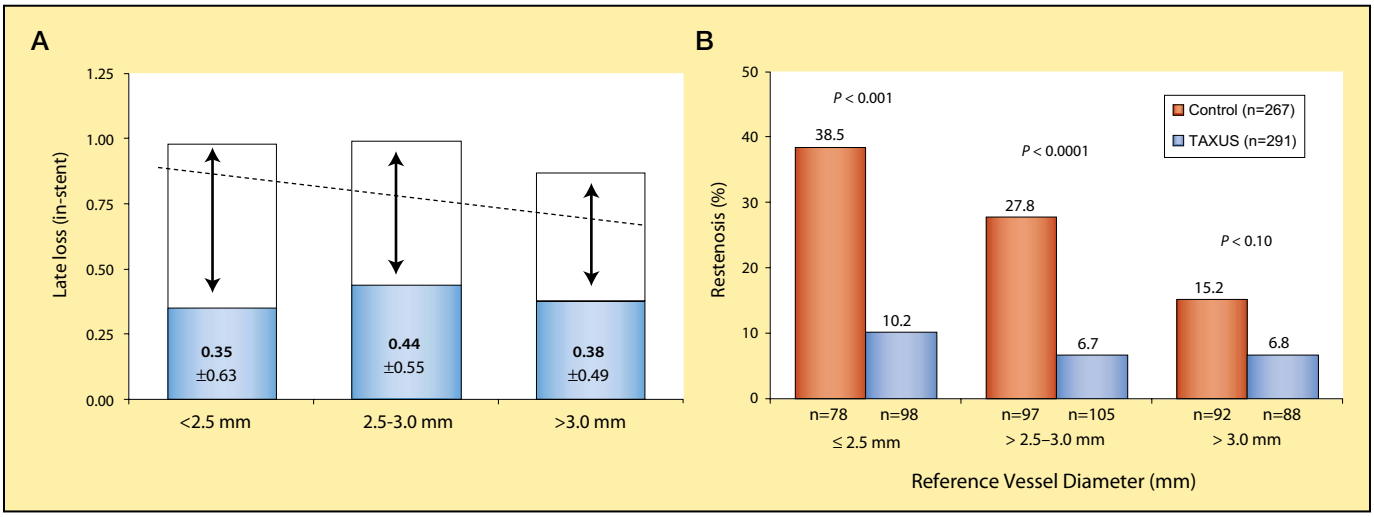


Figure 10. (A) *Late coronary lumen loss in-stent by quantitative coronary angiography is shown by reference vessel diameter for the TAXUS™ drug-eluting stent (blue shaded areas) versus the control (Express 2™) bare-metal stent (orange-shaded areas). The magnitude of late lumen loss reduction with TAXUS™ versus control appears increased in vessels with the smallest lumen diameter (< 2.5 mm).* **(B)** *Restenosis by quantitative angiography at 9-month follow-up by randomly allocated stent treatment (TAXUS™ vs Express 2™), shown by reference vessel diameter.*

endoluminal injury beyond the stent margin. Although stent strut thickness appears less important for DES, it may nonetheless influence device profile flexibility and deployment pressure, which in turn determine device deliverability as well as the potential for marginal vessel injury.

Data are now available on a second polymer-based DES (TAXUS,™ Boston Scientific Corporation, Natick, MA) and give further insight into the utility of DES in small vessels.[43,44] Analysis of angiographic data from the TAXUS IV trial, grouped by target vessel diameter and randomly allocated treatment device (TAXUS™ versus Express 2,™ Boston Scientific Corporation, stent), demonstrates no apparent relationship between vessel diameter and either in-stent late loss or in-segment binary restenosis (Figure 10). CYPHER™ and TAXUS™ are both relatively thick strut devices (0.0055" for CYPHER™; 0.0052" for Express 2™/TAXUS™).

Although comparisons made across trials have prohibitive limitations due to differences in patient demographics, trial definitions, and completeness of follow-up, an appreciable increase in restenosis for the smallest vessels (< 2.5 mm) evaluated was not observed in the TAXUS trial. In addition to the above noted factors, as well as the play of chance, differences in the balloon stent delivery system, lipophilicity of the medication being delivered, or in the kinet-

Table 6
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

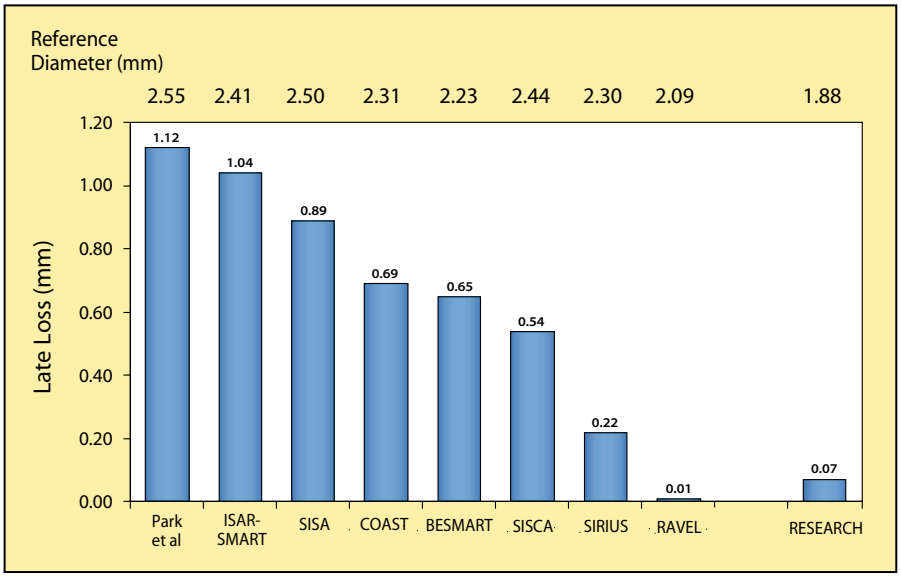


Figure 11. *Late lumen loss and reference vessel diameter by quantitative angiography from the SIRIUS and RAVEL trials (smallest vessel tertiles), 6 randomized trials of stent vs balloon angioplasty for small vessels, and the RESEARCH Registry. COAST, Heparin-Coated Stents in Small Arteries Trial; RESEARCH, Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital. Reproduced with permission from Lemos et al.*[45]

ics of drug delivery may influence the apparent salutary effects of TAXUS™ versus CYPHER™ in the smallest caliber vessels.

More recently, registry data in patients studied following the use of the 2.25 mm diameter CYPHER™ stent have documented remarkably low values for late lumen loss (in-stent) and binary restenosis (10.7%). In-stent late lumen loss was at least comparable to that previously documented for the smallest tertile of vessels enrolled into the SIRIUS or the Randomized Study With the Sirolimus Coated Bx Velocity Balloon Expandable Stent in the Treatment of Patients With de Novo Native Coronary Artery Lesions (RAVEL) trials (Figure 11). Indeed, in 112 coronary stenoses treated with the 2.25 mm diameter CYPHER™ stent, the average late lumen loss was 0.07 mm (reference vessel diameter 1.88 mm).[45,46] These registry observations are confirmed by the results of the recently published Canadian Study of the Sirolimus-Eluting Stent in the Treatment of Patients with Long de novo Lesions in Small Native Coronary Arteries (C-SIRIUS) trial.[47] In C-SIRIUS, 100 patients were randomly assigned to treatment with either the CYPHER™ (n=50, mean reference vessel diameter 2.65 ± 0.30 mm) or Bx Velocity™ (n=50; mean reference vessel diameter 2.62 ± 0.35 mm) stents. At 8 months, late lumen loss (in-stent) was 0.12 ± 0.37 vs. 1.02 ± 0.69 mm and binary restenosis was 2.3 vs. 52.3% for the CYPHER™ vs. Bx Velocity™ stents, respectively.[47]

A View to the Future

Although it is likely that the obligate increment in late lumen loss provoked by stent therapy in small coronary arteries can be overcome by polymer-based drug delivery, meticulous attention to the drug-delivery platform remains essential (Table 6). The ability to easily access

Main Points

- Early randomized, comparative trials of balloon angioplasty versus stenting for the treatment of atherosclerotic coronary obstructions demonstrated a reduction in late clinical and angiographic restenosis and a correlative reduction in the need for repeat target vessel revascularization in patients who were randomly allocated to stent deployment. However, these trials only included patients with a target vessel diameter greater than 3.0 mm.
- Stent design, strut thickness, and choice of metal alloy are all determining factors of the neointimal response to stent deployment and the possibility of late restenosis.
- Patient variables, such as reference vessel diameter, lesion versus stent length, and the presence or absence of diabetes mellitus, may have as great an influence on rates of late lumen loss and restenosis in stenting procedures.
- With the advent of drug-eluting stent technology, renewed interest and enthusiasm has been generated in stenting small coronary vessels. The SIRIUS trial of drug-eluting stents showed no difference in rates of late loss and restenosis, regardless of target vessel diameter.
- The MULTI-LINK PIXEL® coronary stent combines 5 crest circumferential coverage (compared with the standard 6 crest Multi-Link stent design) with thinner strut thickness to optimize scaffolding while reducing metal thickness/strut-induced injury during small-vessel stenting.

small-caliber vessels will preferentially drive use of DES for small vessel stenting. In addition, the best DES platform will be that which both facilitates access and limits endoluminal injury beyond the stent margins. Limited balloon extension ("focal balloon" technology) or self-expanding stents, which deploy at low pressures, minimizing barotrauma, may be desirable. In addition, although the concept of less metal is appealing in regard to profile, flexibility, and ease of deployment (balloon expandability), adequate endoluminal surface coverage must be provided for scaffolding as well as uniform and adequate drug delivery. Newer metal alloys, such as cobalt chromium, may allow maximized endoluminal surface area coverage while still providing flexibility and distal coronary access. In addition, the physicochemical attributes of the polymer coating may directly influence parameters of stent performance including flexibility, recoil, and foreshortening.[48] The elastomeric or rigid qualities of a specific polymer must be considered in efforts to design the optimal small-vessel stent. DES specifically designed for small vessel application will likely become the standard for small vessel PCI. ■

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