

# Impact of Final Stent Dimensions on Long-Term Results Following Sirolimus-Eluting Stent Implantation

## Serial Intravascular Ultrasound Analysis From the SIRIUS Trial

Shinjo Sonoda, MD,\* Yoshihiro Morino, MD,\* Junya Ako, MD,\* Mitsuyasu Terashima, MD,\* Ali H. M. Hassan, MD,\* Heidi N. Bonneau, RN, MS,† Martin B. Leon, MD, FACC,‡ Jeffrey W. Moses, MD, FACC,‡ Paul G. Yock, MD, FACC,\* Yasuhiro Honda, MD,\* Richard E. Kuntz, MD, MSc,§ Peter J. Fitzgerald, MD, PhD, FACC,\* for the SIRIUS Investigators  
*Stanford and San Jose, California; New York, New York; and Boston, Massachusetts*

<b>OBJECTIVES</b>	We assessed the predictive value of minimum stent area (MSA) for long-term patency of sirolimus-eluting stents (SES) implantation compared to bare metal stents (BMS).
<b>BACKGROUND</b>	Although MSA is a consistent predictor of in-stent restenosis, its predictive value in BMS is still limited because of biologic variability in the restenosis process.
<b>METHODS</b>	From the SIRoIImUS (SIRIUS) trial, 122 cases (SES: 72; BMS: 50) with complete serial intravascular ultrasound (IVUS) (baseline and 8-month follow-up) were analyzed. Postprocedure MSA and follow-up minimum lumen area (MLA) were obtained. Based on previous physiologic studies, adequate stent patency at follow-up was defined as MLA >4 mm <sup>2</sup> .
<b>RESULTS</b>	In both groups, a significant positive correlation was observed between baseline MSA and follow-up MLA (SES: $p < 0.0001$ , BMS: $p < 0.0001$ ). However, SES showed higher correlation than BMS (0.8 vs. 0.65) with a higher regression coefficient (0.92 vs. 0.59). The sensitivity and specificity curves identified different optimal thresholds of MSA to predict adequate follow-up MLA: 5 mm <sup>2</sup> for SES and 6.5 mm <sup>2</sup> for BMS. The positive predictive values with these cutoff points were 90% and 56%, respectively.
<b>CONCLUSIONS</b>	In this SIRIUS IVUS substudy, SES reduced both biologic variability and restenosis, resulting in increased predictability of long-term stent patency with postprocedure MSA. In addition, SES had a considerably lower optimal MSA threshold compared to BMS. (J Am Coll Cardiol 2004;43:1959–63) © 2004 by the American College of Cardiology Foundation

Despite the widespread use of intracoronary stents, in-stent restenosis remains a major clinical problem (1,2). Intravascular ultrasound (IVUS) permits detailed cross-sectional imaging of the coronary arteries and has been used to optimize stent deployment. Several studies have demonstrated that IVUS-derived lumen dimension after stent deployment (minimum stent area [MSA]) is a consistent predictor of in-stent restenosis (3,4). In bare metal stents (BMS), however, the predictive value of IVUS is still limited because of biologic variability in the in-stent restenosis process. Current treatment with anti-proliferative drug-coated stents appears to be a promising approach to mechanically remodeling target lesions and biologically reducing neointimal hyperplasia (5,6). Initial clinical applications of sirolimus-eluting stents (SES) in single primary lesions were shown to be safe and feasible in preventing neointimal hyperplasia, with complete abolition of resteno-

sis (7,8). These results may indicate consistent efficacy of drug-eluting stents irrespective of degree of biologic activity (patient, lesion profile, and risk factors) in each lesion. The aim of this study was to report the impact of the final stent dimension (as assessed by IVUS) on long-term results in SES compared to BMS.

## METHODS

**Study population and design.** The SIRIUS trial is a U.S. multicenter randomized double-blind study of the sirolimus-eluting stent to evaluate the safety and efficacy of the sirolimus-eluting Bx-Velocity stent compared with a BMS (uncoated metal Bx-Velocity stent) in the prevention of in-stent restenosis (Cordis Corp., Johnson and Johnson, Warren, New Jersey) (9).

This study was specifically designed to include a more restenosis-prone de novo native coronary lesion subset than either the Randomized study with the sirolimus-eluting Velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions (RAVEL) (10) or the First in Man trial (7). The institutional review board at all investigational sites approved the study protocol, and written informed consent was obtained from all patients. We studied an IVUS subgroup of 122 patients (SES: 72; BMS: 50) with complete serial IVUS analyses from the SIRIUS trial.

From the \*Center for Research in Cardiovascular Interventions, Stanford University Medical Center, Stanford, California; †Highlands Consulting Inc., San Jose, California; ‡Lenox Hill Hospital, New York, New York; and §Brigham and Women's Hospital, Boston, Massachusetts. Dr. Sonoda is supported by Fukuda Memorial Foundation for Medical Technologies, Tokyo, Japan and Japan North America Medical Exchange Foundation, Tokyo, Japan. Dr. Yock: grant, stock shareholder (Johnson and Johnson); Dr. Leon: stock shareholder (Johnson and Johnson); Dr. Moses: consultant, stock shareholder (Johnson and Johnson); Dr. Fitzgerald: consultant (Cordis, Johnson and Johnson).

Manuscript received November 4, 2003; revised manuscript received January 8, 2004, accepted January 27, 2004.

**Abbreviations and Acronyms**

- BMS = bare metal stents
- IVUS = intravascular ultrasound
- MLA = minimum lumen area
- MSA = minimum stent area
- SES = sirolimus-eluting stents

**IVUS analysis.** All cineangiograms and IVUS images were independently analyzed at independent core laboratories blind to the treatment protocol. Serial angiography and IVUS were performed after intracoronary administration of nitroglycerin immediately after the procedure and at eight-month follow-up. Quantitative IVUS analysis was performed using commercially available planimetry software (TapeMeasure/EchoPlaque, Indec System, Mountain View, California) according to previously validated and published protocols. Vessel, stent, lumen, and neointimal area were computed for the stented segment. Postprocedure MSA, eight-month follow-up minimum lumen area (MLA), and neointimal area at the MLA site were obtained. Percent neointimal area was calculated as neointimal area divided by stent area. Percent stent expansion was calculated as MSA divided by average reference lumen area. Based on previous clinical studies, adequate stent patency at follow-up was defined as  $MLA > 4 \text{ mm}^2$  (11).

**Statistical analysis.** Statistical analysis was performed with StatView 5.0 software (SAS Institute, Cary, North Carolina). Quantitative data are presented as mean  $\pm$  SD and qualitative data are presented as frequencies. Comparison was performed with unpaired Student *t* test and chi-square test. Linear regression analysis and Bland-Altman analysis were performed to evaluate the correlation between postprocedure MSA and follow-up MLA. A value of  $p < 0.05$  was considered statistically significant. Optimal MSA thresholds were determined on the basis of the same sensitivity and specificity values because the availability of a

**Table 1.** Clinical and Procedural Characteristics

	BMS (n = 50)	SES (n = 72)	p Value
Age (yrs)	61.8 $\pm$ 9.9	59.0 $\pm$ 9.9	0.13
Male (%)	68	76	0.31
Risk factors (%)			
Hypertension	60	67	0.45
Diabetes	32	25	0.40
Hyperlipidemia	68	71	0.74
Smoking	28	31	0.76
Vessel treated			
LAD/RCA/LCX (%)	42/30/28	44/31/25	0.93
Reference lumen diameter (mm)	2.80 $\pm$ 0.47	2.76 $\pm$ 0.45	0.61
Lesion length (mm)	15.65 $\pm$ 5.11	14.14 $\pm$ 4.85	0.10
Final balloon size (mm)	3.28 $\pm$ 0.53	3.01 $\pm$ 0.40	$p < 0.05$
Maximum inflation pressure (atm)	16.6 $\pm$ 2.6	17.1 $\pm$ 2.9	0.34

BMS = bare metal stents; LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; SES = sirolimus-eluting stents.

**Table 2.** Angiographic and IVUS Measurements at Postprocedure

	BMS (n = 50)	SES (n = 72)	p Value
Coronary angiography			
Reference lumen diameter (mm)	2.80 $\pm$ 0.47	2.76 $\pm$ 0.45	0.61
Minimum lumen diameter (mm)	2.72 $\pm$ 0.44	2.72 $\pm$ 0.38	0.97
Diameter stenosis (%)	5.1 $\pm$ 7.1	3.3 $\pm$ 7.1	0.18
IVUS			
Reference lumen area (mm <sup>2</sup> )	7.32 $\pm$ 2.52	7.89 $\pm$ 3.69	0.34
Minimum stent area (mm <sup>2</sup> )	6.03 $\pm$ 2.15	5.84 $\pm$ 1.76	0.59
% stent expansion	84.4 $\pm$ 19.9	80.2 $\pm$ 24.6	0.32

BMS = bare metal stents; IVUS = intravascular ultrasound; SES = sirolimus-eluting stents.

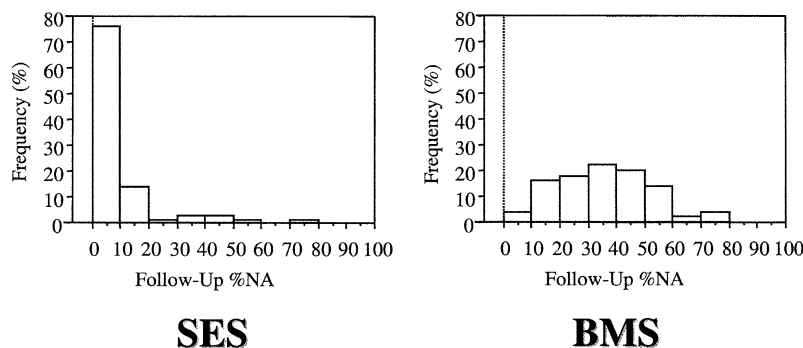
better sensitivity through a decreased cutoff point would result in a worse specificity. In addition, we analyzed the points of intersection of both the sensitivity and specificity curves as optimal cutoff points for predicting adequate follow-up MLA.

**RESULTS**

Baseline characteristics of cases used in this analysis were comparable to the overall enrolled patient population. Baseline lesion and procedural characteristics were similar in both groups except for the final balloon size (Table 1). Quantitative coronary angiography and IVUS data at postprocedure are shown in Table 2. The MSA at postprocedure was  $5.8 \pm 1.8 \text{ mm}^2$  in SES and  $6.0 \pm 2.1 \text{ mm}^2$  in BMS ( $p = \text{NS}$ ). The MLA at eight-month follow-up was  $5.3 \pm 2.0 \text{ mm}^2$  in SES and  $3.6 \pm 1.9 \text{ mm}^2$  in BMS ( $p < 0.0001$ ). Sirolimus-eluting stents significantly reduced late lumen loss compared with BMS (SES:  $0.6 \pm 1.2 \text{ mm}^2$ , BMS:  $2.4 \pm 1.6 \text{ mm}^2$ ,  $p < 0.0001$ ) because of overall reduction of neointimal tissue growth at the site of MLA (% neointimal area, SES:  $8.5 \pm 13.4\%$ , BMS:  $36.2 \pm 16.9\%$ ,  $p < 0.0001$ ). In addition, the distribution curves indicated significantly reduced variability in neointimal tissue growth among the SES cases (Fig. 1).

Although a highly significant positive correlation was observed between postprocedure MSA and follow-up MLA in both groups (SES:  $p < 0.0001$ , BMS:  $p < 0.0001$ ), SES showed higher correlation than BMS (0.80 vs. 0.65), with a higher regression coefficient (0.92 vs. 0.59) (Fig. 2). The sensitivity and specificity curves identified different optimal thresholds of MSA to predict adequate follow-up MLA:  $5.0 \text{ mm}^2$  for SES and  $6.5 \text{ mm}^2$  for BMS (Fig. 3). The positive predictive values with these cutoff points were 90% in SES and 56% in BMS, respectively (Table 3).

The diagnostic value of absolute MSA was then compared to that of relative parameter to the reference artery (MSA divided by mean reference vessel area [REFVA]). The receiver operating characteristic curves showed that



**Figure 1.** Distribution of percentage of neointimal area (%NA, neointimal area/stent area) at the site of follow-up minimum lumen area for sirolimus-eluting stents (SES) (left) and bare metal stents (BMS) (right).

absolute MSA was more diagnostic than MSA/REFVA (Fig. 4). In addition, in the subset of 66 patients (SES: 41; BMS: 25) with lesions in small coronary arteries (reference vessel diameter of <2.8 mm as measured by quantitative coronary angiography), smaller optimal thresholds of MSA to predict adequate follow-up MLA were obtained (SES: 4.5 mm<sup>2</sup>; BMS: 6 mm<sup>2</sup>).

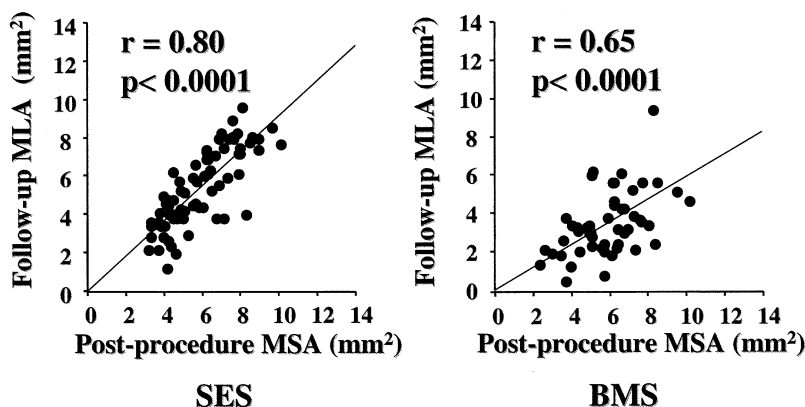
**DISCUSSION**

**Conventional stent era.** The guiding principle of stent deployment was to achieve the largest lumen area possible in each lesion. This paradigm, so-called bigger-is-better, was based upon a theory verified in several clinical studies: although late lumen loss increases with initial lumen gain, larger postprocedure lumen generally results in greater net lumen outcome at follow-up because of the relatively uniform late loss index or “tax rate” (0.44 to 0.47) across conventional stents (12,13). However, the degree of biologic response to the acute mechanical injury by stent implantation and/or sustained stimuli from the rigid metal struts, namely the amount of neointimal proliferation, follows a near-Gaussian distribution (14). As seen in the BMS group of the present study, this biologic variability significantly limits the ability to predict the probability of stent patency for the individual patient based on the mechanical param-

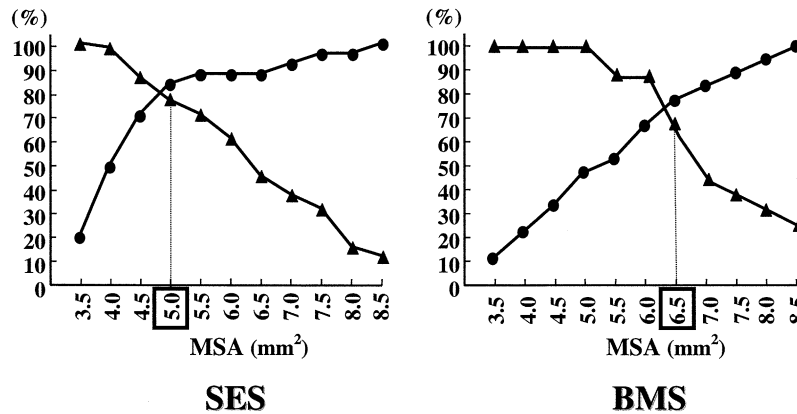
eter alone (15-17). For this reason, achieving the largest postprocedure lumen is further underscored to ensure the greatest “safety margin” for unexpectedly large neointimal hyperplasia that can occasionally follow conventional stenting.

**Drug-eluting stent era.** In the current study, however, the overall amount of late loss in SES was less than BMS because of significant suppression of neointimal tissue growth. Furthermore, a tighter positive correlation was observed between baseline MSA and follow-up MLA in SES than in BMS. Hence, SES had a considerably lower optimal MSA threshold (5.0 mm<sup>2</sup>) compared to BMS (6.5 mm<sup>2</sup>) to predict eight-month stent patency. On one hand, an MSA of 5.0 mm<sup>2</sup> discriminates between adequate versus inadequate lumens at follow-up, indicating that a smaller MSA may be clinically adequate post-SES compared with BMS. On the other hand, this MSA has a specificity of 83%, indicating that an inadequate MSA determines most of the cases of restenosis post-SES. Thus, whereas a smaller MSA may be acceptable post-SES, SES underexpansion can result in restenosis.

**Small vessel subset.** The acute results of stenting in small coronary arteries are variable (18), and the long-term outcomes are worse compared to the stenting of large coronary arteries (19). Proportional parameter to the refer-



**Figure 2.** Relationship between postprocedural minimum stent area (MSA) and follow-up minimum lumen area (MLA). Sirolimus-eluting stents (SES) showed higher correlation than bare metal stents (BMS) (0.80 vs. 0.65) with a higher regression coefficient (0.92 vs. 0.59), indicating consistent efficacy of SES, irrespective of variable degrees of biological activity in each individual lesion.



**Figure 3.** The sensitivity and specificity curves identified different optimal thresholds of minimum stent area (MSA) to predict adequate follow-up minimum lumen area (MLA): 5.0 mm<sup>2</sup> for sirolimus-eluting stents (SES) and 6.5 mm<sup>2</sup> for bare metal stents (BMS). Sirolimus-eluting stents may achieve better longer-term outcome with an “optimized” lower MSA threshold. **Triangles** = sensitivity; **circles** = specificity.

ence vessel size may potentially be of use, especially in smaller coronary arteries (15). However, absolute MSA was considered to be more predictive for long-term stent patency compared to MSA/REFVA in the current study. Despite the small number of this subset, the current study also suggested optimal MSA thresholds of 4.5 mm<sup>2</sup> in SES and 6.0 mm<sup>2</sup> in BMS in small coronary arteries. This threshold in BMS (6.0 mm<sup>2</sup>) was consistent with previous study in small vessels (20).

**Clinical implications.** These observations have potentially important clinical implications. In conventional stenting, deep vessel wall injury resulting from aggressive stent expansion may contribute to greater neointimal proliferation following larger acute lumen gain. Nevertheless, the bigger-is-better strategy is critically important owing to the unpredictability of biologic response in individual lesions. In contrast, drug-eluting stents may not require as large a safety margin for biologic variability as conventional stents and, therefore, aggressive dilation to achieve the largest lumen area possible may no longer provide additional clinical benefit. The higher predictability of follow-up stent dimensions may also facilitate “adequate” deployment of drug-eluting stents to minimize vessel wall injury and subsequent neointimal proliferation and/or vessel shrinkage at stent edges.

**Study limitations.** First, the results obtained are limited to vessel diameters and stent lengths used in the SIRIUS trial. These findings should be confirmed in real-world registries

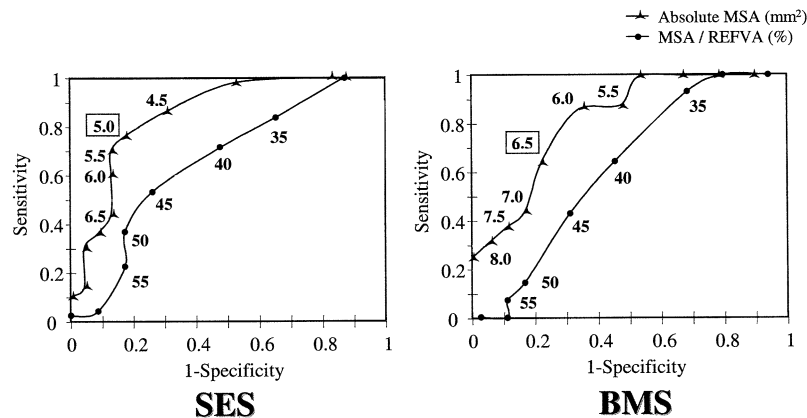
that may enroll more complex lesions in smaller vessels. Second, data analysis to determine follow-up MLA was restricted to the stented segment, given that the cause of stent edge restenosis is complex. Previous studies have indicated several periprocedural predictors of subsequent stent edge restenosis. Injury from the stent deployment balloon in the adjacent area and postprocedural cross-sectional narrowing of the contiguous stent margins tend to trigger stent edge restenosis (21). Natural lumen tapering at the stent margins may cause stent edge restenosis (22). Furthermore, limited diffusion of drug in the stent margins may also trigger stent edge restenosis. The stent edge issue was considered beyond the scope of this study. Third, complete serial IVUS quantitative analysis was available in only 122 cases and thus selection bias may have been present. In fact, in baseline patient/lesion and procedural characteristics, there was a significant difference in the final balloon size, which was significantly larger in those receiving BMS. This difference, however, would tend to bias our results in a direction opposite from that shown in the final outcome.

**Conclusions.** In this SIRIUS IVUS substudy, SES reduced biologic variability and increased predictability of long-term stent patency with postprocedure MSA. In addition, SES had a considerably lower optimal MSA threshold compared to BMS. Overall, stent underexpansion should be avoided because MSA <5.0 mm<sup>2</sup> was responsible for the majority of SES restenosis.

**Table 3.** Diagnostic Values of Optimal Threshold for SES and BMS

	Optimal Threshold	PPV	Sensitivity	Specificity	Accuracy
SES (n = 72)	5.0 mm <sup>2</sup>	90%	76%	83%	78%
BMS (n = 50)	6.5 mm <sup>2</sup>	56%	63%	78%	73%

BMS = bare metal stents; PPV = positive predictive value; SES = sirolimus-eluting stents.



**Figure 4.** The receiver operating characteristic (ROC) curves showed comparison of the diagnostic value between absolute minimum stent area (MSA) and relative parameter to the reference artery (MSA/reference vessel area [REFVA]). These curves interpreted that absolute MSA was a more simple and stronger predictive parameter than MSA/REFVA. BMS = bare metal stents; SES = sirolimus-eluting stents.

### Acknowledgments

The authors thank Brian K. Courtney, MSEE, for his critical review of the manuscript.

**Reprint requests and correspondence:** Dr. Peter J. Fitzgerald, Center for Research in Cardiovascular Interventions, Stanford University Medical Center, 300 Pasteur Drive, H3554, Stanford, California 94305-5637. E-mail: ivus@crci.stanford.edu.

### REFERENCES

- Dussailant GR, Mintz GS, Pichard AD, et al. Small stent size and intimal hyperplasia contribute to restenosis: a volumetric intravascular ultrasound analysis. *J Am Coll Cardiol* 1995;26:720-4.
- Hoffmann R, Mintz GS, Dussailant GR, et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. *Circulation* 1996;94:1247-54.
- Hoffmann R, Mintz GS, Mehran R, et al. Intravascular ultrasound predictors of angiographic restenosis in lesions treated with Palmaz-Schatz stents. *J Am Coll Cardiol* 1998;31:43-9.
- de Feyter PJ, Kay P, Disco C, Serruys PW. Reference chart derived from post-stent-implantation intravascular ultrasound predictors of 6-month expected restenosis on quantitative coronary angiography. *Circulation* 1999;100:1777-83.
- Heldman AW, Cheng L, Jenkins GM, et al. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. *Circulation* 2001;103:2289-95.
- Brieger D, Topol E. Local drug delivery systems and prevention of restenosis. *Cardiovasc Res* 1997;35:405-13.
- Sousa JE, Costa MA, Abizaid AC, et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation* 2001;103:192-5.
- Sousa JE, Costa MA, Abizaid AC, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation* 2001;104:2007-11.
- Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315-23.
- Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346:1773-80.
- Abizaid AS, Mintz GS, Mehran R, et al. Long-term follow-up after percutaneous transluminal coronary angioplasty was not performed based on intravascular ultrasound findings: importance of lumen dimensions. *Circulation* 1999;100:256-61.
- Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS. Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. *J Am Coll Cardiol* 1993;21:15-25.
- Foley DP, Melkert R, Umans VA, et al. Differences in restenosis propensity of devices for transluminal coronary intervention. A quantitative angiographic comparison of balloon angioplasty, directional atherectomy, stent implantation and excimer laser angioplasty. *CARPORT, MERCATOR, MARCATOR, PARK, and BENESTENT Trial Groups. Eur Heart J* 1995;16:1331-46.
- Weissman NJ, Wilensky RL, Tanguay JF, et al. Extent and distribution of in-stent intimal hyperplasia and edge effect in a non-radiation stent population. *Am J Cardiol* 2001;88:248-52.
- Moussa I, Moses J, Di Mario C, et al. Does the specific intravascular ultrasound criterion used to optimize stent expansion have an impact on the probability of stent restenosis? *Am J Cardiol* 1999;83:1012-7.
- Morino Y, Honda Y, Okura H, et al. An optimal diagnostic threshold for minimal stent area to predict target lesion revascularization following stent implantation in native coronary lesions. *Am J Cardiol* 2001;88:301-3.
- Kataoka T, Grube E, Honda Y, et al. 7-hexanoyltaxol-eluting stent for prevention of neointimal growth: an intravascular ultrasound analysis from the Study to Compare REstenosis rate between QueST and QuaDS-QP2 (SCORE). *Circulation* 2002;106:1788-93.
- Schunkert H, Harrell L, Palacios IF. Implications of small reference vessel diameter in patients undergoing percutaneous coronary revascularization. *J Am Coll Cardiol* 1999;34:40-8.
- Akiyama T, Moussa I, Reimers B, et al. Angiographic and clinical outcome following coronary stenting of small vessels: a comparison with coronary stenting of large vessels. *J Am Coll Cardiol* 1998;32:1610-8.
- Iakovou I, Mintz GS, Dangas G, et al. Optimal final lumen area and predictors of target lesion revascularization after stent implantation in small coronary arteries. *Am J Cardiol* 2003;92:1171-6.
- Hoffmann R, Mintz GS, Kent KM, et al. Serial intravascular ultrasound predictors of restenosis at the margins of Palmaz-Schatz stents. *Am J Cardiol* 1997;79:951-3.
- Javier SP, Mintz GS, Popma JJ, et al. Intravascular ultrasound assessment of the magnitude and mechanism of coronary artery and lumen tapering. *Am J Cardiol* 1995;75:177-80.