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Long-Term Clinical Outcomes With Sirolimus-Eluting Coronary Stents

Five-Year Results of the RAVEL Trial

Marie-Claude Morice, MD, FACC, FESC,* Patrick W. Serruys, MD, PHD, FACC,† Paul Barragan, MD,‡ Christoph Bode, MD,§ Gerrit-Anne Van Es, PHD,‖ Hans-Peter Stoll, MD,¶ David Snead, PHD,# Laura Mauri, MD, MSC, FACC,** Donald E. Cutlip, MD, FACC,** Eduardo Sousa, MD, PHD, FACC††

Massy and Marseille, France; Rotterdam, the Netherlands; Freiburg, Germany; Waterloo, Belgium; Warren, New Jersey; Boston, Massachusetts; and Sao Paulo, Brazil

Objectives This study examined the clinical outcomes at 5 years in RAVEL (A Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization), the first controlled trial of drug-eluting stents.

Background The 6-month rate of angiographic coronary restenosis has been markedly lowered by sirolimus-eluting stents (SES). The long-term performance of drug-eluting stents, however, is under close scrutiny.

Methods The trial included 238 patients (mean age 60.7 ± 10.4 years, 76% men) with a single, de novo native coronary artery lesion, randomly assigned to treatment with SES versus bare-metal stents (BMS). Rates of major adverse cardiac events (MACE), defined as all-cause mortality, myocardial infarction, and percutaneous or surgical revascularization up to 5 years of follow-up, and rates of stent thrombosis were compared between the 2 treatment groups.

Results Complete datasets were available in 92.5% of patients treated with SES and 89.1% of patients assigned to BMS. The 1-, 3-, and 5-year rates of survival free from target lesion revascularization (TLR) were, respectively, 99.2%, 93.8%, and 89.7% in the SES group versus 75.9%, 75.0%, and 74.0% in the control group ($p < 0.001$; log-rank). Rates of all MACE at 5 years were 25.8% in patients treated with SES versus 35.2% in patients assigned to BMS ($p = 0.03$; log-rank). Rates of stent thrombosis, per protocol or by the Academic Research Consortium definitions, were similar in both groups.

Conclusions The 5-year rate of TLR associated with SES was significantly lower than that with BMS. There was no apparent adverse effect associated with the use of SES, although the trial was not powered to examine uncommon complications. (J Am Coll Cardiol 2007;50:1299–304) © 2007 by the American College of Cardiology Foundation

The RAVEL (A Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization) study was the first of several randomized clinical trials that demonstrated the superior efficacy of coronary sirolimus-eluting stents (SES) in the prevention of neointimal proliferation and restenosis (1–4). The number of patients enrolled in the trial was calculated in order to compare the efficacy of SES versus that of conventional bare-metal stents (BMS) on angiographic end points, with a primary trial end point of in-stent late loss at 6 months of follow-up. This pioneering study was also initially planned for a clinical follow-up limited to 1 year. However, it was subsequently extended to 5 years. The 6-month angiographic and 3-year clinical results (1,5) and a detailed intravascular ultrasound-based study in a subset of 95 patients (6) have been published. This report describes the final clinical outcomes observed in RAVEL, up to 5 years of follow-up.

From the *Institut Cardiovasculaire Paris Sud, Massy, France; †Erasmus Medical Center, Rotterdam, the Netherlands; ‡Clinique Beauregard, Marseille, France; §Albert-Ludwigs-Universitätskliniken, Kardiologie, Freiburg, Germany; ‖Cardialysis, Rotterdam, the Netherlands; ¶Cordis Clinical Research, Waterloo, Belgium; #Cordis Clinical Research, Warren, New Jersey; **Harvard Clinical Research Institute, Boston, Massachusetts; and the ††Instituto Dante Pazzanese, Sao Paulo, Brazil. This study was sponsored by Cordis Corporation (a Johnson & Johnson Company), Clinical Research Europe, Belgium, and Warren, New Jersey.

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Methods

Patient selection. The design and detailed methods of this randomized, double-blind clinical trial have been reported (1,5). In brief, the 238 patients randomly assigned to SES

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Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
MACE = major adverse cardiac events
MI = myocardial infarction
QCA = quantitative coronary angiography
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization
TVR = target vessel revascularization

versus BMS had stable or unstable angina pectoris, or silent ischemia due to a single, 51% to 99% diameter stenosis de novo coronary lesion, which could be treated with a single 18-mm stent, in a vessel between 2.5 and 3.5 mm in diameter. Major exclusion criteria included evolving myocardial infarction (MI), a ≥50% stenosis in an unprotected left main coronary artery, an ostial target lesion, a calcified lesion that could not be successfully predilated with an angioplasty balloon, or an angiographically visible thrombus within the target lesion, a left ventricular ejection fraction ≤30%, a serum creatinine concentration >3.0 mg/dl, and any contraindication to coronary artery bypass graft surgery. Direct stenting was not allowed. The study was reviewed and approved by each participating institution's ethical review committee, and all patients provided written informed consent before enrollment.

Study procedures. After successful predilatation of the target lesion, patients were randomly assigned 1:1 in a double-blind fashion to a BMS, versus an SES. Direct stenting was not allowed. Postdilatation was performed as necessary. Procedural success was defined as attainment of a <30% vessel diameter stenosis and freedom from in-hospital major adverse cardiac events (MACE) after implantation of the assigned study device. Postprocedural dual antiplatelet therapy consisted of aspirin 325 mg daily, indefinitely, and either clopidogrel 75 mg daily or ticlopidine 250 mg twice daily, for 8 weeks.

Patient follow-up. Patients returned for yearly follow-up evaluations to monitor the possible interim development of angina or MACE. Follow-up angiography with quantitative coronary angiography (QCA) was systematically performed at 180 ± 30 days as described previously (1). The decision to perform further target lesion revascularization (TLR) target or vessel revascularization (TVR) after the 6-month angiographic follow-up was left to the investigator's discretion, by protocol design.

Study end points and definitions. The main study objective was to assess the effectiveness of the CYPHER (Cordis Corp., Johnson & Johnson, Miami Lakes, Florida) SES in reducing angiographic in-stent late loss in de novo native coronary lesions as compared with the Bx VELOCITY (Cordis Corp.) balloon-expandable BMS of identical design and appearance. The primary end point of the study was angiographic, in-stent late loss at 6 months of follow-up, measured by QCA. Secondary end points of the trial included: 1) postprocedural, in-stent mean percent diameter stenosis measured by QCA; 2) in-target vessel segment and in-stent minimum luminal diameter at 6 months; 3) MACE; and 4) TVR, up to 5 years of follow-up. Major adverse cardiac events were a composite end point including: 1) death from all causes; 2) Q-wave or non–Q-wave MI; and 3) surgical or percutaneous TLR.

Stent thrombosis. PER-PROTOCOL DEFINITIONS. In March 2000, when the study protocol was developed, stent thrombosis was prospectively defined as a composite 30-day end point including death, Q-wave MI, and abrupt vessel closure requiring revascularization. It was defined as *acute* when occurring within the first 24 h after stent implantation, and *subacute* when occurring between 24 h and 30 days after the index procedure. In 2002, when its importance had become apparent, *late* stent thrombosis was defined post hoc by the clinical events committee, with the endorsement of the steering committee, as all target-vessel-related MI with angiographic evidence of vessel occlusion occurring past 30 days after the index procedure, in absence of interim TLR.

ACADEMIC RESEARCH CONSORTIUM (ARC) DEFINITIONS. In 2006, the ARC redefined the criteria for stent thrombosis applicable to clinical trials (7). The ARC definitions consider the *timing* and *probability* of occurrence of stent thrombosis. With respect to *timing*, stent thrombosis is defined as *acute* if it occurred between 0 and 24 h, *subacute* between 25 h and 30 days, *late* between 31 days and 1 year, and *very late* beyond 1 year after stent implantation. With respect to *probability*, stent thrombosis is defined as *definite*, *probable*, or *possible*.

Definite stent thrombosis is considered to have occurred on the basis of either angiographic or pathological evidence.

ANGIOGRAPHIC CONFIRMATION OF STENT THROMBOSIS. Stent thrombosis has been confirmed angiographically if: Thrombolysis In Myocardial Infarction flow is: a) grade 0 with occlusion originating in the stent or in the segment, 5 mm proximal or distal to the stent, in presence of a thrombus, or b) grade 1, 2, or 3 originating in the stent or in the segment, 5 mm proximal or distal to the stent, in presence of a thrombus, and at least 1 of the following criteria has been fulfilled within a 48-h time window: a) acute onset of typical chest pain at rest, lasting >20 min, b) new electrocardiographic changes consistent with acute myocardial ischemia, and c) typical rise and fall in cardiac biomarkers. The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms (silent occlusion) is not considered a confirmed stent thrombosis.

PATHOLOGICAL CONFIRMATION OF STENT THROMBOSIS. Stent thrombosis is confirmed when there is presence of recent thrombus within the stent, found at autopsy or by examination of tissue retrieved at the time of thrombectomy.

Probable stent thrombosis is considered to have occurred in case of: 1) unexplained death within the first 30 days after

stent implantation; or 2) MI in the territory of the implanted stent, in absence of another obvious cause, without angiographic confirmation of stent thrombosis and regardless of its timing after the index procedure.

Possible stent thrombosis is considered to have occurred as a cause of any unexplained death past 30 days after intracoronary stenting, until the end of trial follow-up.

Unlike the RAVEL protocol definition, ARC includes events consistent with stent thrombosis that occur after repeat TLR.

Data management and study oversight. The angiographic and clinical data were collected by monitors independent of the sponsor and were transferred to Cardialysis (Rotterdam, the Netherlands), an independent contract research organization. Cardialysis managed and analyzed the data, and performed the angiographic core laboratory analyses.

During the course of the study, end points were adjudicated by an independent clinical events committee, managed by Cardialysis. In addition, a data safety monitoring board not affiliated with the study sponsor reviewed the data and identified potential safety issues related to the conduct of the study. Finally, in September 2006, after the ARC definitions of stent thrombosis had been formulated, adverse clinical events were readjudicated retrospectively by the Harvard Clinical Research Institute, Boston, Massachusetts, from the database transferred by Cardialysis.

Statistical analyses. For the primary (angiographic) end point, it was estimated that a sample size of 95 in each group had an 87% power to detect a difference in means of 0.25 mm (the difference between a BMS late loss mean of 0.80 mm and a SES late loss mean of 0.55 mm) assuming that the common standard deviation is 0.55, using a 2-group *t* test with a 0.05 1-sided significance level. The sample size was increased to 110 in each group to account for noncompliance to the 6-month angiographic follow-up.

All analyses were based on the intention-to-treat principle. The rates of end points were estimated with the use of the Kaplan-Meier method, and the differences between groups were estimated with the use of the log-rank test. Event-free survival from MACE, TLR, and the composite of death and MI occurring during the 5-year follow-up were analyzed using the Kaplan-Meier method. Differences between the event-free survival curves for the 2 groups were compared with the use of the log-rank test. A 2-sided p value <0.05 was considered statistically significant. All statistical analyses were performed using SAS statistical software (SAS Institute, Cary, North Carolina).

Results

The baseline clinical characteristics of the RAVEL trial population have been described in detail previously (1,5). Except for a significantly higher percentage of men in the group treated with BMS, the 2 study groups were similar with respect to all demographic and disease-related characteristics examined. The flow of patients through the trial is shown in Figure 1. At 5 years, 14 patients had died and 4 patients were lost to follow-up in the SES-treated group, and 8 patients had died and 9 were lost to follow-up in the BMS-treated group. Among 106 SES and 110 BMS recipients who were not confirmed to have died, complete datasets were available at 1,825 days in 98 patients treated with SES (92.5%) and 98 patients assigned to BMS (89.1%). The cumulative numbers and percentages of patients who experienced MACE or underwent TVR through the 5-year follow-up are listed in hierarchical and nonhierarchical orders in Table 1. A significant difference ($p = 0.03$) persisted in rate of MACE in favor of the SES-treated group, mostly attributable to a lower number of repeat TLR. The 5-year actuarial survival rates for freedom from death and MI (Fig. 2) in patients assigned to SES versus patients assigned to BMS were similar. In contrast, significant differences were observed in the MACE- (Fig. 3) and TLR-free (Fig. 4) survivals. Specifically, the 1-, 3-, and

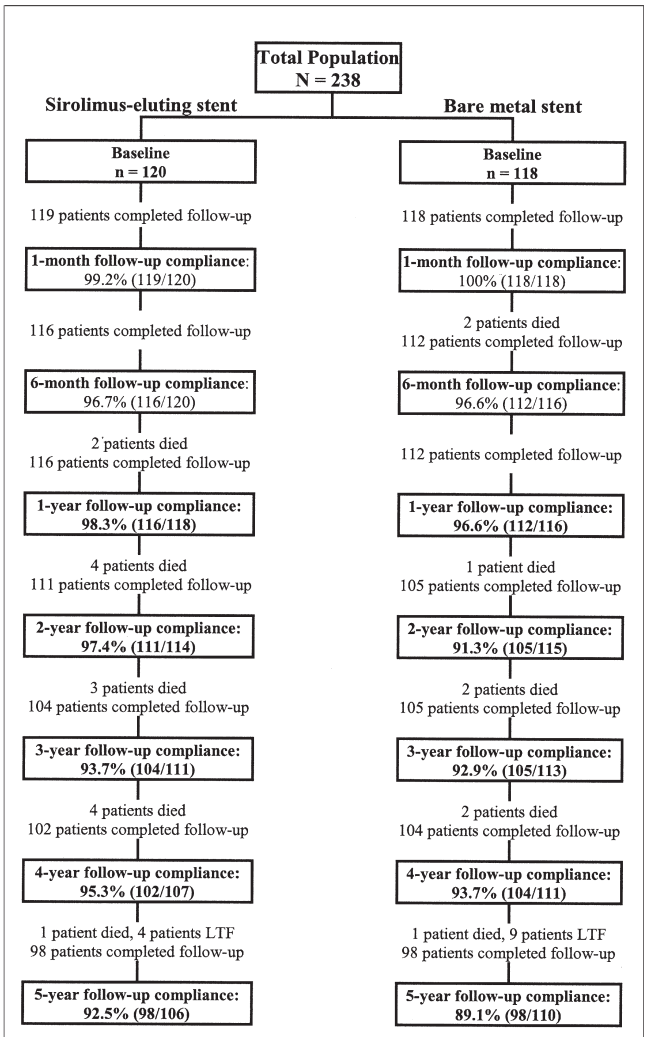

Figure 1 Flow of Patients Through the Trial

LTF = lost to follow-up.

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Table 1 Cumulative Incidence of MACE Observed Up to 5 Years in 120 SES Versus 118 BMS Recipients

	SES	BMS	p Value
Hierarchical ranking			
Death	14 (12.1)	8 (7.1)	0.20
Nonfatal myocardial infarction	8 (7.3)	4 (3.5)	—
Target lesion revascularization			
Surgical	3 (2.7)	2 (1.8)	—
Percutaneous	5 (4.7)	27 (23.2)	—
All MACE	30 (25.8)	41 (35.2)	0.03
Nonhierarchical ranking			
Death	14 (12.1)	8 (7.1)	0.20
Myocardial infarction	10 (8.9)	8 (6.9)	0.65
Target lesion revascularization	11 (10.3)	30 (26.0)	<0.001
Surgical	4 (3.6)	2 (1.8)	0.41
Percutaneous	8 (7.5)	28 (24.2)	<0.001
Target vessel revascularization*	3 (2.7)	3 (2.6)	0.98

Values indicate numbers (%) of patients; p values were determined by the log-rank test. Rates of adverse events were estimated by the Kaplan-Meier method. *Not involving the target lesion.
BMS = bare-metal stent; MACE = major adverse cardiac events (any death, myocardial infarction, or target lesion revascularization); SES = sirolimus-eluting stent.

5-year survival rates free from TLR were, respectively, 99.2%, 93.8%, and 89.7% in the SES group versus 75.9%, 75.0%, and 74.0% in the BMS group ($p < 0.001$; log-rank).

Stent thrombosis. According to the *per-protocol* definitions, 1 late thrombosis occurred at 1,217 days in a SES recipient (Table 2). After readjudication of the events according to the ARC definitions, a single definite, very late stent thrombosis (0.8%) was observed in each study group, 2 versus 3 definite or probable thromboses were observed in the SES versus BMS groups, respectively, and a total of 4 thromboses of any kind (3.3%) was observed in the SES-treated group, versus 8 thromboses of any kind (6.8%) in the BMS-treated-group, a nonsignificant difference (Table 2).

Deaths during follow-up. The RAVEL trial protocol did not distinguish between cardiac and noncardiac deaths. At the end of 5 years, 14 patients assigned to SES (12.1%) versus 8 patients (7.1%) in the control group had died ($p = 0.20$). The ages and diagnoses at the time of death for the 14 patients who died in the group assigned to SES and the 8 patients assigned to BMS are listed in Table 3.

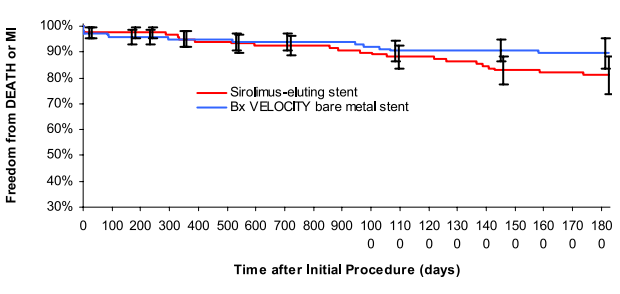

Figure 2 Survival Free From Death or MI

The sirolimus-eluting stent group is represented by a **red line** and the control group by a **blue line**. Error bars indicate ± 1.5 standard error. MI = myocardial infarction.

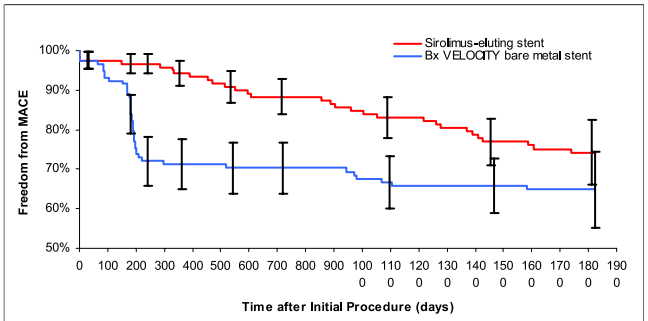

Figure 3 Survival Free From MACE

The sirolimus-eluting stent group is represented by a **red line** and the control group by a **blue line**. Error bars indicate ± 1.5 standard error. MACE = major adverse cardiac events.

Discussion

Main study findings. The main impetus for pursuing a 5-year follow-up in this trial was the importance of confirming a durable antirestenotic effect of SES. When RAVEL was designed, observations in animal models suggested that, instead of being effectively suppressed, restenosis might merely have been delayed by sirolimus elution (8). The observation, in this double-blind, randomized trial, of a statistically significant difference in rates of MACE between SES and BMS, mostly attributable to a lower TLR rate, persisting up to 5 years, confirms the absence of a "catch-up" effect and the durability of the treatment effect observed in the "First-in-Man" study by Sousa et al. (9). Likewise, a significant difference in MACE rate persisted at 5 years between the 2 small study groups, mostly attributable to the higher TLR rate among the BMS than the SES recipients.

Since the introduction of SES in clinical practice, other drug-eluting coronary stents have been developed and found to have antirestenotic effects (10–13). The RAVEL study, however, has been the longest ongoing

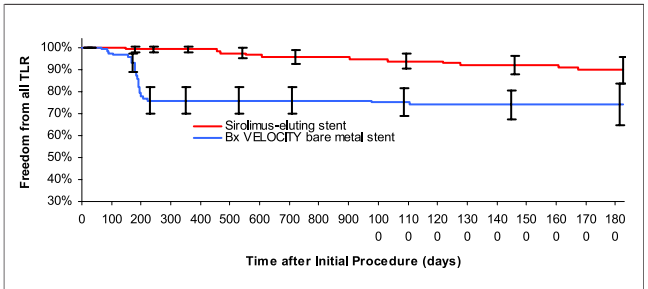

Figure 4 Survival Free From TLR

The sirolimus-eluting stent group is represented by a **red line** and the control group by a **blue line**. Error bars indicate ± 1.5 standard error. TLR = target lesion revascularization.

Table 2 Stent Thromboses Adjudicated Per Protocol and According to the ARC Definitions in Each Study Group

	SES, n (%)				BMS, n (%)			
	Acute	Subacute	Late	Very Late	Acute	Subacute	Late	Very Late
Per-protocol definitions	0	0	1	NA	0	0	0	NA
All per protocol		1				0		
ARC definitions								
Definite	0	0	0	1 (0.8)	0	0	0	1 (0.8)
Probable	0	0	0	1 (0.8)	0	0	2 (1.7)	0
Possible	0	0	0	2 (1.7)	0	0	1 (0.8)	4 (3.4)
Definite + probable	0	0	0	2 (1.7)	0	0	2 (1.7)	1 (0.8)
Any	0	0	0	4 (3.3)	0	0	3 (2.5)	5 (4.2)
All ARC		4 (3.3)				8 (6.8)		

Between-groups differences are not significant.
ARC = Academic Research Consortium; NA = not applicable; other abbreviations as in Table 1.

controlled clinical trial. Although it was not designed originally to examine long-term clinical outcomes, its 5-year results do not suggest that the beneficial antirestenotic effects of SES were negated by short- or long-term adverse clinical events. In particular, the difference between the study groups in rates of death and MI, up to 5 years, was not significant.

In recent months, authors of meta-analyses or clinical studies have suggested that important safety concerns might be associated with drug-eluting stents, an excess of death, and stent thrombosis in particular. As a result, a team of experts as well as scientific societies have more accurately and comprehensively redefined stent thrombosis (ARC definitions). Therefore, this report presents the stent thrombosis rates calculated according to the per-protocol as well as the ARC definitions. It is noteworthy that, as defined by the protocol and up to 5 years of follow-up, a single stent thrombosis occurred in an SES recipient. Because it occurred past the 3-year follow-up, this event did not appear in prior publications of the RAVEL results. According to the ARC definitions, the stent thrombosis rate was low in both groups and not higher in the SES than in the BMS group, by any definition. This observation is particularly important since the 2-month course of antiplatelet therapy was the shortest administered among all trials of drug-eluting stents. These reassuring results must, however, be interpreted with caution because: 1) the study was not designed or powered to compare rates of infrequent adverse clinical events; and 2) the lesions treated in this study were generally low risk.

Study limitations. The main limitation of this analysis out to 5 years is the sample size and small number of events, such that it was not powered to detect statistically significant between-group differences in rates of rare adverse clinical events, such as death, MI, or stent thrombosis.

Conclusions

This trial demonstrates that the initial clinical benefit conferred by SES is sustained at 5 years, as shown by a

Table 3 Deaths During Follow-Up in Each Study Group

SES			BMS	
Diagnosis	Age (yrs)	Patient #	Diagnosis	Age (yrs)
Oro-pharyngeal cancer	80	1	Perforated gastric ulcer	57
Sudden death	79	2	Sudden death	74
Intestinal cancer	66	3	Cardiac death*	85
Internal hemorrhage	79	4	Cardiac death*	62
Heart failure	71	5	Sudden death	73
Stroke	78	6	Gastric hemorrhage	72
Pulmonary embolism	71	7	Sudden death	75
Heart failure	72	8	Acute myocardial infarction	52
Cerebral hemorrhage	70	9		
Subarachnoidal hemorrhage	57	10		
Pancreatic cancer	78	11		
Heart failure	74	12		
Prostate cancer	69	13		
Respiratory failure	76	14		

*Circumstances at time of death unclear.
Abbreviations as in Table 1.

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significantly lower rate of TLR. Although there was no apparent adverse effect associated with the use of SES, this safety issue needs to be further evaluated in larger randomized trials and meta-analyses with a larger number of clinical events.

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Reprint requests and correspondence: Dr. Marie-Claude Morice, Institut Hospitalier Jacques Cartier, Avenue du Noyer Lambert, 91300 Massy, France. E-mail: mc.morice@icps.com.fr.

REFERENCES

1. Morice M-C, Serruys PW, Sousa JE, et al., RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
2. Moses JW, Leon MB, Popma JJ, et al., SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
3. Schofer J, Schluter M, Gershlick AH, et al., E-SIRIUS Investigators. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003;362:1093–109.
4. Schampaert E, Cohen EA, Schluter M, et al., C-SIRIUS Investigators. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). J Am Coll Cardiol 2004;43:1110–5.
5. Fajadet J, Morice MC, Bode C, et al. Maintenance of long-term clinical benefit with sirolimus-eluting coronary stents. Three-year results of the RAVEL trial. Circulation 2005;111:1040–4.
6. Serruys PW, Degertekin M, Tanabe K, et al., RAVEL Study Group. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. Circulation 2002;106:798–803.
7. Cutlip DE, Windecker S, Mehran R, et al., Consortium ObotAR. Clinical endpoints in coronary stent trials—a case for standardized definitions. Circulation 2007;115:2344–51.
8. Carter AJ, Aggarwal M, Kopia GA, et al. Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model. Cardiovasc Res 2004;63:617–24.
9. Sousa JE, Costa MA, Abizaid A, 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.
10. Colombo A, Drzewiecki J, Banning A, et al., TAXUS II Study Group. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003;108:788–94.
11. Stone GW, Ellis SG, Cox DA, et al., TAXUS-IV Investigators. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. Circulation 2004;109:1942–7.
12. Fajadet J, Wijns W, Laarman GJ, et al., ENDEAVOR II Investigators. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. Circulation 2006;114:798–806.
13. Beijk MA, Piek JJ. XIENCE V everolimus-eluting coronary stent system: a novel second generation drug-eluting stent. Expert Rev Med Devices 2007;4:11–21.

APPENDIX

For a list of the trial organization, co-investigators, and participating institutions, please see the online version of this article.