Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 55, No. 11, 2010
ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2009.11.049

5-Year Clinical Outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the Sirolimus-Eluting Stent in the Treatment of Patients With Multivessel De Novo Coronary Artery Lesions

Patrick W. Serruys, MD, PHD,* Yoshinobu Onuma, MD,* Scot Garg, MBCHB,* Pascal Vranckx, MD,† Bernard De Bruyne, MD, PHD,‡ Marie-Claude Morice, MD,§ Antonio Colombo, MD,‖ Carlos Macaya, MD,¶ Gert Richardt, MD,# Jean Fajadet, MD,** Christian Hamm, MD,†† Monique Schuijer, PHD,‡‡ Tessa Rademaker, MSC,‡‡ Kristel Wittebols, MSC,§§ Hans Peter Stoll, MD,§§ on behalf of the ARTS II Investigators

Rotterdam, the Netherlands, Hasselt, Aalst, and Waterloo, Belgium; Paris and Toulouse, France; Milan, Italy; Madrid, Spain; and Bad Segeberg and Bad Nauheim, Germany

Objectives The purpose of this study is to compare the 5-year clinical outcomes, safety, and efficacy of sirolimus-eluting stents (SES) in the ARTS II (Arterial Revascularization Therapies Study II) with the outcomes of coronary artery bypass graft (CABG) and bare-metal stenting (BMS) from the ARTS I.

Background The long-term outcomes after SES implantation in patients with multivessel disease remains to be established.

Methods The ARTS I was a randomized trial of 1,205 patients with multivessel disease comparing CABG and BMS. The ARTS II study was a nonrandomized trial with the Cypher sirolimus-eluting stent (Cordis, a Johnson & Johnson Company, Warren, New Jersey), applying the same inclusion and exclusion criteria, end points, and protocol definitions. The ARTS II trial enrolled 607 patients, with an attempt to enroll at least one-third of patients with 3-vessel disease.

Results At 5-year, the death/stroke/myocardial infarction event-free survival rate was 87.1% in ARTS II SES, versus 86.0% ($p = 0.1$) and 81.9% ($p = 0.007$) in ARTS I CABG and BMS cohorts, respectively. The 5-year major adverse cardiac and cerebrovascular event (MACCE) rate in ARTS II (27.5%) was significantly higher than ARTS I CABG (21.1%, $p = 0.02$), and lower than in ARTS I BMS (41.5%, $p < 0.001$). The cumulative incidence of definite stent thrombosis was 3.8%. Thirty-two percent (56 of 176) of major adverse cardiac events (MACE) at 5 years were related to possible, probable, or definite stent thrombosis.

Conclusions At 5 years, SES had a safety record comparable to CABG and superior to BMS, and a MACCE rate that was higher than in patients treated with CABG, and lower than in those treated with BMS. Approximately one-third of the events seen with SES could be prevented through the elimination of early, late, and very late stent thrombosis. (J Am Coll Cardiol 2010;55:1093–101) © 2010 by the American College of Cardiology Foundation

The randomized RAVEL (Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization), SIRIUS (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions), and TAXUS VI studies have all demonstrated the efficacy and safety of drug-eluting stents (DES) compared with bare-metal stent (BMS) at 5-year follow-up (1–3). These studies, however, enrolled patients with simple de novo lesions, and although important, their results are not applicable to the 60% to 70% of today's percutaneous coronary intervention (PCI) patients who receive DES for "off-label" indications (4). Compared with "on-label" use, the use of DES for off-label indications is

From the *Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands; †Hartcentrum, Hasselt, Belgium; ‡Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium; §Cardiovascular Institute, Paris, France; ‖San Raffaele Hospital, Milan, Italy; ¶Hospital Clinico San Carlos, Madrid, Spain; #Segeberger Kliniken GmbH, Bad Segeberg, Germany; **Clinique Pasteur, Toulouse, France; ††Kerckhof-Klinik, Bad Nauheim, Germany; ‡‡Cardialysis BV, Rotterdam, the Netherlands; and §§Cordis Clinical Research EMEA, a Johnson and Johnson Company, Waterloo, Belgium. Ms. Wittebols and Dr. Stoll are employees of Cordis Clinical Research. Dr. Hamm is a consultant for Cordis and Medtronic, and has received research support from Boston Scientific.

Manuscript received September 2, 2009; revised manuscript received November 11, 2009, accepted November 30, 2009.

JACC Vol. 55, No. 11, 2010
March 16, 2010:1093–101

Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
CABG = coronary artery bypass graft
CVA = cerebrovascular accident
DES = drug-eluting stent(s)
MACCE = major adverse cardiac and cerebrovascular event(s)
MACE = major adverse cardiac event(s)
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
SES = sirolimus-eluting stent(s)
ST = stent thrombosis

associated with poorer outcomes and a higher risk of stent thrombosis (ST); conversely, for off-label lesions, DES are associated with superior outcomes when compared with BMS (4–8). These data are limited to only short- and medium-term follow-up, and the outcomes at 5 years in this complex patient group remain to be fully established. The ARTS II (Arterial Revascularization Therapies Study II) population clearly represents off-label use of sirolimus-eluting stents (SES), with a mean of 3.7 stents implanted per patient, and a mean total stent length of 72.5 mm per patient. Therefore, although a nonrandomized trial, ARTS II can address important issues regarding the safety of DES implantation in patients with complex multivessel disease.

The present analysis is the final report on the 5-year safety and effectiveness of the SES in patients with multivessel disease: it compares the outcomes of ARTS II with the outcomes of the 2 historical arms of ARTS I, and assesses the impact on long-term outcome of ST, which has been readjudicated according to the new Academic Research Consortium (ARC) definitions (9).

Methods

Study design. ARTS II was a multicenter, nonrandomized, open-label trial designed to compare the safety and efficacy of the SES in patients with de novo multivessel coronary artery disease, with the surgical group of ARTS I acting as a historical control (10–16). In order to obtain a population comparable to ARTS I, patients were stratified by clinical site in order to ensure the inclusion of at least one-third of patients with 3-vessel disease. The details of patient selection and end point definitions are described elsewhere (16–21). In the current analysis, the ARTS II population, the PCI arm, and CABG arm from the ARTS I trials are labeled as SES, BMS, and coronary artery bypass graft (CABG) groups, respectively.

Study objectives. The primary objective of ARTS II was to compare the safety and effectiveness of coronary stent implantation using the SES with the surgical arm of ARTS I. End points are measured in terms of major adverse cardiac and cerebrovascular events (MACCE) comprising all-cause death, any cerebrovascular accident (CVA), nonfatal myocardial infarction (MI), or any repeat revascularization, which is equivalent to the patient-oriented clinical end points of ARC definition (9).

The secondary objectives of this study were to compare the ARTS II patients with both arms of ARTS I with respect to: MACCE at 30 days and 1, 3, and 5 years; the composite end point of death, CVA, and MI; the itemized outcomes of death, CVA, MI, and repeat revascularization; resource utilization at 30 days and 1 year; cost effectiveness at 1 year; and quality of life at 6 months and 1, 3, and 5 years. Finally, the study aimed at describing the prognostic value of the SYNTAX score (22,23) on the MACCE rates in the ARTS II population.

The tertiary objectives of the current study were to report the rate of ST and major cardiac adverse events (MACE; defined as a composite of all-cause death, nonfatal MI, or repeat revascularization) with post hoc readjudication of events according to the ARC definition, which was first described during the follow-up of this trial (9).

End point measurement. In ARTS II, the interventional procedure was performed within 48 h of inclusion, whereas in ARTS I, patients were randomized after informed consent had been obtained, after which, patients were placed on a waiting list; there were 3 deaths in the ARTS I CABG arm while patients were awaiting revascularization. To compensate for the temporal difference in allocation between groups, events for the present report were counted from the time of the procedure for all 3 arms and not from the time of allocation as previously published.

In ARTS I and II, only data on subacute thrombotic occlusion (<30 days) were collected in the case record form. In ARTS II, ST was readjudicated according to the ARC definitions. In this process, all coronary angiograms, both procedure-related (n = 104) and nonprocedure-related (n = 165), were reviewed by an independent core laboratory and adjudicated by an independent critical event committee. Thus far, no attempt has been made to assess data on ST in ARTS I in a similar fashion.

In addition, a detailed coronary risk score that has been previously published and tested in a subgroup of ARTS II patients with 3-vessel disease (the SYNTAX score) was used to characterise the complexity of the coronary anatomy (19). In brief, each coronary lesion producing ≥50% luminal obstruction, in vessels ≥1.5 mm, was separately scored and added to provide the overall SYNTAX score. The SYNTAX score was calculated using dedicated software that integrates the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the score of Leaman et al. (24), and the morphologic features of each single lesion, as previously reported (23). This SYNTAX score is now available for the entire ARTS II population and its implications in terms of prognosis at 5 years are reported in the current paper.

Statistical analysis. Binary variables are reported as percentages, and the difference between groups was presented with 95% confidence intervals. Time-to-event variables are

presented as Kaplan-Meier curves, and incidences were compared using the log-rank test.

A separate multivariate regression analysis was performed to determine independent predictors of MACE and ST (according to ARC definition) within the ARTS II population only. The following variables were tested on a per patient basis by univariate analysis to determine suitability for inclusion in the multivariate model: sex, previous history of MI, current smoking habit, left ventricular ejection fraction, presence of diabetes, hypertension, 3-vessel disease, family history of MI or sudden death at age <55 years, presentation with unstable angina, use of glycoprotein IIb/IIIa inhibitors, logistic euroSCORE, and SYNTAX score. Finally, a logistic regression model was built using the significant univariate predictors ($p < 0.1$).

Results

Baseline and procedural characteristics. Between April 1997 and June 1998, a total of 1,205 patients were randomly assigned to PCI with BMS (n = 600) or CABG (n = 605) in 67 participating centers in the ARTS I trial. Between February 2003 and November 2003, 607 patients at 45 participating centers were treated by PCI using SES and entered into the ARTS II study. Table 1 presents their baseline demographic and angiographic characteristics. Patients treated in ARTS II were significantly older than those in ARTS I. ARTS II had a significantly higher incidence of diabetes mellitus, hypertension, hypercholesterolemia, and silent ischemia, and a lower percentage of current smokers or patients with a history of prior MI as compared with the CABG groups. Seven patients did not receive any stents during the index procedure (4 underwent elective CABG, 1 required emergent CABG, 1 underwent PCI 35 days later, and 1 remained on medical therapy).

The percentage of percutaneous 3-vessel treatment was 46.6% in SES versus 18.0% in BMS ($p < 0.001$). The mean number of significant lesions per patient was 3.6 ± 1.3 in SES versus 2.8 ± 1.0 in CABG ($p < 0.001$) and 2.8 ± 1.0 in BMS. SES patients received 3.7 ± 1.5 stents with an average total stented length of 72 ± 32 mm compared with 2.8 ± 1.3 stents and 48 ± 22 mm in BMS patients ($p < 0.001$). In the SES population, SYNTAX score and logistic euroSCORE were 20.8 ± 9.51 and 2.16 ± 15.2, respectively.

5-year follow-up. MACCE. Clinical follow-up at 5 years was available in 97.6% of ARTS II population (Fig. 1). The 5-year event rates are depicted in Table 2 and Figure 2. The survival rate in ARTS II was comparable to the historical, surgical, and PCI groups from ARTS I (SES: 94.5%, CABG: 92.6%, BMS: 92.0%). The death/CVA/MI event-free survival was 87.1% in ARTS II, versus 86.0% (log-rank p = 0.42) and the 81.9% (log-rank p = 0.008) in the CABG and BMS cohorts, respectively. At 5-years follow-up, the MACCE-free survival rate in ARTS II (72.5%), which had been comparable to the surgical cohort of ARTS I at 3 years, was significantly lower than CABG (78.9%, p = 0.02), and significantly higher than BMS (58.5%, log-rank $p < 0.001$).

ST ACCORDING TO THE ARC DEFINITIONS. In ARTS II, a total of 57 patients (Table 3) experienced at least 1 stent thrombotic event (definite, probable, or possible) at 5 years. The rate of ST (definite or probable or possible) in ARTS II was 1.5% at 30 days, 3.1% at 1 year, 4.4% at 2 years, 6.4% at 3 years, and 9.4% at 5 years, respectively. The rate of definite ST was 1.0% at 30 days, 1.6% at 1 year, 2.1% at 2 years, 3.5% at 3 years, and 3.8% at 5 years. Among the 23 patients with definite ST, the numbers experiencing acute (<30 days), late (>30 days, <1 year), and very late (>1 year) ST were 6, 4, and 13, respectively. Four of the acute thrombotic events occurred within the first 4 days post-procedure.

Although clopidogrel was only recommended for 3 months, a total of 266 patients were still using thienopyridines at 1 year. The impact of ST on the ARC-defined patient-oriented composite end point is presented in Figure 3A. If none of these ST events (definite, probable, and possible) had occurred, the event-free rate from mortality, the composite of mortality or any MI, and the patient-oriented composite end point would have increased from 94.5%, 84.3%, 70.7% to 96.8%, 92.7%, 78.0%, respectively (absolute difference: 2.3%, 8.4%, and 7.3%).

IMPACT OF SYNTAX SCORE ON CLINICAL OUTCOME. A significant separation of MACCE-free survival was observed when patients were stratified according to SYNTAX score tertiles, with low, intermediate, and high groups defined by SYNTAX scores of <16 (n = 209), 16 to 24 (n = 199) (Fig. 4). When compared with the lowest tertile group (SYNTAX score: <16, 5-year MACE-free rate: 80.1%), both the intermediate (SYNTAX score: 16 to 24) and high (SYNTAX score: >24) tertile groups demonstrated a lower MACE-free survival rate (intermediate: 70.1%, log-rank p = 0.02; high: 67.1%, p = 0.001).

Multivariate analysis. Univariable and multivariable independent predictors for 5-year MACE and ST were presented in Table 4. In univariate analysis, diabetes, logistic euroSCORE, and SYNTAX score were significant predictors of MACE. In multivariate analysis, diabetes (odds ratio [OR]: 1.68 [95% CI: 1.24 to 2.28]), logistic euroSCORE (OR 1.09 [95% CI: 1.003 to 1.14]), and SYNTAX score (OR: 1.68 [95% CI: 1.24 to 2.28]) remained significant, although history of carotid surgery was not. With respect to ST (definite, probable, or possible), SYNTAX score, use of glycoprotein IIb/IIIa inhibitors, and logistic euroSCORE were significant predictors in the univariate analysis, whereas multivariate analysis demonstrated that only SYNTAX score (OR: 1.03 [95% CI: 1.00 to 1.05]) and the use of glycoprotein IIb/IIIa inhibitors (OR: 1.71 [95% CI: 0.99 to 1.32]) were independent predictors of ST at 5 years.

JACC Vol. 55, No. 11, 2010
March 16, 2010:1093–101

Table 1 Baseline and Procedural Characteristics of ARTS II and I Population

	SES (n = 607)	CABG (n = 605)	BMS (n = 600)	SES/CABG Difference (95% CI)	SES/BMS Difference (95% CI)
Baseline characteristics					
Male sex	77	76	77	0.6% (−4.2% to 5.4%)	−0.4% (−5.2% to 4.4%)
Age (yrs)	63 ± 10	61 ± 9	61 ± 10	1.5 (0.4 to 2.6)	2.1 (1.0 to 3.2)
Body mass index (kg/m^2)	27.5 ± 4.1	27.4 ± 3.7	27.2 ± 3.7	0.2 (−0.3 to 0.6)	0.3 (−0.1 to 0.8)
Risk factors					
Myocardial infarction	34	42	44	−7.6% (−13.0% to −2.1%)	−9.9% (−15.4% to −4.4%)
Diabetes	26	16	19	10.3% (5.8% to 14.9%)	7.5% (2.8% to 12.2%)
Hypertension	67	45	45	22.3% (16.8% to 27.7%)	22.5% (17.1% to 28.0%)
Hypercholesterolemia	74	58	58	16.4% (11.2% to 21.7%)	16.1% (10.8% to 21.4%)
Family history of MI or sudden death at age <55 yrs	36	42	39	−6.0% (−11.5% to −0.5%)	−3.2% (−8.7% to 2.2%)
Current smoker	19	26	28	−6.5% (−11.2% to −1.8%)	−8.7% (−13.4% to −3.9%)
Peripheral vascular disease	7	5	6	1.8% (−0.9% to 4.5%)	1.4% (−1.3% to 4.2%)
Indication for treatment					
Stable angina	53	58	56	−4.8% (−10.4% to −0.8%)	−3.1% (−8.7% to 2.5%)
Unstable angina	36	37	38	−0.8% (−6.2% to 4.6%)	−1.3% (−6.7% to 4.2%)
Silent ischemia	10	5	6	5.6% (2.6% to 8.5%)	4.4% (1.3% to 7.5%)
Angiographic characteristics					
Ejection fraction	60 ± 12	60 ± 13	61 ± 12	−0.2 (−1.6 to 1.3)	−0.8 (−2.2 to 0.7)
No. of lesions with stenosis >50%	3.6 ± 1.3	2.8 ± 1.0	2.8 ± 1.0	0.8 (0.6 to 0.9)	0.8 (0.6 to 0.9)
No. of diseased vessels					
1	0	4	4	−3.4% (−5.0% to −1.8%)	−3.6% (−5.3% to −2.0%)
2	46	66	69	−20.1% (−25.6% to −14.6%)	−22.4% (−27.9% to −17.0%)
3	54	30	27	23.5% (18.1% to 28.9%)	26.1% (20.7% to 31.4%)
Vessel territory with stenosis (% of lesions)					
Right coronary artery	29	29	31	−0.4% (−3.3% to 2.5%)	−2.1% (−5.0% to 0.9%)
Left main	0	0	0	−0.1% (−0.2% to 0.1%)	−0.1% (−0.2% to 0.1%)
Left anterior descending	42	41	39	0.4% (−2.7% to 3.6%)	2.1% (−1.1% to 5.3%)
Left circumflex artery	29	29	29	0.0% (−2.9% to 3.0%)	0.0% (−2.9% to 3.0%)
Lesion length (visual) (% of lesions)					
Discreet (<10 mm)	61	68	66	−7.3% (−10.4% to −4.2%)	−4.7% (−7.9% to −1.5%)
Tubular (10–20 mm)	27	25	27	2.0% (−0.9% to 4.9%)	−0.1% (−3.0% to 2.8%)
Diffuse (>20 mm)	12	7	7	5.3% (3.4% to 7.2%)	4.8% (2.9% to 6.7%)
Lesion classification (% of lesions)					
Type A	7	7	6	0.0% (−1.6% to 1.6%)	0.9% (−0.7% to 2.5%)
Type B1	23	31	26	−7.9% (−10.8% to −5.1%)	−3.0% (−5.8% to −0.2%)
Type B2	56	54	60	1.9% (−1.3% to 5.1%)	−3.7% (−6.9% to −0.5%)
Type C	14	8	8	6.0% (4.0% to 8.0%)	5.9% (3.9% to 7.8%)
Procedural characteristics					
Bifurcation requiring double wiring	34	32	35	2.2% (−0.9% to 5.3%)	−0.6% (−3.7% to 2.6%)
Number of stents implanted	3.7 ± 1.5	—	2.8 ± 1.3	—	0.9 (0.7 to 1.0)
Total stent length (mm)	72.5 ± 32.1	—	47.6 ± 21.7	—	24.9 (21.8 to 28.1)
Maximum dilatation pressure (atm)	16.4 ± 2.9	—	14.6 ± 2.8	—	1.7 (1.4 to 2.1)
Direct stenting (% of lesions)	34.6	—	3.3	—	31.3% (29.1% to 33.6%)
Duration of procedure (min)	85 ± 43	193 ± 67	99 ± 50	−108.2 (−114.6 to −101.8)	−13.6 (−18.9 to −8.3)
Post-procedural hospital stay (days)	3.4 ± 2.7	9.6 ± 4.9	3.9 ± 3.7	−6.2 (−6.6 to −5.8)	−0.5 (−0.9 to −0.2)

Values are % or mean ± SD. Data are expressed per patient unless stated otherwise.
BMS = bare-metal stent(s); CABG = coronary artery bypass graft; CI = confidence interval; MI = myocardial infarction; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stent(s).

Discussion

The current analysis reports the 5-year outcomes of patients with multivessel disease treated with SES, and historical cohorts treated with CABG and BMS. The main findings of the study are the following: 1) 5-year mortality was similar between SES, CABG, and BMS groups; 2) the 5-year composite safety end point of death, stroke, and MI in the SES group was comparable to the CABG group, and lower than the BMS group; 3) at 5 years, the MACCE rate in the SES group was higher than the CABG group, which was mainly driven by a higher rate of repeat revascularization in the SES group; however, the MACCE rate of the SES group remained lower than that of the BMS group; 4) at 5-year follow-up, ST events (early, late, and very late) were potentially involved in approximately one-third of

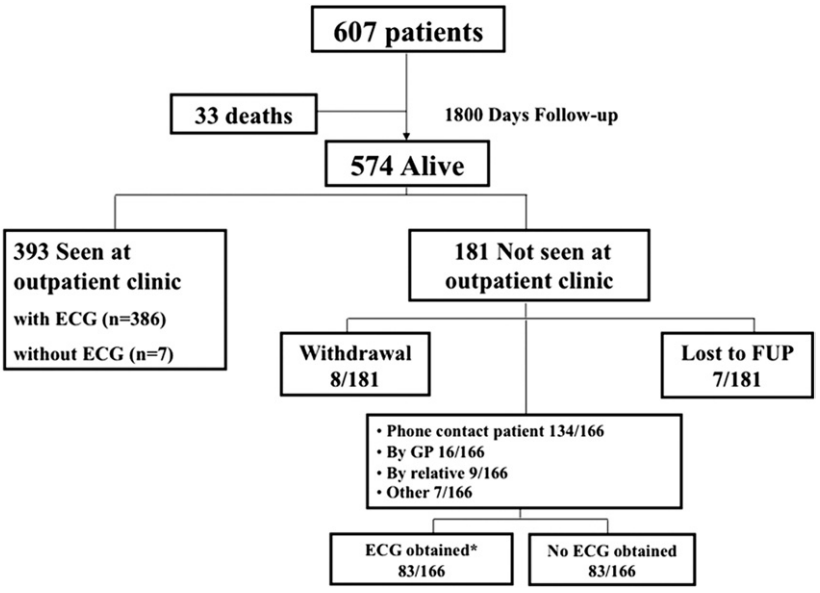

Figure 1 Flow Chart of 5-Year Follow-Up

*Electrocardiogram (ECG) obtained by center. FUP = follow-up; GP = general practitioner.

MACE events; and 5) baseline SYNTAX score has a role in the prediction of 5-year MACCE events.

Long-term safety. Despite the more complex angiographic profile and clinical risk factors in the SES cohort, there was no difference in 5-year mortality between the ARTS II and I cohorts. Although the present study might have been underpowered to demonstrate any significant difference in mortality, the findings concur with the meta-analyses of randomized trials of CABG versus BMS and more specifically, CABG versus multivessel stenting with BMS (25,26). In the current study, the composite end point of mortality, stroke, and MI was lowest in the SES group and was significantly better than in the BMS cohort.

Long-term efficacy. The significantly higher MACCE rate in the SES group compared with the CABG cohort (21.1% vs. 17.5%, p = 0.02) at 5-years was not observed consistently through the study. At 1 year, the MACCE rate was slightly lower in the SES cohort compared with the CABG group, whereas at 2 and 3 years, following a

Table 2 Clinical End Points at 5 Years (Hierarchical and Nonhierarchical MACCE Up to 1,800 Days, Per Patient) Counted Since Date of Procedure

	SES (n = 607)	CABG (n = 602)*	BMS (n = 600)	SES/CABG Difference (95% CI)	SES/BMS Difference (95% CI)
Hierarchical					
Death	33 (5.4)	43 (7.1)	47 (7.8)	−1.7 (−4.4 to 1.0)	−2.4 (−5.2 to 0.4)
CVA	17 (2.8)	16 (2.7)	19 (3.2)		
MI	27 (4.4)	24 (4.0)	41 (6.8)		
Death/CVA/MI	77 (12.7)	83 (13.8)	107 (17.8)	−1.1 (−4.9 to 2.7)	−5.1 (−9.2 to −1.1)
Revascularization	88 (14.5)	42 (7.0)	140 (23.3)		
(re) CABG	15 (2.5)	5 (0.8)	47 (7.8)		
(re) PTCA	73 (12)	37 (6.1)	93 (15.5)		
Any MACCE	165 (27.2)	125 (20.8)	247 (41.2)	6.4 (1.6 to 11.2)	−14 (−19.3 to −8.7)
Nonhierarchical					
CVA	22 (3.6)	20 (3.3)	23 (3.8)	0.3 (−1.8 to 2.4)	−0.2 (−2.3 to 1.9)
MI	35 (5.8)	34 (5.6)	49 (8.2)	0.1 (−2.5 to 2.7)	−2.4 (−5.3 to 0.5)
Revascularization	123 (20.3)	52 (8.6)	181 (30.2)	11.6 (7.7 to 15.5)	−9.9 (−14.8 to −5.0)
(re) CABG	17 (2.8)	7 (1.2)	63 (10.5)	1.6 (0.1 to 3.2)	−7.7 (−10.5 to −4.9)
(re) PTCA	108 (17.8)	49 (8.1)	138 (23.0)	9.7 (5.9 to 13.4)	−5.2 (−9.7 to −0.7)

Values are n (%). *3 patients on the waiting list died.

CVA = cardiovascular accident; MACCE = major adverse cardiac and cerebrovascular event; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table 1.

JACC Vol. 55, No. 11, 2010
March 16, 2010:1093–101

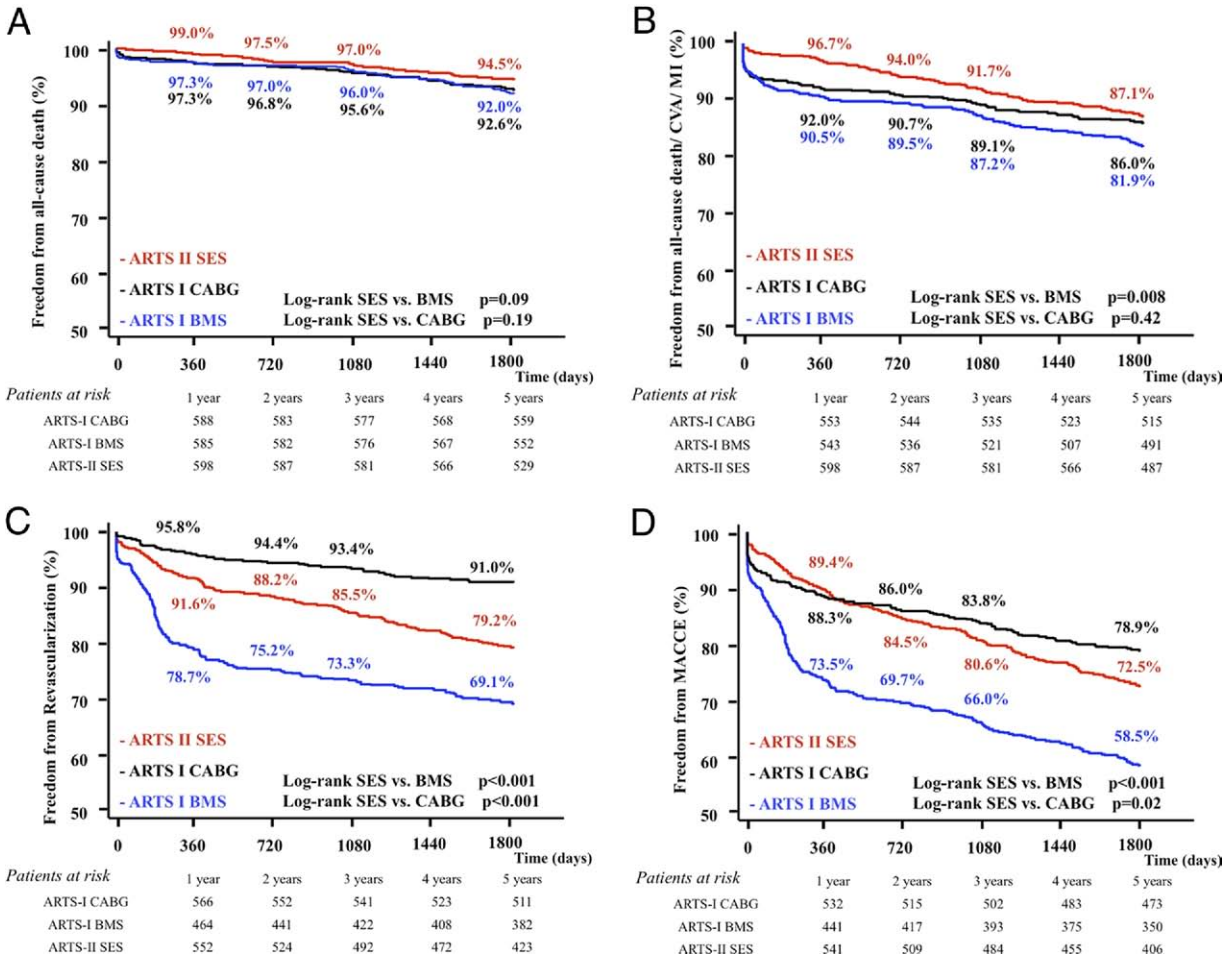

Figure 2 **Kaplan-Meier Curves of Freedom From Clinical Events**

Kaplan-Meier estimates up to 1,800 days of: **(A)** freedom from all-cause mortality; **(B)** freedom from a composite of death, cerebrovascular accident (CVA), or myocardial infarction (MI); **(C)** freedom from revascularization; and **(D)** freedom from major adverse cardiac and cardiovascular events (MACCE) (all-cause mortality, any MI, CVA, or any reintervention). ARTS = Arterial Revascularization Therapy Study; BMS = bare-metal stent(s); CABG = coronary artery bypass graft; SES = sirolimus-eluting stent(s).

comparatively greater number of additional MACCE events in the SES group, the overall MACCE rate was insignificantly higher in the SES group compared with CABG (17,27). This reversal was mainly driven by the relatively higher rates of reintervention in patients in SES compared with CABG, such that the absolute difference in repeat revascularization between the 2 groups increased progressively from 4.2 % at 1 year to 6.2%, 7.9%, and 11.6% at 2, 3, and 5 years, respectively. Therefore, the current trial confirms that surgical revascularization is more durable than percutaneous revascularization. It is noteworthy, however, that the freedom from surgical or percutaneous reintervention at 5 years increased from 69.1% in the BMS to 79.2% in SES. Furthermore, at 5 years, only 2.8% of patients from the SES cohort required CABG compared with 10.5% from the BMS cohort.

Table 3 **ST According to the ARC Definitions**

	ARTS II	Death Up to 1,800 Days	MI Up to 1,800 Days*
Acute/subacute (<30 days)	9 (1.4%)	1/9 (11%)	9/9 (100%)
Late (<1 yr)	9 (1.4%)	3/9 (30.0%)	4/9 (40.0%)
Very late (>1 yr)	39 (6%)	10/39 (26%)	29/39 (74%)
Definite	23 (4%)	2/23 (9%)	19/23 (83%)
Definite or probable	46 (8%)	3/46 (7%)	42/46 (91%)
Definite, probable or possible	57 (9%)	14/57 (25%)	42/57 (74%)

*MI according to ARC definition.
ARC = Academic research consortium; MI=myocardial infarction; ST = stent thrombosis.

ST. Occurrence of late and very late ST has been recognized as a long-term safety concern with drug-eluting stents (28,29). Recent studies have suggested that in patients with 2- and 3-vessel disease, ST negatively impacts long-term outcomes (30). There was a gradual rise in the rate of ST during follow-up, but overall rates of definite ST were similar to those reported in all-comer

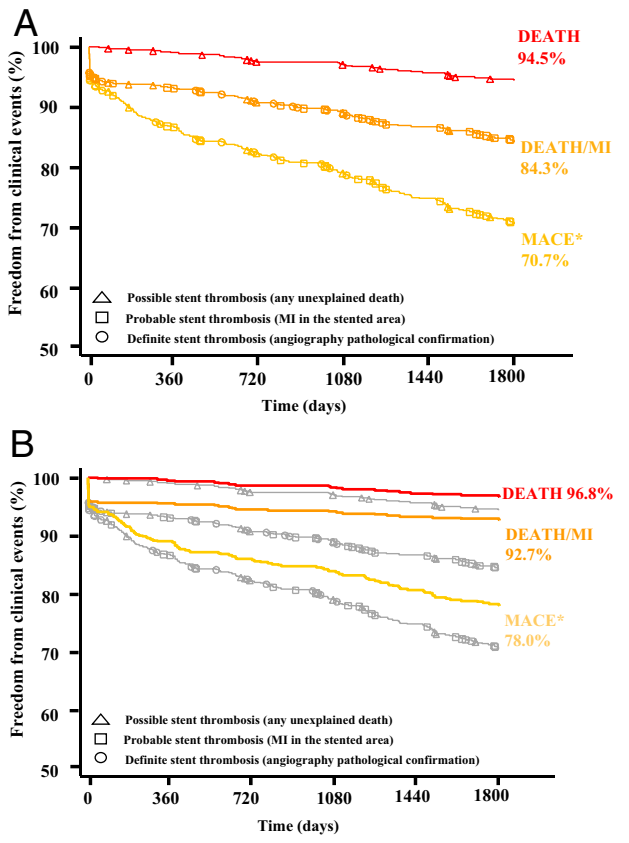

Figure 3 **Kaplan-Meier Curves of Freedom From ARC-Defined MACE, With or Without ST**

Kaplan-Meier estimates of freedom from death **(red lines)**, death or myocardial infarction (MI) **(orange lines)**, and major adverse cardiac events (MACE) (all-cause mortality, MI, or revascularization) **(yellow lines)** according to Academic Research Consortium (ARC) definition **(A)**. Possible stent thrombosis (ST) is superimposed on the Kaplan-Meier curves as a **triangle**, probable stent thrombosis as a **square**, and definite stent thrombosis as a **circle**. If all these ST-related events had been eliminated **(B)**, freedom from death at 5 years would have increased from 94.5% to 96.8%, freedom from death or death/MI from 84.3% to 92.7%, and freedom from MACE from 70.5% to 78.0%. Please note MI and MACE were readjudicated according to ARC definition. *All-cause death, MI, or any revascularization according to ARC definition. Troponin was not collected in the ARTS II.

populations treated with DES (28,29). When analyzing the impact of ST on safety outcomes, reassurance can be obtained by considering the rate of all-cause mortality (5-year mortality, SES: 5.4% vs. BMS: 7.8%) and MI (5-year MI, SES: 5.8% vs. BMS: 8.2%), because despite the fact that two-thirds of the patients with definite ST sustained an MI or underwent a repeat revascularization, only 2 of these 23 patients died at 5-year follow-up. The ST events from ARTS I PCI have not been reported because of the absence of any adjudication of late and very late stent thrombotic events.

Figure 3 illustrates the fact that early, late, and very late, as well as definite, probable, or possible ST all contributed to a deterioration in the treatment effect expressed as freedom from death, death/MI, and death/MI/repeat revascularization. Of the 176 patients who had a major adverse cardiac event (ARC definitions), 22 had definite ST, 45 definite or probable ST, and 56 definite, probable, or possible ST (32% of adverse events). Thus, one-third of adverse events occurring during 5-year follow-up could be explained, and potentially prevented, by eliminating ST. These results emphasize the importance of optimal stent implantation, development of less thrombogenic devices such as DES with biocompatible or bioabsorbable coatings, or fully bioabsorbable DES, and in addition, more effective antithrombotic therapies (31–35).

Impact of SYNTAX score on long-term clinical outcome. The recently reported SYNTAX trial compared surgery with percutaneous treatment in patients with left main or 3-vessel disease (36). Of interest, when patients with 3-vessel disease from the SYNTAX trial were subdivided into tertiles of SYNTAX score (cutoff of 23 and 33), the lowest tertile group showed similar 1-year MACCE rates

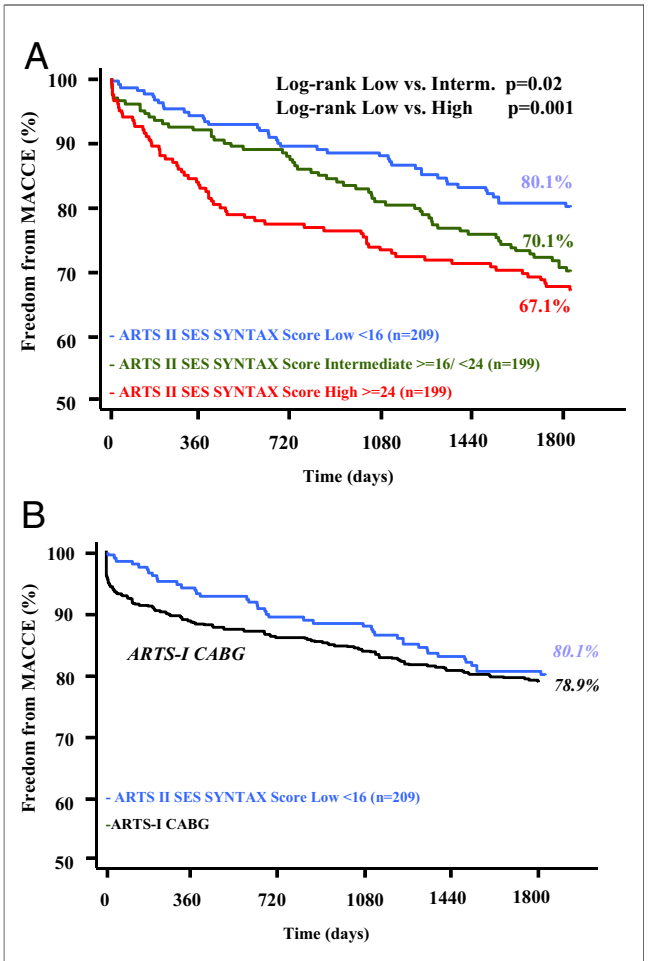

Figure 4 **Kaplan-Meier Curves of Freedom From MACCE According to Tertiles of SYNTAX Score**

Freedom from protocol-defined major adverse cardiac and cerebrovascular event (MACCE) rate according to SYNTAX score tertiles **(A)**. When the coronary artery bypass graft (CABG) MACCE rate is superimposed, the lowest SYNTAX score tertile shows a similar event rate at 5 years **(B)**.

Table 4 Independent Predictors of MACE and ST in the ARTS II Group

	Univariable Predictors at 5 Yrs			Multivariable Predictors at 5 Yrs		
Variables	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
MACE						
Diabetes	1.82	1.35–2.47	<0.001	1.68	1.24–2.28	<0.001
Logistic euroSCORE	1.11	1.03–1.21	0.01	1.09	1.003–1.14	0.04
SYNTAX score	1.04	1.02–1.05	<0.001	1.68	1.24–2.28	0.001
Any ST						
SYNTAX score	1.03	1.00–1.06	0.02	1.03	1.00–1.05	0.04
Use of glycoprotein IIb/IIIa inhibitor	1.68	0.99–2.83	0.05	1.71	1.01–2.89	0.045
Logistic euroSCORE	1.14	0.99–1.31	0.05	1.15	0.99–1.32	0.06

Major adverse cardiac events (MACE) are according to ARC definition (all-cause death, myocardial infarction, or revascularization). Abbreviations as in Tables 1 through 3.

between PCI and CABG. On the other hand, for the highest tertile groups, the 1-year MACCE rate was significantly higher in the PCI group (36).

After applying the tertile division of the SYNTAX score to the ARTS II study (cutoffs 16 and 24), patients with a score of <16 had a MACCE-free survival rate that was greater than patients in the middle or highest tertiles. In addition, the SYNTAX score was identified as an independent predictor of 5-year ST and MACE, indicating that it has a role in the risk stratification of patients with multivessel disease. Furthermore, the MACE rate was similar between the lowest tertiles of the ARTS II group and the entire surgical cohort from ARTS I (Fig. 4). These results further support the notion that patients with multivessel disease and a low SYNTAX score may be adequately treated with PCI, whereas those patients with high SYNTAX scores benefit more from CABG.

Of note, the cutoff values for the tertile division of the SYNTAX score in the SYNTAX trial (23 and 33) are for obvious reasons different from those in the ARTS II trial (16 and 24). Further assessment of the distribution and clinical impact of the SYNTAX score in various populations is warranted; however, only a propensity-matched analysis based on SYNTAX score will allow a definitive comparison of outcomes between the SYNTAX randomized controlled trial and the ARTS II registry.

Study limitations. First, it was nonrandomized, and thus the groups are not directly comparable, precluding a formal noninferiority comparison. In view of the higher risks anticipated as a result of the greater severity of disease in the ARTS II population compared with the ARTS I population, the clinical outcomes may be biased against ARTS II; however, this may be partially offset by other advances in interventional technology. Statistical adjustment therefore might be required to correct for the differences. This is currently being conducted and will be presented in a separate report. Second, there was a 5-year time lag between the enrollment periods of the ARTS I and II cohorts. With recent improvements in surgical techniques and concomitant medication (statins), it is more than likely that the clinical results of a true randomized trial would have come out more in favor of surgical treatment. Third, the incidence and impact of ST was not readjudicated according to the ARC definitions in the ARTS I study, which was primarily because pieces of clinical information required for readjudication were missing and not obtainable retrospectively. Finally, the baseline SYNTAX scores in the historical cohorts have not been calculated because the baseline cineangiograms are no longer available.

Reprint requests and correspondence: Dr. Patrick W. Serruys, Thoraxcenter, Ba-583, 's Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Weisz G, Leon MB, Holmes DR Jr., et al. Five-year follow-up after sirolimus-eluting stent implantation results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) trial. J Am Coll Cardiol 2009;53:1488–97.
2. Morice MC, Serruys PW, Barragan P, et al. Long-term clinical outcomes with sirolimus-eluting coronary stents: five-year results of the RAVEL trial. J Am Coll Cardiol 2007;50:1299–304.
3. Grube E, Dawkins K, Guagliumi G, et al. TAXUS VI final 5-year results: a multicentre, randomised trial comparing polymer-based moderate-release paclitaxel-eluting stent with a bare metal stent for treatment of long, complex coronary artery lesions. EuroIntervention 2009;4:572–7.
4. Kirtane AJ, Gupta A, Iyengar S, et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. Circulation 2009;119:3198–206.
5. Lasala JM, Cox DA, Lewis SJ, et al. Expanded use of the TAXUS Express Stent: two-year safety insights from the 7,500 patient ARRIVE Registry programme. EuroIntervention 2009;5:67–77.
6. Win HK, Caldera AE, Maresh K, et al. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. JAMA 2007;297:2001–9.
7. Farb A, Boam AB. Stent thrombosis redux—the FDA perspective. N Engl J Med 2007;356:984–7.
8. Brodie BR, Stuckey T, Downey W, et al. Outcomes and complications with off-label use of drug-eluting stents: results from the STENT (Strategic Transcatheter Evaluation of New Therapies) group. JACC Cardiovasc Interv 2008;1:405–14.
9. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
10. Serruys PW, Ong AT, van Herwerden LA, et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of

multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. J Am Coll Cardiol 2005;46:575–81.
11. Ix JH, Mercado N, Shlipak MG, et al. Association of chronic kidney disease with clinical outcomes after coronary revascularization: the Arterial Revascularization Therapies Study (ARTS). Am Heart J 2005;149:512–9.
12. Gruberg L, Mercado N, Milo S, et al. Impact of body mass index on the outcome of patients with multivessel disease randomized to either coronary artery bypass grafting or stenting in the ARTS trial: the obesity paradox II? Am J Cardiol 2005;95:439–44.
13. Aoki J, Ong AT, Arampatzis CA, et al. Comparison of three-year outcomes after coronary stenting versus coronary artery bypass grafting in patients with multivessel coronary disease, including involvement of the left anterior descending coronary artery proximally (a subanalysis of the arterial revascularization therapies study trial). Am J Cardiol 2004;94:627–31.
14. Legrand VM, Serruys PW, Unger F, et al. Three-year outcome after coronary stenting versus bypass surgery for the treatment of multivessel disease. Circulation 2004;109:1114–20.
15. van den Brand MJ, Rensing BJ, Morel MA, et al. The effect of completeness of revascularization on event-free survival at one year in the ARTS trial. J Am Coll Cardiol 2002;39:559–64.
16. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117–24.
17. Serruys PW, Ong ATL, Morice M-C, et al. Arterial Revascularisation Therapies Study Part II: sirolimus-eluting stents for the treatment of patients with multivessel de novocoronary artery lesions. EuroIntervention 2005;1:147–56.
18. Tsuchida K, Colombo A, Lefevre T, et al. The clinical outcome of percutaneous treatment of bifurcation lesions in multivessel coronary artery disease with the sirolimus-eluting stent: insights from the Arterial Revascularization Therapies Study part II (ARTS II). Eur Heart J 2007;28:433–42.
19. Valgimigli M, Serruys PW, Tsuchida K, et al. Cyphering the complexity of coronary artery disease using the syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007; 99:1072–81.
20. Daemen J, Kuck KH, Macaya C, et al. Multivessel coronary revascularization in patients with and without diabetes mellitus: 3-year follow-up of the ARTS II (Arterial Revascularization Therapies Study-Part II) trial. J Am Coll Cardiol 2008;52:1957–67.
21. Vaina S, Voudris V, Morice MC, et al. Effect of gender differences on early and mid-term clinical outcome after percutaneous or surgical coronary revascularisation in patients with multivessel coronary artery disease: insights from ARTS I and ARTS II. EuroIntervention 2009;4:492–501.
22. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.
23. Serruys P, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study EuroIntervention 2009;5:50–6.
24. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. Circulation 1981;63:285–99.
25. Daemen J, Boersma E, Flather M, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. Circulation 2008;118:1146–54.
26. Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet 2009;373:1190–7.
27. Serruys PW, Daemen J, Morice M-C, et al. Three-year follow-up of the ARTS II: sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease. EuroIntervention 2007;3: 450–9.
28. Wenaweser P, Daemen J, Zwahlen M, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. J Am Coll Cardiol 2008;52:1134–40.
29. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.
30. Kukreja N, Onuma Y, Garcia-Garcia HM, Daemen J, van Domburg R, Serruys PW. Three-year survival following multivessel percutaneous coronary intervention with bare-metal or drug-eluting stents in unselected patients. Am J Cardiol 2009;103:203–11.
31. Serruys PW, Ormiston JA, Onuma Y, et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet 2009;373: 897–910.
32. Ormiston JA, Serruys PW, Regar E, et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. Lancet 2008;371:899–907.
33. Kukreja N, Onuma Y, Daemen J, Serruys PW. The future of drug-eluting stents. Pharmacol Res 2008;57:171–80.
34. Wykrzykowska JJ, Onuma Y, Serruys PW. Advances in stent drug delivery: the future is in bioabsorbable stents. Expert Opin Drug Deliv 2009;6:113–26.
35. Wiviott SD, Braunwald E, McCabe CH, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. Lancet 2008;371: 1353–63.
36. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.

Key Words: multivessel disease ■ sirolimus-eluting stent ■ long-term outcomes.