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Impact of Stable Versus Unstable Coronary Artery Disease on 1-Year Outcome in Elective Patients Undergoing Multivessel Revascularization With Sirolimus-Eluting Stents

A Subanalysis of the ARTS II Trial

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Objectives We sought to evaluate the impact of unstable coronary artery disease (CAD) on short- and mid-term outcomes in patients with multivessel disease treated by multiple sirolimus-eluting stents (SES) as part of ARTS II (Arterial Revascularization Therapies Study Part II).

Background The differential safety/efficacy profile of SES when implanted in patients with unstable angina (UA) in comparison with stable angina (SA) undergoing multivessel intervention is largely unknown.

Methods Between February 2003 and November 2003, 607 patients at 45 participating centers were treated; 221 of them (36%) presented with UA.

Results At 30 days, the cumulative rate of death, myocardial infarction—defined as any creatine kinase (CK)/CK-myocardial band elevation beyond the upper limit of normal—cerebrovascular accident, and repeat revascularization (i.e., major adverse cardiac and cerebrovascular events [MACCEs]) was 19.9% in both groups. Angiographic subacute stent occlusion was documented in 1 (0.5%) and 4 (1%) patients in the UA and SA groups, respectively. At 1 year, the cumulative incidence of MACCEs was 27.1% in the UA and 24.9% in the SA group ($p = 0.56$). Two late occlusions occurred, both in the SA group. After adjustment for baseline and procedural characteristics, the presence of UA was not identified as an independent predictor of MACCE (hazard ratio 0.94; 95% confidence interval 0.41 to 2.12; $p = 0.88$). These findings remained consistent after increasing the CK/CK-myocardial band threshold to define periprocedural myocardial infarction up to at least 3 or 5 times the upper limit of normal.

Conclusions In ARTS II, an unstable clinical presentation did not exert a negative impact on short- and mid-term outcome after SES implantation for multivessel disease. (ARTS II Trial; http://clinicaltrials.gov/ct/show/NCT00235170?order=1; NCT00235170). (J Am Coll Cardiol 2007;49:431–41) © 2007 by the American College of Cardiology Foundation

Several clinical studies, focusing on specific patient and lesion characteristics, including long lesions (1), in-stent restenosis (2), small vessels (3), diabetic patients (4), and infarct-related arteries (5), as well as all-comers registries (6) have established the role of the sirolimus-eluting stent (SES) in reducing the need for further reintervention in comparison with bare-metal stents (BMS). However, whether the net safety/efficacy profile of SES differs in relation to the acuity (i.e., stable vs. unstable) of clinical presentation remains an open issue.

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Abbreviations and Acronyms

ACS = acute coronary syndrome
BMS = bare-metal stent
CVA = cerebrovascular accident
CK-MB = creatine kinase-myocardial band
DES = drug-eluting stent
HR = hazard ratio
MACCE = major adverse cardiac and cerebrovascular event
MI = myocardial infarction
SES = sirolimus-eluting stent
TVR = target vessel revascularization

The thrombogenic coronary milieu in patients with an acute coronary syndrome (ACS), coupled with the well-known propensity for hypercoagulability in this patient subset and possible delayed re-endothelialization with drug-eluting stents (DES), has resulted in concerns of an increased risk of stent thrombosis after implantation of these devices in patients with ACS (7). Moreover, several previous studies have identified unstable angina as a risk factor for restenosis after BMS implantation (8,9).

ARTS II (Arterial Revascularization Therapies Study Part II) is a multicenter, European, open-label, nonrandomized trial evaluating the safety and efficacy of SES as compared with the previous results of the randomized ARTS I trial (10). Thirty-six percent of the 607 patients enrolled in ARTS II had unstable angina at presentation.

We sought to evaluate whether clinical outcome in this subset of patients was comparable with that observed in patients with stable angina in the attempt to evaluate whether the net efficacy/safety profile of SES is affected by acuity of clinical presentation. The 1-year outcome in ARTS II, stratified into stable versus unstable presentation, also was compared with that of patients undergoing percutaneous or surgical revascularization in ARTS I, in keeping with the original design of the study.

Methods

Study design. The ARTS II study design has been previously reported (11,12). In brief, patients were consecutively enrolled via a central telephone service, after stratification by clinical site to ensure the inclusion of at least one-third of patients undergoing 3-vessel intervention.

Selection of patients. Patients were eligible for coronary revascularization if they had either stable angina (Canadian Cardiovascular Society class I, II, III, or IV), unstable angina (Braunwald class IB, IC, IIB, IIC, IIIB, or IIIC), or if they had silent ischemia and at least 2 new lesions located in different major epicardial vessels and/or their side branches (not including the left main coronary artery) that were potentially amenable to stent implantation. Patients were required to have multivessel disease with the need for treatment of the left anterior descending artery and at least one other significant lesion (>50% diameter stenosis) in another major epicardial coronary artery. One totally occluded major epicardial vessel also could be included. The stenosis had to be amenable to stenting using a stent with a diameter of 2.5 to 3.5 mm and length of 13 to 33 mm, without any restriction on the total stent length implanted.

Patients with any previous coronary intervention, left main coronary disease, overt congestive heart failure, or a left ventricular ejection fraction of <30% were excluded. Additional exclusion criteria included a history of a cerebrovascular accident and ST-segment elevation myocardial infarction in the preceding week or with persistent elevation of creatine kinase (CK).

Patients requiring nonelective treatment, defined as a procedure conducted on referral before the beginning of the next working day (13), could not be considered for inclusion. Measurement of troponin was not mandatory at screening. Patients with chest pain lasting longer than 30 min within the preceding 12 h were also excluded if CK was equal or more than 2 times the upper limit of normal.

Written, informed consent was obtained from each patient before enrollment. The study was approved by the ethics committee of each participating site.

Procedures and postintervention medications. All interventions were performed according to current standard guidelines and the final interventional strategy, including the use of glycoprotein IIb/IIIa inhibitors, was left entirely to the discretion of the operator, except for the stent utilization. All patients were advised to maintain lifelong aspirin use. Clopidogrel 300 mg as a loading dose, or ticlopidine, administered at a dose of 500 mg, was to be started at least 24 h before the procedure. Clopidogrel 75 mg per day or ticlopidine 250 mg twice a day was prescribed for at least 2 months after revascularization.

Study objectives and end points. The primary objective of this ARTS II subanalysis was to compare the safety and effectiveness of coronary stent implantation using SES in patients with unstable angina with that of patients undergoing similar treatment for the presence of stable angina. For the purpose of the present analysis, patients with stable angina and silent ischemia (defined as the "stable angina" group) were compared with patients who had unstable angina, as previously reported in ARTS I (14). The primary outcome measure was the incidence of major adverse cardiac and cerebrovascular events (MACCEs) at 1 year, comprising all-cause death, any cerebrovascular event, nonfatal myocardial infarction (MI), or any repeat revascularization (either percutaneous or surgical; contemporary comparison).

The secondary objectives of this study are to compare 1-year MACCE in the ARTS II patients, stratified according to clinical presentation (stable vs. unstable) to that of patients with stable and unstable angina who randomly were assigned to either percutaneous BMS implantation or coronary artery bypass grafting (CABG) in the ARTS I trial (historical comparison).

End point definitions. All deaths were considered cardiac unless a noncardiac origin was established clinically or at autopsy. Death from all causes was reported.

Cerebrovascular events were divided into 3 main categories: stroke, transient ischemic attack, and reversible isch-

emic neurologic deficit. In the first 7 days after the intervention, a definite diagnosis of MI was made if there was documentation of new abnormal Q waves (according to the Minnesota code) and either a ratio of serum CK-myocardial band (CK-MB) isoenzyme to total cardiac enzyme that was >0.1 or a CK-MB value that was 5 times the upper limit of normal (1,11,12). Serum CK and CK-MB isoenzyme concentrations were measured 6, 12, and 18 h after the intervention. Beginning 8 days after the intervention (the length of the hospital stay after surgery), either abnormal Q waves or enzymatic changes were sufficient for a diagnosis of MI. This dual method of defining MI was developed for ARTS I to address the difficulty of diagnosing a MI after cardiac surgery. An MI was confirmed only after the relevant electrocardiograms had been analyzed by the electrocardiographic core laboratory and adjudicated by an independent clinical events committee. For the purpose of this analysis, to explore whether the current definition of MI may artificially contribute to minimize the impact of clinical acuity on outcome, the occurrence of non–Q-wave MI in the first 7 days after the index procedure also has been reclassified based on any CK or CK-MB elevation or a CK or CK-MB value that was 3 times or more the upper limit of normal, in keeping with current American College of Cardiology/American Heart Association and European Society of Cardiology recommendations (15,16). All repeat revascularization procedures were recorded. Events were counted from the time of the initial procedure. Thrombotic occlusions were defined according to the protocol as either by angiographic documentation of a complete occlusion (Thrombolysis In Myocardial Infarction [TIMI] flow grade 0 or 1) or angiographic documentation of a flow-limiting thrombus (TIMI flow grade 1 or 2).

To allow cross comparisons with other contemporary investigations (17), stent thrombosis also was determined as the occurrence of any of the following events: angiographic documentation of partial or total stent occlusion detected within 30 days of the procedure (an acute clinical ischemic event in addition to angiographic documentation had to be present when the event occurred after 30 days) or sudden cardiac death or postprocedural MI after successful stent implantation not clearly attributable to another coronary lesion. All events have been reviewed and adjudicated by an independent clinical events committee.

Statistical analysis. Continuous variables are shown as mean ± SD if not otherwise stated and were compared using the Student 2-sample *t* test. Categorical variables are presented as percentages and compared with the chi-square test. Comparison among 3 groups was performed using a general linear model based on a 1-way analysis of variance, repeated for each of the variables to be explained by treatment on 3 levels as an explanatory variable. No correction for multiple analyses was performed because this procedure was only used as an entry criterion for the multivariable analysis. Survival curves were generated by the Kaplan-Meier method, and survival among groups was compared using the log-rank test. Proportional hazards and Weibull models were used to assess risk reduction of adverse events. For the stable versus unstable comparison within the ARTS II study, multivariable analysis, including all variables mentioned simultaneously in the model and considering all variables reported in Tables 1 and 2 with a p value ≤0.10, was performed to adjust for possible confounders and to identify whether clinical presentation was an independent predictor of adverse events. Moreover, a simultaneous interaction test of the predicting variables with clinical presentation was performed based on a likelihood ratio test, using the model −2Log Likelihood, stratified by anginal status and subtracting the sum of the model −2Log Likelihoods for each analysis by anginal status. This difference has a chi-square distribution with $2 \times n - m$ degrees of freedom, with n the degrees of freedom in the by anginal status analysis and m being the degrees of freedom in the stratified analysis. For the comparison of ARTS II versus ARTS I, multivariate analysis considering all variables reported in Table 3 with a p value ≤0.1 were considered to obtain the adjusted hazard ratio. Colinearity in the model was investigated using a correlation matrix and by inspection of the estimate parameters obtained in the model. Moreover, after standardizing the regressors, the condition index was calculated for each considered variable which ranged from 1 to 3.39, thus excluding the presence of colinrearity. Probability was significant at a level of <0.05. All statistical tests were 2-tailed. Statistical analysis was performed with SAS V8.02 (SAS Institute, Cary, North Carolina).

Results

Patients. Between February 2003 and November 2003, 607 patients at 45 participating centers were treated. Table 1 presents their baseline demographic characteristics based on clinical presentation. The patients were predominantly males with preserved left ventricular function; 3-vessel disease was present in more than 50% of the cases. Patients with unstable angina had a slightly lower body mass index and were affected less frequently by hypertension and hypercholesterolemia. The incidence of previous MI in the unstable group was almost double when compared with the stable patient group. Current smoking was more frequent in unstable as compared to stable patients. The 2 groups were otherwise comparable for all other baseline characteristics, including comorbidities.

Overall hospital stay was on average 1.3 days longer in unstable patients (Table 2). Coronary lesions in patients with unstable angina were less frequently calcified and more frequently of type A/B1 than of type B2/C, whereas thrombus was more commonly observed in this group. There was no other difference in procedural characteristics between the 2 groups, including use of glycoprotein IIb/IIIa inhibitors (Table 2).

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Table 1 Baseline Patient Demographics

Patient Parameters Measured	Unstable Angina (n = 221 Patients)	Stable Angina (n = 386 Patients)	Difference (95% CI)	p Value
Age (yrs)				
n	221	386		
Mean ± SD	62.6 ± 10.5	62.9 ± 9.1	−0.3 (−1.9–1.3)	0.70
(Min–max)	(35–80)	(37–80)		
Ejection fraction (%)				
n	204	334		
Mean ± SD	60.0 ± 11.5	60.3 ± 11.6	−0.3 (−2.3–1.7)	0.76
(Min–max)	(30–97)	(30–88)		
Body mass index (kg/m^2)				
n	220	381		
Mean ± SD	27.1 ± 4.2	27.8 ± 4.0	−0.7 (−1.4–0.0)	0.036
(Min–max)	(15.2–42.9)	(18.6–43.0)		
Men	74.2% (164/221)	78.0% (301/386)	−3.8% (−10.9%–3.3%)	0.32
Diabetes mellitus	23.1% (51/221)	28.0% (108/386)	−4.9% (−12.0%–2.2%)	0.21
Hypertension	62.0% (137/221)	70.2% (271/386)	−8.2% (−16.1%–−0.4%)	0.039
Hypercholesterolemia	65.2% (144/221)	78.9% (303/384)	−13.7% (−21.2%–−6.3%)	<0.001
History of CVA	1.4% (3/221)	0.5% (2/385)	0.8% (−0.8%–2.5%)	0.36
Family history of MI/SD <55 yrs	35.5% (78/220)	36.2% (139/384)	−0.7% (−8.7%–7.2%)	0.86
Peripheral vascular disease	7.2% (16/221)	6.8% (26/385)	0.5% (−3.8%–4.7%)	0.87
Previous MI	48.0% (106/221)	26.7% (103/386)	21.3% (13.4%–29.2%)	<0.001
Previous CABG	0.0% (0/221)	0.0% (0/386)	0.0% (0.0%–0.0%)	
Previous PTCA	0.9% (2/221)	0.3% (1/386)	0.6% (−0.7%–2.0%)	0.30
Carotid surgery	1.4% (3/221)	1.3% (5/385)	0.1% (−1.8%–2.0%)	1.00
Chronic obstructive pulmonary disease	2.7% (6/221)	4.2% (16/385)	−1.4% (−4.4%–1.5%)	0.50
Smoking history				
Previous	34.8% (77/221)	44.3% (171/386)	−9.5% (−17.5%–−1.5%)	0.026
Current	24.4% (54/221)	16.3% (63/386)	8.1% (1.4%–14.9%)	0.018
Unstable angina	100.0% (221/221)	—	—	—
Braunwald I	23.1% (51/221)	—	—	—
Braunwald Ib	19.9% (44/221)	—	—	—
Braunwald Ic	3.2% (7/221)	—	—	—
Braunwald II	49.3% (109/221)	—	—	—
Braunwald IIb	38.0% (84/221)	—	—	—
Braunwald IIc	11.3% (25/221)	—	—	—
Braunwald III	27.6% (61/221)	—	—	—
Braunwald IIIb	20.8% (46/221)	—	—	—
Braunwald IIIc	6.8% (15/221)	—	—	—
Stable angina	—	83.7% (323/386)	—	—
CCS I	—	11.1% (43/386)	—	—
CCS II	—	42.2% (163/386)	—	—
CCS III	—	27.7% (107/386)	—	—
CCS IV	—	2.6% (10/386)	—	—
Silent ischemia	—	16.3% (63/386)	—	—
Number of diseased arteries	—			
Single	0.0% (0/221)	0.5% (2/386)	−0.5% (−1.2%–0.2%)	0.54
Double	47.5% (105/221)	45.3% (175/386)	2.2% (−6.1%–10.4%)	0.61
Triple	52.5% (116/221)	54.1% (209/386)	−1.7% (−9.9%–6.6%)	0.74

Braunwald = Braunwald classification; CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society classification; CI = confidence interval (Diff ± 1.96·SE); CVA = cerebrovascular accident; Difference = unstable angina − stable angina; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; SD = sudden death; SE = sqrt(p1·q1/n1 + p2·q2/n2).

Baseline demographic, procedural characteristics, and medications at discharge according to clinical presentation in ARTS II as compared with ARTS I are reported in Table 3.

ARTS II 30-day outcomes. No deaths occurred in the first 30 days in either group. There were no significant differences in patients with unstable with respect to those with stable angina in the cumulative incidence of MACCE (death, infarction, cerebrovascular accident, or repeat revascularization) during the first 30 days irrespective of the applied definition for myocardial infarction (Table 4). The same was true when each component of the MACCE was

Table 2 Hospital Stay, Procedural Characteristics, and Medications

Parameters Measured	Unstable Angina (n = 221 Pts, n = 794 Les)	Stable Angina (n = 386 Pts, n = 1,365 Les)	Difference (95% CI)	p Value
Per-patient analysis				
Hospital stay (days)				
Mean ± SD	6.1 ± 4.6	4.8 ± 3.9	1.3 (0.6 to 2.0)	<0.001
(Min–max)	(1–37)	(1–36)		
Days to procedure since enrollment*				
Mean ± SD	0.1 ± 0.5	0.1 ± 1.3	0.0 (−0.2 to 0.2)	0.92
(Min–max)	(−1–4)	(−7–21)		
Days in hospital since procedure				
Mean ± SD	3.7 ± 3.1	3.2 ± 2.4	0.5 (0.1 to 1.0)	0.021
(Min–max)	(1–31)	(1–30)		
Duration of procedure (mins)				
Mean ± SD	86.2 ± 46.3	84.5 ± 41.4	1.7 (−5.5 to 8.9)	0.64
(Min–max)	(10–281)	(16–293)		
Number of lesions >50% DS				
Mean ± SD	3.6 ± 1.3	3.5 ± 1.3	0.1 (−0.2 to 0.3)	0.62
(Min–max)	(2–8)	(1–8)		
Number of vessels with a lesion >50% DS				
Mean ± SD	2.5 ± 0.5	2.5 ± 0.5	0.0 (−0.1 to 0.1)	0.79
(Min–max)	(2–3)	(1–3)		
Number of stented lesions				
Mean ± SD	3.2 ± 1.2	3.2 ± 1.1	0.0 (−0.2 to 0.2)	0.70
(Min–max)	(0–7)	(0–8)		
Number of stents implanted				
Mean ± SD	3.6 ± 1.5	3.7 ± 1.5	0.0 (−0.3 to 0.2)	0.72
(Min–max)	(0–9)	(0–11)		
Average stent length (mm)				
Mean ± SD	19.4 ± 3.5	19.6 ± 3.5	−0.3 (−0.8 to 0.3)	0.38
(Min–max)	(13–30)	(11–31)		
Total stent length (mm)				
Mean ± SD	71.3 ± 32.1	73.2 ± 32.1	−1.9 (−7.2 to 3.4)	0.48
(Min–max)	(18–209)	(12–253)		
IIB/IIIA inhibitors (%)	32.6 (72/221)	32.4 (125/386)	0.2% (−7.5% to 7.9%)	1.00
Lipid-lowering agent (%)	88.2 (195/221)	90.7 (350/386)	−2.4% (−7.6% to 2.7%)	0.33
Beta-blockers (%)	82.4 (182/221)	74.9 (289/386)	7.5% (0.9% to 14.1%)	0.034
Angiotensin-converting enzyme inhibitors (%)	57.9 (128/221)	45.6 (176/386)	12.3% (4.1% to 20.5%)	0.004
Per lesion analysis (%)				
Ostial lesions	4.7	4.1	0.7% (−1.2% to 2.5%)	0.50
Moderate-to-heavy calcification	27.4	33.4	−6.0% (−10.1% to −1.9%)	0.005
Thrombus present	1.2	0.2	1.0% (0.2% to 1.8%)	0.003
Occlusion <3 months	0.3	0.1	0.2% (−0.2% to 0.6%)	0.56
Occlusion >3 months	2.3	2.4	−0.1% (−1.4% to 1.2%)	1.00
Lesion classification				
Type A/B1	33.0	28.6	4.5% (0.4% to 8.6%)	0.032
Type B2/C	67.0	71.4	−4.5% (−8.6% to −0.4%)	0.032

Numbers are % (counts/available field sample size) or mean ± 1 standard deviation. *In ARTS II, in total 6 patients have been enrolled after the procedure.
CI = confidence interval (Diff±1.96·SE); Difference = unstable angina − stable angina; DS = diameter stenosis; Les = lesion; Pts = patients; SD = standard deviation; SE = sqrt(p1·q1/n1 + p2·q2/n2).

separately analyzed (Table 4). Up to discharge, 3 angiographically confirmed thrombotic occlusions occurred in the stable angina group (3 of 386, 0.8%) versus none in unstable angina patients (p = 0.56). From discharge to 30 days, one additional thrombotic occlusion in each group was observed, resulting in a cumulative rate of 1% in the stable angina versus 0.5% in unstable angina group (relative risk [RR] 0.44; 95% confidence interval [CI] 0.05 to 3.88; p = 0.66).

ARTS II 365-day outcomes. At 1 year, the cumulative incidence of MACCE was identical in the 2 groups (10.4%, RR 1.00; 95% CI 0.62 to 1.63; p = 1.00), reflecting a similar rate death (0.9% vs. 1.0%), cerebrovascular accident (CVA) (0.5% vs. 1.0%), MI (0.9% vs. 1.3%), and repeat revascularization (8.1% vs. 7.0%) in unstable and stable angina groups, respectively. Unadjusted Kaplan-Meier estimates of MACCE, death, MI/

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Table 3 Characteristics: Stable Versus Unstable Angina Group

	Unstable Angina Group				Stable Angina Group			
	ARTS II-SES (n = 221 Pts, n = 794 Les)	ARTS I-BMS (n = 226 Pts, n = 628 Les)	ARTS I-CABG (n = 224 Pts, n = 622 Les)	p Value	ARTS II-SES (n = 386 Pts, n = 1,366 Les)	ARTS I-BMS (n = 374 Pts, n = 978 Les)	ARTS I-CABG (n = 381)	p Value
Male gender (%)	74.2	80.1	75.1	0.27	78	75.1	76.6	0.65
Age, yrs (mean ± SD)	62.6 ± 10.5	61 ± 9.6	60.9 ± 9.5	0.12	62.9 ± 9.1	60.5 ± 9.7	61.4 ± 9.2	0.001
BMI, kg/m^2 (mean ± SD)	27.1 ± 4.2	26.7 ± 3.4	27.1 ± 3.8	0.50	27.8 ± 4	27.5 ± 3.8	27.5 ± 3.6	0.49
Diabetes (%)	23.1	18.6	14.2	0.055	28	18.7	16.8	<0.001
Hypertension (%)	62	49.1	43.1	<0.001	70.2	42	46.1	<0.001
Hypercholesterolemia (%)	65.2	51.3	54	0.007	78.9	61.9	59.7	<0.001
Family history (%)	35.5	35.3	42	0.26	36.2	41.5	42	0.20
Current smoking (%)	24.4	32	47.6	0.10	16.3	25.5	21.6	0.008
Previous MI (%)	48	45.1	47.6	0.81	26.7	43.9	38.7	<0.001
Stable angina (%)	—	—	—	—	—	—	—	—
CCS 1	—	—	—	—	11.1	7.8	7.6	0.16
CCS 2	—	—	—	—	42.2	41.7	41.8	0.99
CCS 3	—	—	—	—	27.7	35	37.4	0.01
CCS 4	—	—	—	—	2.6	5.9	5.5	0.05
Silent ischemia (%)	—	—	—	—	16.3	9.6	7.6	<0.001
Unstable angina (%)	—	—	—	—	—	—	—	—
Braunwald I	23.1	22.6	19.1	0.54	—	—	—	—
Braunwald Ib	19.9	15.9	16.0	0.47	—	—	—	—
Braunwald Ic	3.2	6.6	3.1	0.14	—	—	—	—
Braunwald II	49.3	50.4	49.8	0.97	—	—	—	—
Braunwald IIb	38	34.1	36.9	0.68	—	—	—	—
Braunwald IIc	11.3	16.4	12.9	0.29	—	—	—	—
Braunwald III	27.6	27	31.1	0.58	—	—	—	—
Braunwald IIIb	20.8	22.6	26.2	0.39	—	—	—	—
Braunwald IIIc	6.8	4.4	4.9	0.53	—	—	—	—
Ejection fraction (%)	60 ± 11.5	62 ± 13.1	58.7 ± 13.6	0.03	60.3 ± 11.6	60.3 ± 11.7	61.3 ± 2.9	0.44
No. of diseased vessels	2.5 ± 0.5	2.3 ± 0.5	2.3 ± 0.6	<0.001	2.5 ± 0.5	2.2 ± 0.5	2.3 ± 0.5	<0.001
2-vessel (%)	47.5	68.3	61.8	<0.001	45.3	68.7	68.8	<0.001
3-vessel (%)	52.5	28.9	33.2	<0.001	54.1	26.6	28.2	<0.001
Location of lesion (%)	—	—	—	—	—	—	—	—
RCA	31	30.4	28.9	0.70	28.0	31.6	29.8	0.16
LAD	41.1	41.2	41.2	0.99	41.8	38.2	41.0	0.20
CX	28	28.2	29.7	0.74	30.2	30.2	29.1	0.82
No. of lesions treated	3.2 ± 1.2	2.6 ± 1.0	2.9 ± 1.0	<0.001	3.2 ± 1.1	2.4 ± 0.9	2.8 ± 1	<0.001
Type A/B1 lesions	33	32.2	38.6	0.033	28.6	32.4	37.9	<0.001
Type B2/C lesions (%)	67	67.8	61.4	0.033	71.4	67.6	62.1	<0.001
No. of stents implanted	3.6 ± 1.5	2.8 ± 1.2	—	<0.001	3.7 ± 1.5	2.8 ± 1.3	—	<0.001
Total stent length (mm)	71.3 ± 32.1	47.5 ± 19.3	—	<0.001	73.2 ± 32.1	47.6 ± 23	—	<0.001
Lesion length <10 mm (%)	61.8	67.9	67	0.039	60.3	64.1	68.9	<0.001
Lesion length 10–20 mm (%)	26.4	24.4	27.2	0.52	27.7	29.3	24.1	0.029
Lesion length >20 mm (%)	11.7	7.7	5.8	<0.001	11.9	6.6	7.0	<0.001
Occlusion <3 months (%)	0.3	3.0	4.3	<0.001	0.1	3.2	3.9	<0.001
Occlusion >3 months (%)	2.3	0.2	1.8	<0.001	2.4	0.7	0.8	<0.001
Moderate-to-heavy calcification (%)	27.4	16.6	15.4	<0.001	33.4	18.1	14.4	<0.001
Thrombus present (%)	1.2	1.5	1.7	0.68	0.2	1	1.3	0.001
Maximal dilation pressure (atm)	16.4 ± 2.8	14.9 ± 2.7	—	<0.001	16.3 ± 2.9	14.5 ± 2.8	—	<0.001
Lipid-lowering agent (%)	88.2	33.0	28.5	<0.001	90.7	42.2	33.6	<0.001
Beta-blockers (%)	82.4	58.9	57.9	<0.001	74.9	60.5	53.0	<0.001
ACE inhibitors (%)	57.9	21.9	16.7	<0.001	45.6	28.1	14.6	<0.001

ACE = angiotensin-converting enzyme; ARTS = Arterial Revascularization Therapies Study; BMI = body mass index; BMS = bare-metal stent; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society classification; CX = left circumflex coronary artery; LAD = left anterior descending artery; Les = lesion; MI = myocardial infarction; Pts = patients; RCA = right coronary artery; SES = sirolimus-eluting stents.

Table 4 Clinical Outcome in ARTS II According to Clinical Presentation

	Unstable Angina (n = 221 Patients)	Stable Angina (n = 386 Patients)	Relative Risk (95% CI)	p Value
30-day outcome (%)				
Nonhierarchical complications				
MACCE*	2.7 (6/221)	3.4 (13/386)	0.81 (0.31–2.09)	0.81
MACCE†	5.4 (12/221)	5.2 (20/386)	1.05 (0.52–2.10)	1.00
MACCE‡	19.9 (44/221)	19.9 (71/386)	1.00 (0.72–1.39)	1.00
Death/CVA/MI*	0.9 (2/221)	1.0 (4/386)	0.87 (0.16–4.73)	1.00
Death/CVA/MI†	4.1 (9/221)	4.1 (16/386)	0.98 (0.44–2.19)	1.00
Death/CVA/MI‡	19 (42/221)	19.2 (74/386)	0.99 (0.71–1.39)	1.00
Death	0.0 (0/221)	0.0 (0/386)	—	—
CVA	0.0 (0/221)	0.3 (1/386)	—	1.00
Myocardial infarction†	4.1 (9/221)	3.9 (15/386)	1.05 (0.47–2.35)	1.00
Q-wave MI	0.9 (2/221)	0.8 (3/386)	1.16 (0.20–6.92)	1.00
Non–Q-wave MI*	0.0 (0/221)	0.0 (0/386)	—	—
Non–Q-wave MI†	3.6 (8/221)	3.1 (12/386)	1.16 (0.48–2.8)	0.81
Non–Q-wave MI‡	18.6 (41/221)	18.1 (70/386)	1.05 (0.72–1.45)	0.91
Revascularization	2.3 (5/221)	2.6 (10/386)	0.87 (0.3–2.52)	1.00
CABG	1.4 (3/221)	1.3 (5/386)	1.05 (0.25–4.34)	1.00
RPTCA	0.9 (2/221)	1.3 (4/386)	0.87 (0.16–4.73)	1.00
Subacute occlusion	0.5 (1/221)	1 (4/386)	0.70 (0.14–3.57)	1.00
Stent thrombosis	0.9 (2/221)	1.5 (6/386)	0.58 (0.12–2.90)	0.77
365-day outcome				
Hierarchical complications				
MACCE*	10.4 (23/221)	10.4 (40/386)	1.00 (0.62–1.63)	1.00
MACCE†	12.7 (28/221)	11.9 (46/386)	0.80 (0.40–1.60)	0.59
MACCE‡	27.1 (60/221)	24.9 (96/386)	1.09 (0.83–1.44)	0.56
Death	0.9 (2/221)	1.0 (4/386)	0.87 (0.16–4.73)	1.00
CVA without death	0.5 (1/221)	1.0 (4/386)	0.44 (0.05–3.88)	0.66
MI without death or CVA‡	19 (42/221)	18.9 (73/386)	1.00 (0.72–1.29)	1.00
Q-wave MI	0.9 (2/221)	0.8 (3/386)	1.16 (0.20–6.92)	1.00
Non–Q-wave MI*	0.0 (0/221)	0.5 (2/386)	—	0.54
Non–Q-wave MI†	2.7 (6/221)	3.4 (13/386)	0.82 (0.16–4.73)	0.72
Non–Q-wave MI‡	19 (42/221)	18.7 (72/386)	1.02 (0.72–1.44)	0.91
Revascularization without death or CVA or MI	8.1 (18/221)	7.0 (27/386)	1.16 (0.66–2.07)	0.63
CABG without death or CVA or MI	2.3 (5/221)	1.8 (7/386)	1.25 (0.40–3.88)	0.77
RPTCA without death or CVA or MI	5.9 (13/221)	5.2 (20/386)	1.14 (0.58–2.24)	0.71
Nonhierarchical complications				
Death/CVA/MI*	2.3 (5/221)	3.4 (13/386)	0.67 (0.24–1.86)	0.62
Death/CVA/MI†	5.0 (11/221)	6.2 (24/386)	0.80 (0.40–1.60)	0.59
Death/CVA/MI‡	20.4 (45/221)	20.7 (80/386)	0.98 (0.71–1.36)	1.00
CVA	0.5 (1/221)	1 (4/386)	0.44 (0.05–3.88)	0.66
Myocardial infarction*	0.9% (2/221)	1.6% (6/386)	0.58 (0.12–2.86)	0.72
Myocardial infarction†	4.1 (9/221)	4.7 (18/386)	0.87 (0.40–1.91)	0.84
Myocardial infarction‡	19.5 (43/221)	19.4 (75/386)	1.00 (0.72–1.40)	1.00
Revascularization	9.0% (20/221)	8.0% (31/386)	1.13 (0.66–1.93)	0.65
CABG	2.7 (6/221)	1.8 (7/386)	1.5 (0.51–4.40)	0.56
RPTCA	6.3 (14/221)	6.5 (25/386)	0.98 (0.52–1.84)	1.00
Late occlusion	0% (0/221)	0.5% (2/386)	0.44 (0.05–3.88)	0.54
Stent thrombosis	0.9% (2/221)	1.8% (7/386)	0.50 (0.10–2.38)	0.59

*Based on protocol-mandated MI definition. †Based on MI definition of CK/CK-MB 3 times the upper limit of normal in one or more sample(s). ‡Based on MI definition of any CK/CK-MB above upper limit of normal in one or more sample(s).

ARTS = Arterial Revascularization Therapies Study; CABG = coronary artery bypass grafting; CK = creatine kinase; CK-MB = creatinine kinase-myocardial band; CVA = cerebrovascular accident; MACCE = major adverse cardiac and cerebrovascular event; MI = myocardial infarction; RPTCA = re-percutaneous transluminal coronary angioplasty.

CVA, and target vessel revascularization (TVR) are shown in Figures 1A to 1C, respectively. After reclassifying periprocedural non–Q-wave MI according to current recommendations (15,16), the overall rate of MI at 1 year remained similar in patients with stable angina (4.7%) as compared with the group of patients with unstable angina (4.1%; p = 0.84), as was the case for the cumulative incidence of MACCE based on the revised

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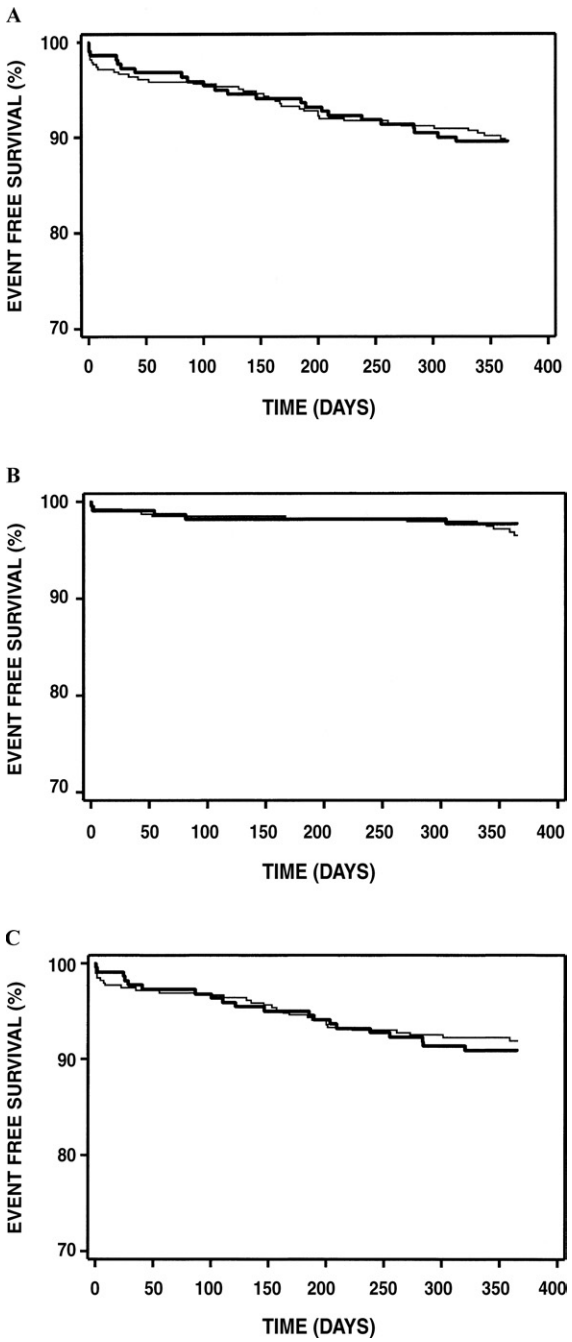

Figure 1 Kaplan-Meier Curves

(A) Major adverse cardiac and cerebrovascular event-free survival; **(B)** death/cerebrovascular accident/myocardial infarction-free survival; and **(C)** freedom from repeat revascularization in the ARTS II study stratified into unstable **(bold lines)** and stable angina **(thin lines)**.

MI definition (11.9% in stable angina vs. 12.7% in unstable angina group, p = 0.80). Defining non–Q-wave MI as any CK/CK-MB elevation beyond the upper limit of normal resulted again in a remarkably similar, although unadjusted, outcome in stable as compared with unstable patients in terms of cumulative MI (19.4% vs. 19.5%, p = 1.00) or MACCE (24.9% vs. 27.1%; p = 0.56), respectively.

Subgroup and multivariable analysis. Focusing on higher risk patients presenting with Braunwald class II or III (n = 170), their outcome in terms of MACCE at 30 days (2.4% vs. 3.4%; p = 0.72) or 1 year (10% vs. 10.4%; p = 0.97) did not differ compared with the stable angina group. On the basis of CK/CK-MB elevation equal to or more than 3 times the upper limit of normal as a definition of non–Q-wave MI, the MACCE rate was 4.7% and 12.4% in patients with Braunwald class II or III as compared with 5.2% (p = 0.99) and 11.9% (p = 0.99) in patients with stable angina at 30 and 365 days, respectively. Finally, considering any CK/CK-MB elevation, the MACCE rate was 17.1% vs. 19.9% (p = 0.84) at 30 days and 24.7% vs. 24.9% (p = 0.94) at 1 year in patients with class II or III unstable angina compared with patients with stable angina.

Using the Weibull modeling and after adjusting for covariates as reported in Tables 1 and 2, the clinical status failed to become an independent predictor of MACCE (hazard ratio [HR] 0.94, 95% CI 0.41 to 2.12, p = 0.88; HR 0.87, 95% CI 0.52 to 1.48, p = 0.61; and HR 0.88, 95% CI 0.62 to 1.25; p = 0.88 based on periprocedural non–Q-wave MI definition of CK/CK-MB elevation ≥5, ≥3, or ≥1 times the upper limit of normal, respectively). Similarly, no statistical interaction was noted between clinical status and the tested covariates in the model, irrespective of the applied periprocedural MI definition (Fig. 2).

ARTS II versus ARTS I. The cumulative incidence of MACCE, death/MI/CVA, and revascularization at 1 year stratified according to clinical presentation in the SES group as compared with the BMS or CABG groups is shown in Figure 3. After adjustment for all confounders among those reported in Table 3, the MACCE rate observed in the ARTS II study remained consistently lower than that observed in the BMS group in stable (HR 0.45, 95% CI 0.16 to 0.58, p = 0.0004) or unstable patients (HR 0.43, 95% CI 0.18 to 0.99, p = 0.034), whereas it did not differ compared to the CABG group in stable (HR 2.38, 95% CI 0.33 to 16.7, p = 0.39) or unstable group (HR 0.33, 95% CI 0.03 to 3.22, p = 0.34) analyzed separately.

Discussion

Despite the growing body of evidence supporting the benefit of DES in different patients/lesion subsets, information regarding their differential safety/efficacy profile in patients with stable versus unstable angina is scanty and in part contradictory. Patients undergoing coronary intervention for unstable atherosclerotic coronary lesions are known to present with a smaller atherosclerotic (18) but larger thrombotic burden as compared with patients who have stable angina. This justifies the need to evaluate whether these devices may perform differently in these 2 patient subsets. In the RESEARCH (Randomized Evaluation of Salvage Angioplasty with Combined Utilization of End points) registry, where 52% of the population presented

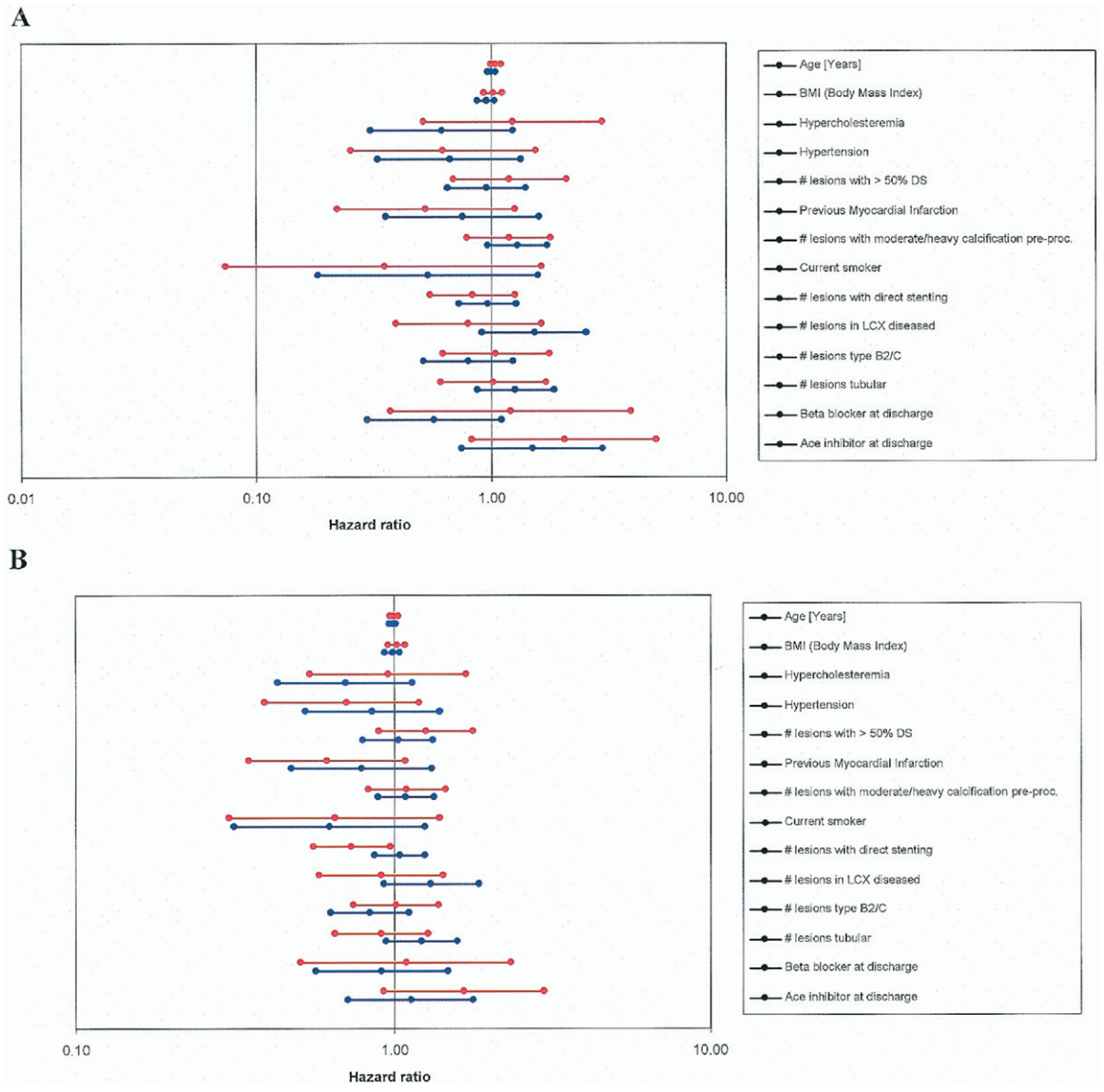

Figure 2 **HRs and 95% CIs of Factors in the Multivariable Model by Anginal Status**

There was no observed interaction between the identified outcome predictors in the model and anginal status at presentation, irrespective of the periprocedural applied definition of myocardial infarction (MI). **(A)** Results based on non–Q-wave MI defined as any creatine kinase (CK) or CK-myocardial band elevation ≥3 times the upper limit of normal are shown, with an overall p value of 0.66 for testing interaction. **(B)** Results based on non–Q-wave MI defined as any CK or CK-myocardial band elevation beyond the upper limit of normal are shown, with an overall p value of 0.58 for testing interaction. **Blue** = stable angina; **red** = unstable angina. ACE = angiotensin-converting enzyme; CI = confidence interval; DS = diameter stenosis; HR = hazard ratio; LCX = left circumflex artery.

with ACS, patients with and without ACS benefited equally from SES implantation, with a relative risk reduction in the need for target vessel revascularization at 1 year in both groups when compared with BMS of 70% and 61%, respectively (6).

Similar information has been provided by the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent vs. Abciximab and Bare-Metal Stent in Myocardial Infarction) trial, in which patients undergoing primary intervention for acute myocardial infarction allocated to receive SES had a 70% relative reduction of TVR as compared with the BMS group (5). In both studies, the rate of thrombotic occlusion was low and not different in the SES with respect to control groups, suggesting that the safety profile of SES is maintained in patients with ACS.

In a subanalysis of the TAXUS IV trial, an even-lower restenosis rate was reported in patients with ACS as compared with stable patients receiving paclitaxel-eluting stents (PES) (7). However, patients with ACS treated with PES had a trend toward a higher rate of stent thrombosis at 30 days (0.8% vs. 0%, p = 0.06) and, of concern, cardiac death at 1 year also trended higher in patients with ACS receiving PES (2.5% vs. 0.7%; p = 0.051) (7). Thus, whether there is a specific risk in

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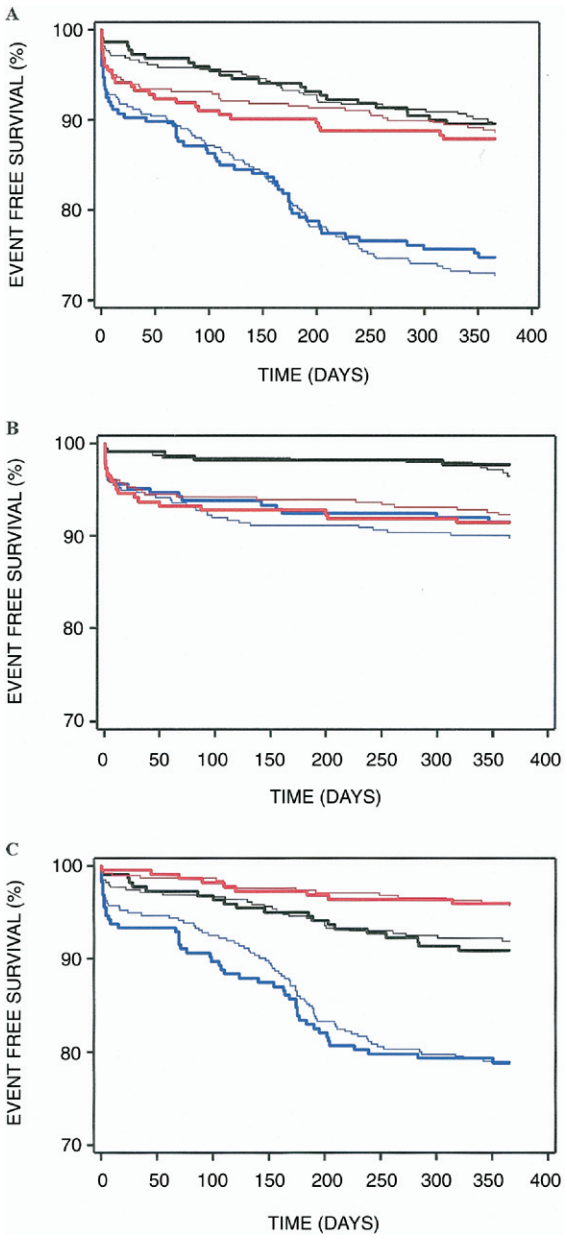

Figure 3 **Kaplan-Meier Curves Out to 1 Year in Both Study Arms**

(A) Major adverse cardiac and cerebrovascular event-free survival; **(B)** death/cerebrovascular accident/myocardial infarction-free survival; and **(C)** freedom from repeat revascularization. **Black** = sirolimus-eluting stent in the ARTS II study; **red** = coronary artery bypass grafting in the ARTS I study; **blue** = bare-metal stent in the ARTS I study. **Bold lines** = unstable angina; **thin lines** = stable angina.

patients with ACS undergoing DES implantation remains largely debatable based on the available data.

In this subanalysis of the ARTS II study, the hypothesis that SES may perform differently according to clinical presentation (i.e., stable vs. unstable), which in itself reflects a difference in biology and coronary plaque composition, has been formally tested.

The main conclusion of this analysis is that elective multivessel patients with unstable angina who are undergoing SES-supported coronary revascularization show a similar short- and medium-term outcome with respect to those treated for stable ischemic syndromes. This conclusion is based mainly on the similar incidence of major adverse events in these 2 groups of patients. It is further reinforced by the observation that each individual component of MACCE (i.e., death, reinfarction, CVA, and repeat revascularization) was very similar at 30 days as well as at 1 year in these 2 groups of patients. The rate of MI and the cumulative rate of MACCE remained remarkably similar at both univariate and multivariable-adjusted analysis between patients with stable and unstable angina after reclassification of MI based on the elevation of CK/CK-MB at 3 or even 1 times the upper limit of normal. Focusing on higher-risk patients, identified according to class II or III of Braunwald classification, their short- and long-term outcome was consistently similar compared with the stable angina group.

Finally, the rate of thrombotic occlusion, although not statistically different between the 2 groups of patients, actually was numerically lower in unstable angina patients, confirming previous findings (5,6).

These results, based on a contemporary cohort of patients, were supported by the comparison of outcomes in ARTS II versus ARTS I, stratified according to clinical presentation. When adjusted for the baseline and procedural imbalance, the MACCE rate was significantly lower in both stable and unstable patients in the ARTS II with respect to those treated with BMS in ARTS I, whereas no difference was noted with respect to patients allocated to CABG, irrespective of stable or unstable presentation. The main analysis of ARTS II versus ARTS I based on a Bayesian statistical approach was reported recently (12). The results suggested that the use of SES in patients undergoing multivessel intervention is equivalent to the rate of major adverse events as compared with CABG treatment. In the present subanalysis, a conventional statistical approach was used to separately compare the 2 contemporary patient cohorts (i.e., unstable angina and stable angina) with the same historical cohorts of ARTS I. Our current findings suggest the efficacy and safety of SES implantation irrespective of stable versus unstable presentation in the context of elective multivessel disease patients undergoing percutaneous intervention.

Study limitations. Against the consistent background of favorable results when the treatment with SES is compared with BMS implantation in randomized trials so far conducted, the ARTS II study should be regarded as an intermediate step before the fulfillment of the next era of randomized trials of DES-supported percutaneous revascularization versus surgery, such as CARDIA (Coronary Artery Risk Development in Young Adults), FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) and SYNTAX (SYNergy Between PCI With TAXUS and Cardiac Surgery), and COMBAT (Comparison of

Bypass Surgery and Angioplasty Using Sirolimus-Eluting Stents in Patients With Unprotected Left Main Coronary Artery Disease). When ARTS II was designed, the decision was taken to use a historical control (ARTS I) to assess the improvement in clinical outcome when SES are implanted. This decision precluded the possibility of adjusting for unmeasured confounders between the 2 groups of individuals and necessitates the use of the previous definitions of primary end point and patient classification, such as death (cardiac and noncardiac), cerebrovascular accident (e.g., transient ischemic attack, reversible ischemic neurologic deficit, stroke), MI (Q wave and CK ≥5 times the upper limit of normal), all revascularization (without target lesion revascularization, TVR assessment), ACS (use of original Braunwald classification without systematic troponin triage), or thrombotic stent occlusion (angiographic definition). In this study, the antiplatelet regimen was different from ARTS I as a result of the mandatory loading dose with thienopyridines administered 24 h before the intervention. This may have contributed in part to the more favorable outcome of ARTS II in comparison with ARTS I-BMS. Moreover, whether the neutral impact of clinical instability on outcome observed here is reproducible in the context of nonsystematic thienopyridines pretreatment remains to be tested. Similarly, our results reasonably apply to medium- to low-risk ACS patients and cannot be extrapolated to patients with ongoing or recent myocardial necrosis, haemodynamic instability, or refractory ischemia because they were excluded from the study. Finally, despite the rate of confirmed or possible stent thrombosis was numerically even lower in the unstable angina group both at 30 days and 1 year compared with the stable angina group, we cannot rule out the possibility that a type II error may have confounded our findings.

Conclusions. In elective patients with multivessel disease who underwent SES-supported coronary revascularization after adequate pretreatment with thienopyridines, the rate of short- and medium-term major adverse events was not affected by acuity of clinical presentation, irrespective of the applied definition of periprocedural myocardial infarction. The performance of SES in patients with multivessel disease presenting with both stable and unstable coronary syndromes appears a promising alternative to conventional surgical revascularization. This hypothesis, however, remains to be formally tested in the setting of a prospective randomized controlled trial.

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