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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

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Objectives The purpose of this study was to assess the 3-year outcome of coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) using sirolimus-eluting stents (SES) in patients who had multivessel coronary artery disease with and without diabetes mellitus.

Background The optimal method of revascularization in diabetic patients remains in dispute.

Methods The ARTS-II (Arterial Revascularization Therapies Study–Part II) trial is a single-arm study (n = 607) that included 159 diabetic patients treated with SES whose 3-year clinical outcome was compared with that of the historical diabetic and nondiabetic arms of the randomized ARTS-I trial (n = 1,205, including 96 diabetic patients in the CABG arm and 112 in the PCI arm).

Results At 3 years, among nondiabetic patients, the incidence of the primary composite of death, CVA, myocardial infarction (MI), and repeat revascularization (major adverse cardiac and cerebrovascular events [MACCE]), was significantly lower in ARTS-II than in ARTS-I PCI (adjusted odds ratio [OR]: 0.41; 95% confidence interval [CI]: 0.26 to 0.64) and similar to ARTS-I CABG. The ARTS-II patients were at significantly lower risk for death, CVA, and MI as compared with both the ARTS-I PCI (adjusted OR: 0.55; 95% CI: 0.34 to 0.91) and ARTS-I CABG patients (adjusted OR: 0.56; 95% CI: 0.35 to 0.92). Among diabetic patients, the incidence of MACCE in ARTS-II was similar to that of both PCI and CABG in ARTS-I. Conversely, the incidence of death, CVA, and MI was significantly lower in ARTS-II than in ARTS-I PCI (adjusted OR: 0.67; 95% CI: 0.27 to 1.65) and was similar to that of ARTS-I CABG.

Conclusions At 3 years, PCI using SES for patients with multivessel coronary artery disease seems to be safer and more efficacious than PCI using bare-metal stents, irrespective of the diabetic status of the patient. Hence, PCI using SES appears to be a valuable alternative to CABG for both diabetic and nondiabetic patients. (J Am Coll Cardiol 2008;52:1957–67) © 2008 by the American College of Cardiology Foundation

The optimal method of revascularization for diabetic patients with concomitant multivessel coronary artery disease remains in dispute. Although several randomized controlled trials have demonstrated a similar safety profile for percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG) up to 5 years, CABG was associated with a significantly lower risk for repeat revascularizations as compared with PCI using bare-metal stents

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Abbreviations and Acronyms

BMS = bare-metal stent(s)
CABG = coronary artery bypass graft surgery
CI = confidence interval
CK-MB = creatine kinase-myocardial band
CVA = cerebrovascular accident
DES = drug-eluting stent(s)
MACCE = major adverse cardiac and cerebrovascular event(s)
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
SES = sirolimus-eluting stent(s)

(BMS), a benefit that proved to be most apparent among diabetic patients (1–6).

However, when drug-eluting stents (DES) were shown to significantly reduce the need for repeat revascularizations, interventionalists quickly added DES treatment arms to the pivotal randomized PCI versus CABG trials (7,8). As a result, the 1-year results of the ARTS-II (Arterial Revascularization Therapies Study–Part II) trial and the ERACI-III (Argentine Randomized Trial of Coronary Angioplasty With Stenting Versus Coronary Artery Bypass Surgery in Patients With Multivessel Disease) study suggested that PCI using sirolimus-eluting stents (SES) was safe and effective and could be a viable alternative for the treatment of multivessel coronary artery disease (7,8). Nevertheless, the higher susceptibility to repeat adverse cardiac events among diabetic patients makes extrapolation of these findings to this high-risk patient population uncertain. Diabetic patients are known to have an accelerated and more aggressive form of atherosclerosis with higher restenosis rates and less favorable long-term survival than nondiabetic patients (9–12). Furthermore, diabetes mellitus has been a strong and consistent predictor of late stent thrombosis in patients treated with DES. This observation has raised some concerns about potential erosion of the initial treatment benefit due to the occurrence of stent thrombosis, a finding that only became apparent after multiple years of follow-up (13–15).

The present study reports on the 3-year safety and effectiveness of SES for diabetic patients with multivessel disease in the ARTS-II trial compared with the historical outcomes of the surgical and percutaneous arms of the ARTS-I study.

Methods

ARTS-II study design. The ARTS-II study is a multicenter, nonrandomized, open label trial designed to assess the safety and efficacy of SES for patients with de novo multivessel coronary artery disease and compare them with the surgical group of the ARTS-I trial as a historical control (16). To obtain a population comparable to that of the ARTS-I trial, patients were stratified by clinical site to ensure the inclusion of at least one-third of patients with 3-vessel disease.

Patients were eligible for coronary revascularization if they had either stable angina (Canadian Cardiovascular Society functional class I to IV), unstable angina (Braunwald class I to IIIB or C), or silent ischemia, and at least 2 lesions located in different major epicardial vessels, including their side branches (except for the left main coronary artery), that were potentially amenable to stent implantation (17,18). Patients were required to have multivessel disease that included treatment of the left anterior descending artery and at least 1 other significant lesion (>50% diameter stenosis) in another major epicardial coronary artery. The goal was to achieve complete anatomic revascularization (19). One totally occluded major epicardial vessel or side branch could be included. The stenosis had to be amenable to stenting using an SES with a diameter of 2.5 to 3.5 mm and a length of 13 to 33 mm, without restriction on the total implanted stent length. Decisions to place stents in lesions with bifurcations, fresh thrombus, calcification, diffuse disease, complex anatomy, or stenting of side branches were left to the discretion of the operators.

Patients with previous coronary intervention, left main coronary artery disease, overt congestive heart failure, or a left ventricular ejection fraction of <30% were excluded. Additional exclusion criteria were as follows: history of cerebrovascular accident (CVA), transmural myocardial infarction (MI) in the preceding week, severe hepatic or renal disease, neutropenia or thrombocytopenia, intolerance of or contraindication to acetylsalicylic acid or thienopyridines, need for concomitant major surgery, and life-limiting major concomitant noncardiac diseases. Written informed consent was obtained from each patient before enrollment. The study was approved by the ethics committee of each participating site.

Study population. Between April 1997 and June 1998, a total of 1,205 patients was randomly assigned to PCI with BMS (n = 600) or CABG (n = 605) at 67 participating centers in the ARTS-I trial. Diabetes mellitus was present in 112 patients in the ARTS-I BMS arm and in 96 patients in the ARTS-I CABG arm. Between February 2003 and November 2003, 607 patients, of whom 159 were diabetic, were treated with SES at 45 participating centers in the ARTS-II trial.

Study objectives. The primary objective of this study was to assess the safety and efficacy of SES in the ARTS-II study as compared with both the stent and the surgical arms of the ARTS-I trial among patients with or without diabetes. The primary safety end point was the composite end point of death, MI, and CVA. The primary efficacy end point was major adverse cardiac and cerebrovascular events (MACCE), defined as the occurrence of major adverse cardiac and cerebrovascular accidents, death, stroke, MI, and ischemia-driven repeat revascularization. Secondary end points were the itemized outcome parameters of death, CVA, MI, repeat revascularization, and stent thrombosis in the ARTS-II population.

Baseline and end point definitions. Hypertension was defined as blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic or was based on current antihypertensive treatment. Dyslipidemia was classified as total serum cho-

lesterol level ≥6.2 mmol/l or the use of lipid-lowering drugs. Death was categorized as cardiac or noncardiac. Cerebrovascular events were divided into 3 main categories: stroke, transient ischemic attacks, and reversible ischemic neurologic deficits. All repeat revascularization procedures were recorded. In the first 7 days after the intervention, a definite diagnosis of MI was made if there was documentation of new abnormal Q waves and either a ratio of serum creatine kinase-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 (20). Serum creatine kinase 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, as described in the previous text, were sufficient for a diagnosis of MI. An MI was confirmed only after the relevant electrocardiograms had been analyzed by the core laboratory and

Table 1 Baseline Patient Demographics and Clinical Characteristics in Nondiabetic Patients

Nondiabetic Patients	ARTS-II (n = 448)	ARTS-I–CABG (n = 488)	ARTS-I–PCI (n = 509)	ARTS-II:I–CABG p Value	ARTS-II:I–PCI p Value
Baseline characteristics					
Male, %	80.1	77.4	77.9	0.34	0.42
Age, yrs ± SD	62.1 ± 9.9	61.0 ± 9.4	60.2 ± 9.7	0.07	0.004
Body mass index, kg/m^2 ± SD	27.1 ± 3.8	27.2 ± 3.6	26.9 ± 3.6	0.54	0.38
Risk factors, %					
Hypertension	62.7	42.8	40.2	<0.001	<0.001
Hypercholesterolemia	74.0	59.3	58.6	<0.001	<0.001
Family history of MI or sudden death age <55 yrs	36.7	43.7	38.6	0.029	0.54
Current smoker	21.9	27.5	29.6	0.051	0.007
Peripheral vascular disease	6.5	4.7	5.5	0.26	0.58
Previous MI	36.2	40.7	41.1	0.16	0.006
Indication for treatment, %					
Stable angina	53.1	57.2	55.7	0.22	0.43
Unstable angina	37.9	37.9	37.7	1.00	0.95
Silent ischemia	8.9	4.9	6.6	0.015	0.18
Angiographic characteristics					
Ejection fraction, %	60 ± 12	60 ± 13	61 ± 12	0.94	0.45
No. of lesions with stenosis >50%, n ± SD	3.6 ± 1.3	2.7 ± 1.0	2.8 ± 0.9	<0.001	<0.001
No. of diseased vessels, %					
1	0.2	4.2	4.0	<0.001	<0.001
2	45.1	66.7	69.3	<0.001	<0.001
3	54.7	29.0	26.7	<0.001	<0.001
Vessel territory with stenosis, % of lesions					
Right coronary artery	29.3	29.6	31.3	0.87	0.24
Left main coronary artery	0.0	0.1	0.1	0.46	0.45
Left anterior descending artery	41.8	41.2	40.1	0.74	0.36
Left circumflex artery	28.9	29.2	28.5	0.90	0.84
Lesion length, visual (mm), % of lesions					
Discrete, <10	63.2	67.4	67.0	0.023	0.041
Tubular, 10–20	26.0	26.0	25.8	0.97	0.97
Diffuse, >20	10.8	6.6	7.2	<0.001	0.001
Lesion classification, % of lesions					
Type A	6.9	6.8	6.5	0.88	0.65
Type B1	24.4	31.8	26.4	<0.001	0.23
Type B2	55.7	53.5	58.9	0.23	0.10
Type C	12.9	7.9	8.2	<0.001	<0.001
Procedural characteristics					
Bifurcation requiring double wiring, %	34.7	30.8	35.0	0.029	0.90
Number of stents implanted ± SD	3.7 ± 1.5	—	2.7 ± 1.2	—	<0.001
Total stent length, mm ± SD	72.0 ± 32.1	—	46.4 ± 20.6	—	<0.001
Maximum dilatation pressure, atm ± SD	16.4 ± 2.9	—	14.6 ± 2.8	—	<0.001
Direct stenting, % of lesions	36.0	—	3.4	—	<0.001
GP IIb/IIIa inhibitors during procedure, %	31.9	—	0.0	—	—
Duration of procedure, min ± SD	86 ± 44	191 ± 67	98 ± 50	<0.001	<0.001
Post-procedural hospital stay, days ± SD	3.3 ± 2.6	9.4 ± 4.3	3.8 ± 3.7	<0.001	0.031

ARTS = Arterial Revascularization Therapies Study; CABG = coronary artery bypass graft surgery; GP = glycoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention.

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adjudicated by the clinical events committee. This 2-part method of defining MI was developed for the ARTS-I study to address the difficulty of diagnosing MI after surgery (16). These definitions have been adopted by the Academic Research Consortium (ARC) and are applied whenever a comparison is made between DES and surgery (21).

3-year clinical follow-up. The study protocol required all patients to have clinical follow-up including registration of an electrocardiogram at 1 month, 6 months, 1 year, and 3 years. At each visit, physical examination, anginal status, and use of medications were assessed. Additional information was obtained by telephone interview or from the referring physician when needed. An independent committee adjudicated clinical events and electrocardiograms. Quality of life was assessed (by the European Quality of Life Index and 36-Item Short-Form Health Survey) at 1 month, 6 months, 1 year, and 3 years. Finally, complete 3-year follow-up was available for 99% of the patients in all treatment arms.

End point measurement. In the ARTS-II study, the procedure was performed within 48 h after inclusion. In the ARTS-I trial, patients were randomly allocated to treatment after informed consent had been obtained and then entered on a waiting list. Three deaths occurred in the ARTS-I CABG arm while these patients were still on the waiting list for surgery. To compensate for the temporal difference since allocation between groups, events for the present report were counted from time of procedure for all 3 arms and not from time of allocation, as previously published (3,22,23).

In both the ARTS-I and -II studies, only data on subacute thrombotic occlusions (<30 days) were collected in the case record form. In ARTS-II, stent thrombosis was readjudicated according to the ARC definitions (21). In this process, all coronary angiograms in the ARTS-II study, both procedure related (n = 104) and nonprocedure-related (n = 165), were reviewed by an independent core laboratory and adjudicated by an independent critical events committee. Thus far, no attempt has been made to assess data on stent thrombosis in the ARTS-I study in a similar fashion.

Statistical analysis. Demographic and procedural characteristics of diabetic patients were compared between ARTS-II and -I (CABG and PCI). A similar comparison was performed for nondiabetic patients, and for diabetic patients versus nondiabetic patients in the ARTS-II trial. Continuous variables are expressed as mean ± SD. Binary variables are reported as percentages, and the difference between groups is presented with 95% confidence intervals (CIs). The 2-group *t* test for continuous variables and the Fisher exact test for categorical variables were used. Itemized MACCE rates at 3 years are presented as counts and percentages and were compared in terms of relative risks (ARTS-II vs. both ARTS-I arms) with 95% CI. Time-to-event variables are presented as Kaplan-Meier curves, and the overall incidence was tested using the log-rank test.

A separate multivariate regression analysis was performed to further study treatment effects, considering potential confounders listed in Table 1. Baseline and procedural characteristics listed in Table 1 were tested on a per-patient basis by univariate analysis to determine suitability for inclusion in the multivariate model. Finally, a logistic regression model was built using the statistically significant univariate predictors ($p < 0.1$). The Hosmer and Lemeshow test was used to assess the goodness of fit of the multivariable models.

Table 2 Clinical End Points at 3 Years in Nondiabetic Patients (Hierarchical and Nonhierarchical MACCE to 1,080 Days, per Patient) Counted Since Date of Procedure

Up to 1,080 Days	ARTS-II (n = 448)	ARTS-I–CABG (n = 506)	ARTS-I–PCI (n = 488)	ARTS-II:I–CABG RR (95% CI)	ARTS-II:I–PCI RR (95% CI)
MACCE*	16.3% (73)	15.8% (80)	30.9% (151)	1.03 (0.77–1.38)	0.53 (0.41–0.67)
Death/CVA/MI*	7.8% (35)	10.3% (52)	11.5% (56)	0.76 (0.50–1.14)	0.68 (0.46–1.02)
Death/MI*	6.0% (27)	8.5% (43)	9.0% (44)	0.71 (0.45–1.13)	0.67 (0.42–1.06)
Death	2.2% (10)	4.2% (21)	3.3% (16)	0.54 (0.26–1.13)	0.68 (0.31–1.48)
Cardiac death	1.1% (5)	2.4% (12)	1.8% (9)	0.47 (0.17–1.33)	0.61 (0.20–1.79)
Noncardiac death	1.1% (5)	1.8% (9)	1.4% (7)	0.63 (0.21–1.86)	0.78 (0.25–2.43)
CVA	2.5% (11)	2.6% (13)	2.9% (14)	0.96 (0.43–2.11)	0.86 (0.39–1.87)
Myocardial infarction	4.0% (18)	4.9% (25)	6.1% (30)	0.81 (0.45–1.47)	0.65 (0.37–1.16)
Q-wave	2.5% (11)	4.5% (23)	5.3% (26)	0.54 (0.27–1.10)	0.46 (0.23–0.92)
Non–Q-wave	1.8% (8)	0.4% (2)	1.0% (5)	4.52 (0.96–21.16)	1.74 (0.57–5.29)
Revascularization	11.8% (53)	6.3% (32)	23.6% (115)	1.87 (1.23–2.85)	0.50 (0.37–0.68)
CABG	1.8% (8)	1.0% (5)	8.2% (40)	1.81 (0.60–5.48)	0.22 (0.10–0.46)
CABG TL	0.4% (2)	0.8% (4)	6.1% (30)	0.56 (0.10–3.07)	0.07 (0.02–0.30)
CABG non-TL	1.3% (6)	0.2% (1)	2.0% (10)	6.78 (0.82–56.07)	0.65 (0.24–1.78)
RPTCA	10.3% (46)	5.9% (30)	17.8% (87)	1.73 (1.11–2.69)	0.58 (0.41–0.80)
RPTCA TL	5.8% (26)	3.8% (19)	13.1% (64)	1.55 (0.87–2.75)	0.44 (0.29–0.69)
RPTCA non-TL	5.8% (26)	2.4% (12)	6.4% (31)	2.45 (1.25–4.79)	0.91 (0.55–1.51)

Values are % (n) unless otherwise indicated. *Hierarchical. MACCE was defined as death, CVA, MI, target vessel CABG, and target vessel RPTCA; death, CVA, and MI are adjudicated by the independent clinical events committee.

CI = confidence interval; CVA = cerebrovascular accident; MACCE = major adverse cardiac and cerebrovascular events; RPTCA = repeat percutaneous transluminal coronary angioplasty; RR = relative risk; TL = target lesion; other abbreviations as in Table 1.

Results

Nondiabetic patients in the ARTS-I and -II trials. BASELINE CHARACTERISTICS. Baseline and procedural characteristics of the nondiabetic patients from ARTS-II and -I are depicted in Table 1. In brief, the ARTS-II patients had hypertension and hypercholesterolemia significantly more often than did both the ARTS-I CABG and PCI cohorts. Patients from the ARTS-II trial presented significantly more often with 3-vessel disease and type C lesions as compared with both ARTS-I PCI and CABG patients. Finally, as compared with ARTS-I PCI patients, ARTS-II patients received significantly more stents, which resulted in a significantly longer total stented length.

Clinical end points at 3 years are depicted in Table 2. In brief, the MACCE rate among the ARTS-II nondiabetic patients was significantly lower than that in the ARTS-I PCI arm and similar to that in the ARTS-I CABG arm (Fig. 1A). Adjustment for independent predictors of the combined end point of MACCE resulted in an odds ratio (OR) of 0.41 (95% CI: 0.26 to 0.64) for ARTS-II versus -I PCI and an OR of 0.83 (95% CI: 0.56 to 1.23) for ARTS-II versus -I CABG. There was a trend toward a lower incidence of the combined safety end point of death/CVA/MI among nondiabetic patients from the ARTS-II trial as compared with both arms of the ARTS-I trial; and it reached statistical significance after adjustment for independent predictors for ARTS-II versus -I CABG (OR: 0.56; 95% CI: 0.35 to 0.92) and for ARTS-II versus -I PCI (OR: 0.55; 95% CI: 0.34 to 0.91) (Fig. 1B). The need for repeat revascularizations remained significantly higher in ARTS-II than in ARTS-I CABG, but was significantly lower than in ARTS-I PCI. Adjustment for independent predictors of the combined end point of revascularization resulted in an OR of 1.36 (95% CI: 0.80 to 2.29) for ARTS-II versus -I CABG and an OR of 0.43 (95% CI: 0.27 to 0.69) for ARTS-II versus -I PCI.

Diabetic patients in the ARTS-I and -II trials. BASELINE CHARACTERISTICS. Baseline clinical and procedural characteristics of the diabetic patients are presented in Table 3. Similar to the nondiabetic population, the ARTS-II diabetic patients had a significantly higher rate of hypertension and hypercholesterolemia as compared with both the ARTS-I CABG and PCI cohorts. Patients from the ARTS-II trial presented significantly more often with 3-vessel disease and type C lesions compared with both the ARTS-I PCI and CABG patients. Finally, as compared with ARTS-I PCI, ARTS-II patients received significantly more stents, which resulted in a significantly longer total stented length.

The 3-year results of the ARTS-II diabetic patients, compared with both arms of the randomized ARTS-I trial, are depicted in Table 4. In brief, the MACCE rate in ARTS-II was significantly lower than that in the ARTS-I PCI arm and was similar to that in the ARTS-I CABG arm (Fig. 2A). Adjustment for independent predictors of MACCE resulted in an OR of 0.72 (95% CI: 0.37 to 1.37) for ARTS-II versus -I PCI and an OR of 1.08 (95% CI: 0.41 to 2.84) for ARTS-II versus -I CABG. The incidence of death/CVA/MI was significantly lower among the ARTS-II patients than among the ARTS-I PCI cohort, but was similar to that of the ARTS-I CABG arm (Fig. 2B). Adjustment for independent predictors of the combined end point of death/CVA/MI resulted in an OR of 0.67 (95% CI: 0.27 to 1.65) for ARTS-II versus -I PCI and an OR of 0.67 (95% CI: 0.29 to 1.57) for ARTS-II versus -I CABG.

As expected, the MACCE rate was higher among diabetic patients receiving insulin therapy than among patients not receiving insulin treatment (Fig. 3). The 23.6% difference in MACCE rates between the insulin-treated and noninsulin-treated diabetic patients in the CABG arm is worth noting. However, there were only 16 insulin-treated diabetic patients in the ARTS-II CABG arm, a number

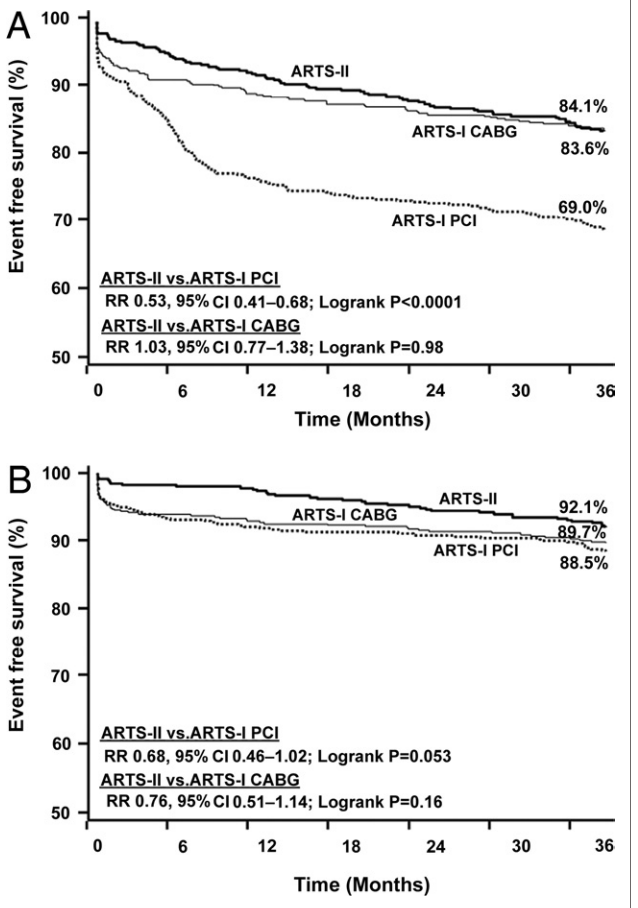

Figure 1 Kaplan-Meier Curve to 3 Years for ARTS-I and -II Nondiabetic Patients

(A) Freedom from major adverse cardiac and cerebrovascular events, the combined end point of all-cause death, cerebrovascular accident (CVA), myocardial infarction (MI), and repeat revascularization, and **(B)** death/CVA/MI. ARTS = Arterial Revascularization Therapies Study; CABG = coronary artery bypass graft surgery; CI = confidence interval; PCI = percutaneous coronary intervention; RR = relative risk.

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Table 3 Baseline Patient Demographics and Clinical Characteristics in Diabetic Patients

Diabetic Patients	ARTS-II (n = 159)	ARTS-I–CABG (n = 96)	ARTS-I–PCI (n = 112)	ARTS-II:I–CABG p Value	ARTS-II:I–PCI p Value
Baseline characteristics					
Male, %	66.7	68.8	73.2	0.78	0.29
Age, yrs ± SD	64.5 ± 8.7	62.6 ± 9.2	62.5 ± 9.1	0.09	0.08
Body mass index, kg/m^2 ± SD	28.9 ± 4.6	28.1 ± 3.8	28.7 ± 3.7	0.16	0.78
Risk factors, %					
Diabetes, insulin treated	17.6	16.7	20.5	1.0	0.64
Hypertension	79.9	56.3	64.3	<0.001	0.005
Hypercholesterolemia	74.1	49.0	55.4	<0.001	0.002
Family history of MI or sudden death age <55 yrs	33.8	32.6	41.4	0.89	0.20
Current smoker	11.9	16.7	20.5	0.35	0.06
Peripheral vascular disease	8.2	7.3	5.4	1.00	0.47
Previous MI	29.6	49.0	41.4	0.002	0.053
Indication for treatment, %					
Stable angina	53.5	62.5	58.9	0.19	0.39
Unstable angina	32.1	33.3	37.5	0.89	0.37
Silent ischemia	14.5	4.2	3.6	0.011	0.003
Angiographic characteristics					
Ejection fraction, %	60 ± 12	60 ± 14	61 ± 13	0.64	0.54
No. of lesions with stenosis >50%, n ± SD	3.6 ± 1.3	3.0 ± 1.1	2.9 ± 1.2	0.001	<0.001
No. of diseased vessels, %					
1	0.6	1.0	3.7	1.00	0.16
2	49.1	63.5	65.4	0.028	0.012
3	50.3	35.4	30.8	0.027	0.002
Vessel territory with stenosis, % of lesions					
Right coronary artery	28.5	29.0	30.4	0.94	0.59
Left main coronary artery	0.0	0.0	0.0	—	—
Left anterior descending artery	40.7	40.7	36.6	1.00	0.25
Left circumflex artery	30.8	30.3	33.0	0.94	0.54
Lesion length, visual, mm (% of lesions)					
Discrete, 10	54.4	71.9	59.9	<0.001	0.13
Tubular, 10–20	30.9	21.7	33.8	0.005	0.40
Diffuse, >20	14.7	6.4	6.4	<0.001	<0.001
Lesion classification, % of lesions					
Type A	6.6	7.2	3.6	0.77	0.06
Type B1	20.4	29.0	26.2	0.006	0.051
Type B2	56.4	56.2	62.8	1.00	0.07
Type C	16.7	7.6	7.4	<0.001	<0.001
Procedural characteristics					
Bifurcation requiring double wiring, %	31.9	36.3	32.6	0.21	0.88
Number of stents implanted ± SD	3.6 ± 1.5	—	3.0 ± 1.5	—	0.002
Total stent length, mm ± SD	73.9 ± 31.9	—	52.7 ± 25.6	—	<0.001
Maximum dilatation pressure, atm ± SD	16.2 ± 2.7	—	14.9 ± 2.9	—	<0.001
Direct stenting, % of lesions	30.6	—	2.6	—	<0.001
GP IIb/IIIa inhibitors during procedure, %	34.0	—	0.0	—	—
Duration of procedure, min ± SD	83 ± 40	201 ± 64	104 ± 51	<0.001	<0.001
Post-procedural hospital stay, days ± SD	3.6 ± 2.9	11.0 ± 7.3	4.6 ± 3.4	<0.001	0.012

Numbers are % (counts/available field sample size) or mean ± 1 SD.
Abbreviations as in Tables 1 and 2.

that precludes any definitive statement about a difference in the relative treatment effect among insulin-treated diabetic patients.

The impact of diabetes in the ARTS-II trial. After adjustment for independent predictors, diabetes proved to be the strongest pre-procedural predictor of MACCE in the ARTS-II trial (OR: 1.76; 95% CI: 1.13 to 2.74, p = 0.012) (24). The clinical end points of the ARTS-II diabetic patients versus nondiabetic patients are depicted in Table 5. In brief, the incidence of MACCE among diabetic patients was significantly higher than it was among nondiabetic patients. This difference was mainly driven by the signif-

Table 4 Clinical End Points at 3 Years in Diabetic Patients (Hierarchical and Nonhierarchical MACCE to 1,080 Days, per Patient) Counted Since Date of Procedure

Up to 1,080 Days	ARTS-II (n = 159)	ARTS-I–CABG (n = 96)	ARTS-I–PCI (n = 112)	ARTS-II:I–CABG RR (95% CI)	ARTS-II:I–PCI RR (95% CI)
MACCE*	27.7% (44)	17.7% (17)	47.3% (53)	1.56 (0.95–2.57)	0.58 (0.43–0.80)
Death/CVA/MI*	9.4% (15)	13.5% (13)	18.8% (21)	0.70 (0.35–1.40)	0.50 (0.27–0.93)
Death/MI*	6.9% (11)	9.4% (9)	14.3% (16)	0.74 (0.32–1.72)	0.48 (0.23–1.00)
Death	5.0% (8)	5.2% (5)	7.1% (8)	0.97 (0.33–2.87)	0.70 (0.27–1.82)
Cardiac death	2.5% (4)	4.2% (4)	6.3% (7)	0.60 (0.15–2.36)	0.40 (0.12–1.34)
Noncardiac death	2.5% (4)	1.0% (1)	0.9% (1)	2.42 (0.27–21.29)	2.82 (0.32–24.87)
CVA	3.8% (6)	6.3% (6)	5.4% (6)	0.60 (0.20–1.82)	0.70 (0.23–2.13)
Myocardial infarction	2.5% (4)	5.2% (5)	9.8% (11)	0.48 (0.13–1.75)	0.26 (0.08–0.78)
Q-wave	1.3% (2)	4.2% (4)	8.0% (9)	0.30 (0.06–1.62)	0.16 (0.03–0.71)
Non–Q-wave	1.3% (2)	1.0% (1)	1.8% (2)	1.21 (0.11–13.14)	0.70 (0.10–4.93)
Revascularization	21.4% (34)	7.3% (7)	38.4% (43)	2.93 (1.35–6.35)	0.56 (0.38–0.81)
CABG	3.8% (6)	2.1% (2)	13.4% (15)	1.81 (0.37–8.79)	0.28 (0.11–0.70)
CABG TL	1.3% (2)	1.0% (1)	8.9% (10)	1.21 (0.11–13.14)	0.14 (0.03–0.63)
CABG non-TL	2.5% (4)	1.0% (1)	4.5% (5)	2.42 (0.27–21.29)	0.56 (0.15–2.05)
RPTCA	18.2% (29)	6.3% (6)	27.7% (31)	2.92 (1.26–6.77)	0.66 (0.42–1.03)
RPTCA TL	13.8% (22)	3.1% (3)	19.6% (22)	4.43 (1.36–14.40)	0.70 (0.41–1.21)
RPTCA non-TL	6.9% (11)	3.1% (3)	9.8% (11)	2.21 (0.63–7.74)	0.70 (0.32–1.57)

Values are % (n) unless otherwise indicated. *Hierarchical. MACCE was defined as death, CVA, MI, target vessel CABG, and target vessel RPTCA; death, CVA, and MI are adjudicated by the independent clinical events committee.

Abbreviations as in Tables 1 and 2.

icantly higher need for repeat revascularizations among the diabetic patients. At 3 years, the difference between diabetic and nondiabetic patients in the incidence of the combined safety end point of death/CVA/MI did not reach statistical significance.

Remarkably, the incidence of stent thrombosis (definite, probable, or possible) at 3 years was similar for the ARTS-II diabetic and nondiabetic patients (6.9% [11 of 159] vs. 6.3% [28 of 448], respectively; p = 0.85). Definite or probable stent thrombosis occurred in 5.0% (8 of 159) of the diabetic patients as compared with 5.4% (24 of 448) of the nondiabetic patients (p = 1.00), whereas the incidence of only definite stent thrombosis was 3.8% (6 of 159) for the diabetic patients and 3.3% (15 of 448) for nondiabetic patients (p = 0.8). There were no differences in the incidence of stent thrombosis between insulin- and noninsulin-treated diabetic patients. Definite or probable stent thrombosis occurred in 4.6% (6 of 131) of the noninsulin-treated diabetic patients versus 7.1% (2 of 28) of the insulin-treated diabetic patients (p = 0.63).

Among the diabetic patients, of the 44 patients who had a major adverse cardiac event (ARC definitions), 10 (22.7%) had a definite, probable, or possible stent thrombosis. Of the 83 nondiabetic patients in the ARTS-II study who had a major adverse cardiac event, 28 (33.7%) had a definite, probable, or possible stent thrombosis. More specifically, 5 of 26 (19.2%) of the clinically driven percutaneous target lesion revascularizations in the nondiabetic patients and 12 of 22 (54.5%) of the clinically driven percutaneous target lesion revascularizations in the diabetic patients were due to definite stent thrombosis.

Discussion

The present study is the first to compare the long-term safety and efficacy of PCI using SES with CABG in diabetic and nondiabetic patients with multivessel coronary artery disease. In the total ARTS-II population, we recently reported the significantly lower incidence of death/CVA/MI among patients treated with SES as compared with patients in the historical PCI arm of the ARTS-I study. Stratification of these results according to diabetic status revealed that, when adjusting for independent predictors of outcome, the risk of death/CVA/MI for the nondiabetic patients was significantly lower in the ARTS-II trial than it was in both arms of the ARTS-I study. Conversely, for the diabetic cohort, the cumulative incidence of death/CVA/MI in the ARTS-II trial was 9.2% lower than it was in the ARTS-I PCI arm and 4.1% lower than in the ARTS-I CABG arm. However, these differences in the hard clinical end points did not reach statistical significance after adjusting for independent predictors of outcome.

Thus far, no consensus has been reached about differences between PCI and CABG in hard clinical end points. In the pre-stent era, higher survival rates were reported after CABG than after PCI, a difference that was most pronounced among diabetic patients (12,25,26). Comparing PCI using BMS with CABG, a meta-analysis of the ARTS-I, the SoS (Stent or Surgery), the ERACI-II, and the MASS-II (Medicine, Angioplasty, or Surgery Study) trials demonstrated similar mortality rates after both treatment options in both the overall analysis as well as in the diabetic subset at 1 year (2). We observed a clear trend

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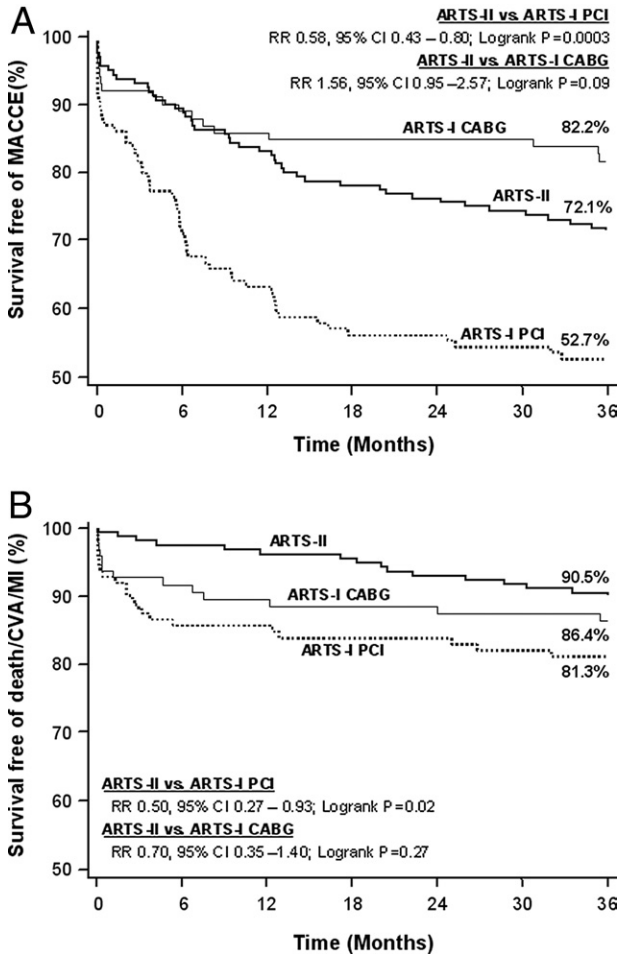

Figure 2 Kaplan-Meier Curve to 3 Years for ARTS-I and -II Diabetic Patients

(A) Freedom from major adverse cardiac and cerebrovascular events (MACCE), the combined end point of all-cause death, CVA, MI, and repeat revascularization, and **(B)** death/CVA/MI. Abbreviations as in Figure 1.

toward a lower incidence of death/CVA/MI among the patients in the ARTS-II trial treated with DES compared with the ARTS-I PCI population. Although the present study was underpowered to make definitive statements about a better survival after PCI using DES as compared with BMS, these findings are in agreement with the 3-year results of the randomized DIABETES trial, in which 6.4% of the patients treated with SES experienced an MI and/or died of a cardiac cause versus 12.6% of the patients treated with BMS (27). Furthermore, various large-scale registries have recently shown a small, but consistent long-term survival advantage when using DES versus BMS in all-comer populations (28–32).

CABG has been associated with a significantly lower risk for repeat revascularizations as compared with PCI with BMS, a benefit that proved to be most apparent among patients with multivessel disease, who often have diabetes (1–6). Although DES proved to tighten the gap between PCI and CABG, it remains unclear whether these findings can be extrapolated to diabetic patients (7,8). Diabetic patients are known to have smaller vessel size, longer lesion length, greater plaque burden, and possibly a different restenotic cascade as compared with nondiabetic patients, making them more susceptible to atherosclerosis and having a higher need for repeat revascularizations (9–12,33,34). This observation is confirmed by the 3-year revascularization rate among the ARTS-II diabetic patients, who had an 81% increased risk for repeat revascularization as compared with that for the nondiabetic patients. The use of CABG remains the most effective method for avoiding reinterventions in diabetic patients. When compared with the ARTS-I PCI population, the incidence of repeat revascularization was 31% lower after surgical revascularization. Although CABG remained significantly superior to PCI with DES in reducing the need for repeat revascularizations, the use of SES in diabetic patients resulted in a 44% decrease in the need for repeat revascularizations as compared with the ARTS-I PCI arm, despite the higher baseline and procedural risk profile of the ARTS-II patient population. Among the nondiabetic patients, conversely, these differences were substantially smaller. The difference was 17.0% between both arms of the ARTS-I trial, whereas the difference in repeat revascularization rates between ARTS-II and -I CABG was 5.5%, confirming the more pronounced efficacy of CABG in diabetic patients.

Diabetes has been associated with enhanced platelet reactivity and reduced responsiveness to antiplatelet agents (35,36). Abnormalities in neovascularization have also been recognized and are hypothesized to enhance atherosclerotic plaque destabilization (37). The latter is reflected by the 70% higher relative risk of MACCE for diabetic patients as compared with nondiabetic patients in the ARTS-II trial. Additionally, the incidence of definite stent thrombosis was 3.8% for the diabetic patients, an incidence in line with those of previously reported studies (15,27,38). Of note, at 3 years, the incidence of definite or probable stent thrombosis (21) was similar among the ARTS-II diabetic and nondiabetic patients, a finding that at first is not entirely consistent with the current literature (13–15) but may be partly explained by the relatively small and specific patient population studied. Clinical and procedural risk factors are usually worse for diabetic patients than for nondiabetic patients. However, in the ARTS-II trial, clinical presentation, lesion calcification, number of stents, and total stented length were similar between the diabetic and nondiabetic patients. As a result, the impact of stent thrombosis on the 3-year MACCE rates in the ARTS-II trial was similar for both the diabetic and nondiabetic populations.

Although the present subset analysis of patients with diabetes was pre-specified in the ARTS-II protocol, this nonrandomized study has several limitations. First, a 5-year time lag exists between the groups that are being compared. Both PCI and CABG as well as concomitant medical

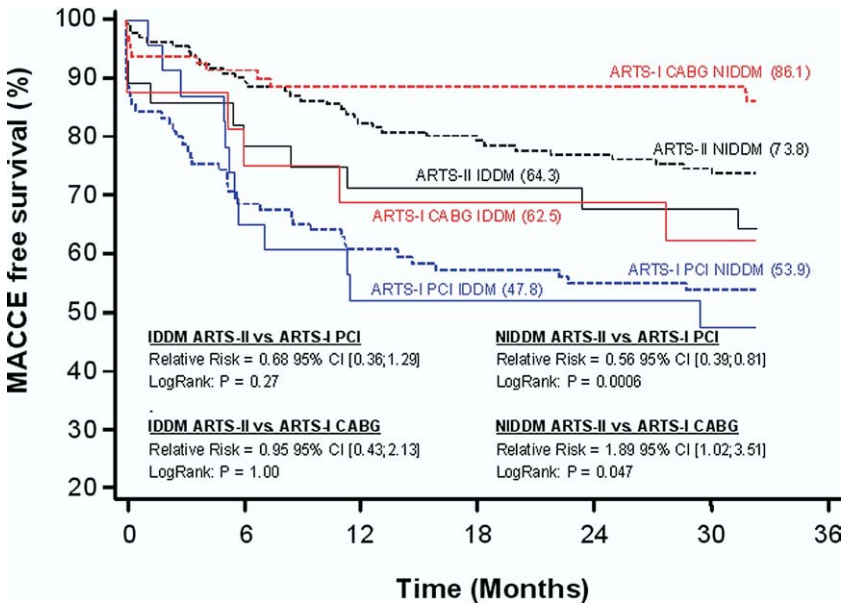

Figure 3 Kaplan-Meier Curve to 3 Years for ARTS-I and -II IDDM Versus NIDDM Patients

Freedom from major adverse cardiac and cerebrovascular events (MACCE), the combined end point of all-cause death, CVA, MI, and repeat revascularization. IDDM = insulin-dependent diabetes mellitus; NIDDM = noninsulin-dependent diabetes mellitus; other abbreviations as in Figure 1.

therapy have improved with time. Secondly, despite the use of complex statistical adjustment methods, it remains unclear whether we were able to fully adjust for the differences between the ARTS-II and -I studies. Third, although the protocol required that the lesions in the ARTS-II trial be potentially treatable by CABG, the absence of dialogue with the surgeons before the intervention may have caused a selection bias. However, this bias is not obvious considering that the patients actually enrolled in the ARTS-II trial were more complex than those enrolled in the ARTS-I trial. Finally, the incidence and impact of stent thrombosis was not readjudicated according to the ARC definitions in the ARTS-I study, preventing the authors from comparing the results of the ARTS-II trial to the historical PCI arm of the

Table 5 Clinical End Points of Diabetic Patients and Nondiabetic Patients at 3 Years in the ARTS-II Trial (Hierarchical and Nonhierarchical MACCE to 1,080 Days, per Patient) Counted Since Date of Procedure

Up to 1,080 Days	Diabetic Patients (n = 159)	Nondiabetic Patients (n = 448)	Relative Risk (95% CI)
MACCE*	27.7% (44)	16.3% (73)	1.70 (1.22–2.36)
Death/CVA/MI*	9.4% (15)	7.8% (35)	1.21 (0.68–2.15)
Death/MI*	6.9% (11)	6.0% (27)	1.15 (0.58–2.26)
Death	5.0% (8)	2.2% (10)	2.25 (0.91–5.61)
Cardiac death	2.5% (4)	1.1% (5)	2.25 (0.61–8.29)
Noncardiac death	2.5% (4)	1.1% (5)	2.25 (0.61–8.29)
CVA	3.8% (6)	2.5% (11)	1.54 (0.58–4.09)
Myocardial infarction	2.5% (4)	4.0% (18)	0.63 (0.22–1.82)
Q-wave	1.3% (2)	2.5% (11)	0.51 (0.11–2.29)
Non–Q-wave	1.3% (2)	1.8% (8)	0.70 (0.15–3.28)
Revascularization	21.4% (34)	11.8% (53)	1.81 (1.22–2.67)
CABG	3.8% (6)	1.8% (8)	2.11 (0.74–6.00)
CABG TL	1.3% (2)	0.4% (2)	2.82 (0.40–19.84)
CABG non-TL	2.5% (4)	1.3% (6)	1.88 (0.54–6.57)
RPTCA	18.2% (29)	10.3% (46)	1.78 (1.16–2.73)
RPTCA TL	13.8% (22)	5.8% (26)	2.38 (1.39–4.08)
RPTCA non-TL	6.9% (11)	5.8% (26)	1.19 (0.60–2.36)

Values are % (n) unless otherwise indicated. *Hierarchical. MACCE was defined as death, CVA, MI, target vessel CABG, and target vessel RPTCA; death, CVA, and MI are adjudicated by the independent clinical events committee.

Abbreviations as in Tables 1 and 2.

ARTS-I trial. As a consequence, we were unable to verify the hypothesized increase in late stent thrombosis among diabetic patients treated with DES as compared with BMS. However, it was reassuring to note the trend toward a lower rate of death and a significantly lower rate of MI, as well as Q-wave MI, in the ARTS-II population compared with the ARTS-I PCI population.

Several large-scale dedicated randomized controlled trials like the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) study (using the paclitaxel-eluting stent), the FREEDOM (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) study (using the paclitaxel-eluting stent and SES), and the CARDia (Coronary Artery Revascularization in Diabetes) study (comparing SES with CABG for diabetic patients) are ongoing to assess the relative safety and efficacy of PCI using DES and CABG (39,40). However, until the long-term outcome data from these trials are revealed, the results from the present study are unique in addressing the relative long-term safety and efficacy of PCI using SES for both diabetic and nondiabetic patients with multivessel coronary artery disease. The results of the randomized FREEDOM and CARDia trials are eagerly awaited to confirm the findings of this analysis.

Conclusions

At 3 years, PCI using SES for patients with multivessel coronary artery disease seems to be safer and more efficacious as compared with PCI using BMS, irrespective of the diabetic status of the patient. Although superior to PCI using BMS, PCI using SES remains inferior to CABG in reducing the need for repeat revascularizations. However, we observed a clear trend toward a lower risk for death, CVA, and MI among the ARTS-II study patients as compared with both arms of the ARTS-I trial. These findings suggest that PCI using SES could be a genuine alternative to CABG. The results of dedicated, large-scale, randomized trials are eagerly awaited to validate our findings.

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Key Words: coronary stents ■ sirolimus-eluting stent ■ diabetes ■ all-comers ■ coronary artery bypass graft surgery.