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Clinical and Economic Impact of Diabetes Mellitus on Percutaneous and Surgical Treatment of Multivessel Coronary Disease Patients

Insights From the Arterial Revascularization Therapy Study (ARTS) Trial

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Background**—**Our aims were to compare coronary artery bypass grafting (CABG) and stenting for the treatment of diabetic patients with multivessel coronary disease enrolled in the Arterial Revascularization Therapy Study (ARTS) trial and to determine the costs of these 2 treatment strategies.

Methods and Results**—**Patients (n=1205) were randomly assigned to stent implantation (n=600; diabetic, 112) or CABG (n=605; diabetic, 96). Costs per patient were calculated as the product of each patient's use of resources and the corresponding unit costs. Baseline characteristics were similar between the groups. At 1 year, diabetic patients treated with stenting had the lowest event-free survival rate (63.4%) because of a higher incidence of repeat revascularization compared with both diabetic patients treated with CABG (84.4%, $P<0.001$) and nondiabetic patients treated with stents (76.2%, $P=0.04$). Conversely, diabetic and nondiabetic patients experienced similar 1-year event-free survival rates when treated with CABG (84.4% and 88.4%). The total 1-year costs for stenting and CABG in diabetic patients were $12 855 and $16 585 ($P<0.001$) and in the nondiabetic groups, $10 164 for stenting and $13 082 for surgery.

Conclusions**—**Multivessel diabetic patients treated with stenting had a worse 1-year outcome than patients assigned to CABG or nondiabetics treated with stenting. The strategy of stenting was less costly than CABG, however, regardless of diabetic status. **(*Circulation*. 2001;104:533-538.)**

Key Words: diabetes mellitus ■ coronary disease ■ revascularization

Diabetes has been found to be an important risk factor for poor outcome after percutaneous transluminal coronary angioplasty (PTCA).[1–6] Subgroup analysis of the Bypass Angioplasty Revascularization Investigation (BARI) randomized trial demonstrated that diabetic patients with multivessel coronary disease had worse long-term outcome when treated with balloon angioplasty than with coronary artery bypass graft surgery (CABG).[7] These findings have been corroborated by the 8-year follow-up analysis of the Emory Angioplasty versus Surgery Trial (EAST).[8]

When interpreting the results from past studies,[9,10] it is important to realize that the introduction of intracoronary stents and the routine use of arterial conduits for bypass surgery have resulted in a remarkable improvement in outcomes after both percutaneous and surgical revascularization.[6,11–17]

The Arterial Revascularization Therapy Study (ARTS) was designed to compare CABG and stenting for the treatment of patients with multivessel coronary disease.[18] The aims of the present study were to compare the results of CABG and stented angioplasty in diabetic patients with multivessel coronary disease enrolled in the ARTS trial and to determine the cost of these 2 treatment strategies.

Methods

ARTS Trial Design

Between April 1997 and June 1998, 1205 patients were randomized to either stent implantation (n=600) or CABG (n=605) at 67 participating centers worldwide. A detailed description of the ARTS protocol has been reported previously.[18] In brief, only patients without previous angioplasty or CABG procedures were included.

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TABLE 1. Baseline Clinical Characteristics

	Diabetes			Nondiabetes		
Characteristics	Stent (n=112)	CABG (n=96)	*P*	Stent (n=488)	CABG (n=509)	*P*
Age, y	62.4	62.6	0.111	60.3	61	0.832
Male, %	73.2	68.8	0.479	77.9	77.4	0.861
Unstable angina, %	39.3	39.6	0.965	39.3	42.4	0.321
Silent ischemia, %	3.6	4.2	0.824	6.6	4.9	0.264
Previous MI, %	41.1	49	0.255	45.1	40.7	0.160
Hypertension, %	64.3	56.3	0.238	40.2	42.8	0.394
Hypercholesterolemia, %	55.4	49	0.785	58.6	59.3	0.816
Family history, %	41.4	32.6	0.192	38.6	43.7	0.103
Current smoking, %	20.5	16.7	0.476	29.6	27.6	0.484
Left ventricular ejection fraction, %	60.5	60.3	0.965	61	60.4	0.796

The indications for revascularization were silent ischemia, stable or unstable angina pectoris, and the presence of ≥2 de novo lesions located in different major epicardial coronary arteries, potentially amenable to stent implantation. Complementary conventional balloon angioplasty was allowed for the treatment of vessels with a reference diameter <2.75 mm. Patients with left main stem stenosis, impaired left ventricular function (left ventricular ejection fraction <30%), previous cerebrovascular accident (CVA), myocardial infarction (MI) within the week preceding randomization, or severe hepatic or renal disease and patients who needed concomitant major surgery were not included in the study.

Stents were implanted according to current clinical practice, with high-pressure postdilatation. Bypass surgery also followed current standard techniques, preferably with the left internal mammary artery for revascularization of the left anterior descending coronary artery and cold potassium cardioplegia (crystalloid or blood) for myocardial protection.

Data Analysis

Angiographic (anatomic) data, including the characteristics of each lesion and target coronary segment, were adjudicated by an independent core laboratory (Cardialysis BV). MI occurring within 7 days of the procedures was defined as the appearance of a new Q wave and cardiac enzymes >5 times the upper limit of normal or a ratio of peak creatine kinase (CK)-MB/CK >0.1. To define an MI after 7 days, either ECG or enzymatic criteria were applied.

The Minnesota criteria code for pathological Q waves[19] was used, and the ECGs were analyzed by an independent core laboratory.

Every itemized clinical event, including death, MI, and any repeat revascularization, as well as the combined major cardiac (death, MI, and repeated revascularization) and cerebrovascular (stroke, transient ischemic attacks, and reversible ischemic neurological deficits) events (MACCE) were counted from the date of randomization until 1-year follow-up. Clinical events were adjudicated by an independent committee.

TABLE 2. Angiographic and Procedure-Related Factors

	Diabetes			Nondiabetes		
Variables	Stent (n=112)	CABG (n=96)	*P*	Stent (n=488)	CABG (n=509)	*P*
No. of segments diseased	3.0±1.3	2.9±1.1	0.554	2.8±1.0	2.8±1.0	1.0
Two vessels, %	62	64	0.774	69	64	0.321
Three vessels, %	38	36	0.877	30	35	0.571
Lesion type*						
A/B1, %	30.4	35.8	0.438	32.9	38.6	0.285
B2/C, %	69.6	64.2	0.438	67.1	61.4	0.264
No. of segments treated	2.8±1.5	2.7±0.8	0.559	2.6±1.1	2.7±0.8	0.1
No. of stents implanted	3.0±1.5			2.7±1.2		
No. of distal anastomoses		2.7±0.7			2.7±0.9	
Target vessel						
Left anterior descending, %	83	92	0.065	84	91	0.196
Right coronary artery, %	63	65	0.756	65	71	0.652
Left circumflex, %	62	78	0.058	55	67	0.214
Total stent length, mm	52.7±25.6			46.4±20.6		
Maximal balloon pressure, atm	14.9±2.9			14.6±2.8		
Abciximab, %	3.5			2.8		
Left internal mammary artery, %		89.3			99.7	

*According to the American College of Cardiology/American Heart Association classification.

TABLE 3. Short-Term Outcome (Up to Discharge)

	Diabetes			Nondiabetes		
	Stent (n=112)	CABG (n=96)	*P*	Stent (n=488)	CABG (n=509)	*P*
Death, n (%)	3 (2.7)	2 (2.1)	0.780	3 (0.6)	6 (1.2)	0.208
Cerebrovascular events, n (%)	0	4 (4.2)	0.041	3 (0.6)	3 (0.6)	0.848
MI, n (%)	3 (2.7)	3 (3.1)	0.848	11 (2.3)	17 (3.3)	0.097
Q-wave, n (%)	3 (2.7)	2 (2.1)	0.780	11 (2.3)	16 (3.1)	0.144
Repeat revascularization						
CABG, n (%)	4 (3.6)	0	0.173	7 (1.4)	1 (0.2)	0.113
PTCA, n (%)	1 (0.9)	0	0.354	8 (1.6)	3 (0.6)	0.197
Event-free, n (%)	101 (90.2)	87 (90.6)	0.762	456 (93.4)	479 (94.1)	0.665
In-hospital stay, d	5.2±4.1	13.2±9.2	<0.001	4.5±4.7	11.2±5.7	<0.001

Cost Analysis

Costs were limited to the direct medical costs per patient, assessed from a societal perspective. Costs per patient were calculated as the product of each patient's use of resources and the corresponding unit costs (US dollars). Data on the use of resources comprised a selection of so-called "big-ticket" items: hospital days, postoperative intensive care, coronary care, nonintensive/noncoronary care unit, and diagnostic and therapeutic procedures (eg, outpatient visits, angiography, intra-aortic balloon pumping, rehabilitation, etc). In addition, data were collected concerning medication and the items (balloons, wires, catheters, stents) that were used during the revascularization procedures as well as data concerning the duration of the various procedures. All data were collected on the case report form, but patients were also given a "passport" so that the corresponding information could be recorded if they were treated at other hospitals. Unit costs were estimated (before analysis of the data) on the basis of detailed information from Dijkzigt Hospital, as reported earlier.[14,20] The costs per procedure, excluding the costs of those items that were specifically recorded, were estimated as the product of (1) the duration of the procedure in minutes and (2) an estimate of the costs per procedure-minute.

Study Population

All patients enrolled in the ARTS trial were eligible for the present investigation. Patients were divided into 2 groups: diabetes (n=208) and nondiabetes (n=997). The steering committee recommended that all diabetic patients be treated with oral hypoglycemic agents or insulin at study entry. Short-term (up to hospital discharge) and 1-year clinical outcomes of patients assigned to stent and CABG were compared within each group. All patients gave written informed consent.

Statistical Analysis

Statistical analysis was performed with SAS 6.12 software (SAS Institute Inc). Continuous variables were expressed as mean±SD and were compared by unpaired Student's *t* test. Fisher's exact test was used for categorical variables. Binary outcome variables are reported as frequencies and percentages and were compared in terms of relative risk with 95% CIs calculated by the formula of Greenland and Robins.[21] Comparisons between stent and CABG were performed within each group (diabetes and nondiabetes). Multivariate logistic regression models were constructed by use of baseline clinical and angiographic characteristics as well as procedure-related factors to identify independent risk factors for MACCE at 1 year in each randomized arm of the ARTS trial (stent or CABG). All statistical tests were 2-tailed, and a value of $P<0.05$ was considered significant.

Results

Baseline clinical and demographic characteristics as well as angiographic and procedure-related variables were similar between patients assigned to stent and CABG within each study group (Tables 1 and 2).

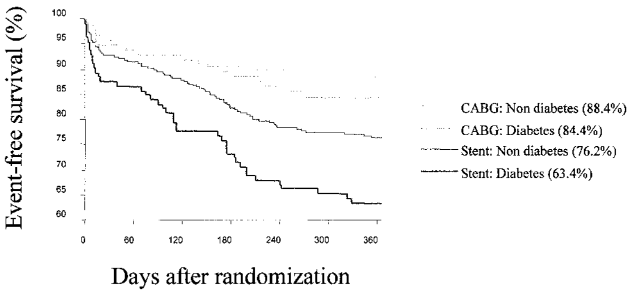
Short-Term Clinical Outcome

Until hospital discharge, patients assigned to stent and CABG had a similar incidence of combined clinical events (Table 3). In the diabetes group, however, repeat revascularization was carried out more often after stenting than after CABG (4.5% versus 0%, $P=0.04$), whereas CVAs occurred only in patients treated with CABG (4.2% versus 0%, $P=0.04$).

TABLE 4. One-Year Clinical Outcome

	Diabetes			Nondiabetes		
	Stent (n=112)	CABG (n=96)	*P*	Stent (n=488)	CABG (n=509)	*P*
Death, n (%)	7 (6.3)	3 (3.1)	0.294	8 (1.6)	14 (2.8)	0.412
Cerebrovascular events, n (%)	2 (1.8)	6 (6.3)	0.096	7 (1.4)	6 (1.2)	0.722
MI, n (%)	7 (6.3)	3 (3.1)	0.294	25 (5.1)	21 (4.1)	0.453
Q-wave, n (%)	6 (5.4)	2 (2.1)	0.222	22 (4.5)	20 (3.9)	0.649
Repeat revascularization*						
CABG, n (%)	9 (8.0)	0	<0.001	19 (3.9)	3 (0.6)	<0.001
PTCA, n (%)	16 (14.3)	3 (3.1)	<0.001	57 (11.7)	15 (2.9)	<0.001
Event-free, n (%)	71 (63.4)	81 (84.4)	<0.001	372 (76.2)	450 (88.4)	<0.001

*$P=0.04$ for diabetes (stent) versus nondiabetes (stent).



Kaplan-Meier event-free survival curves for death, cerebrovascular events, MI, or any repeat revascularization of patients assigned to stenting vs CABG according to diabetes status ($P<0.001$ for stent vs CABG in both diabetes and nondiabetes groups; $P=0.004$ for diabetes/stent vs nondiabetes/stent; P=NS for diabetes/CABG vs nondiabetes/CABG).

One-Year Clinical Outcome

Patients assigned to stenting compared with CABG had a higher incidence of combined MACCE, regardless of diabetic status (Table 4). The incidence of death, CVA, and MI (or the combination of all 3 items), however, was similar between stent and CABG within each group (Table 4).The cause of death in the diabetic patients assigned to stented angioplasty was as follows: procedure-related complication (1 patient), stent thrombosis (2 patients), sudden death (2 patients), MI complicated by heart failure (1 patient), and noncardiac death due to renal cancer (1 patient). In the CABG group, the causes of death were periprocedural MI (2 patients) and sudden death (1 patient).

Diabetic patients treated with stenting had the lowest 1-year event-free survival rate (Figure) because of a higher incidence of repeat revascularization than both diabetic patients treated with CABG and nondiabetic patients (Table 4). Conversely, diabetic and nondiabetic patients experienced similar 1-year event-free survival rates when treated with CABG (Figure).

Predictors of Late Clinical Outcome

Independent risk factors for late clinical outcome (MACCE) in the stent and CABG arms of the ARTS population are displayed in Table 5. Diabetes appeared to be a strong risk factor for the occurrence of MACCE in the population assigned to stenting but not in those assigned to CABG.

Costs

Table 6 presents the difference in costs after 1-year follow-up. The initial costs were significantly higher in the patients assigned to CABG versus stented angioplasty in both groups. Part of the initial difference in costs was lost, however, because of more repeat revascularizations at follow-up after stenting in the nondiabetic patients. Interestingly, there was no significant difference in follow-up costs between stent versus CABG in the diabetes groups (Table 6). Expenses with respect to rehospitalization (40 of 96 diabetic CABG patients were readmitted) in the diabetes group were primarily due to comorbid factors related to the presence of diabetes rather than the additional cost of repeat revascularization. The main causes of rehospitalization in the diabetic CABG group were sternal infection (7 patients), CVA (6 patients), gastrointestinal bleeding (3 patients), renal insufficiency (3 patients), pulmonary embolism (2 patients), and heart failure (2 patients). At 1 year, the net difference in favor of the percutaneous treatment was $3730 in the diabetes and $2918 in the nondiabetes groups, respectively.

Discussion

This study, which is a subanalysis of the ARTS trial,[18] reveals that in patients with diabetes mellitus and multivessel coronary artery disease, surgical revascularization with routine use of arterial bypass conduits provides a superior 1-year clinical outcome compared with percutaneous treatment, even when a strategy of stented angioplasty is applied.

In the present investigation, surgery carried a substantial risk of CVA in the diabetic patients (Table 3). These patients

TABLE 5. Independent Correlates With One-Year MACCE

	Stent (n=600)		CABG (n=605)	
	P	Odds Ratio	*P*	Odds Ratio
Diabetes mellitus	0.002	2.1		
Maximal balloon pressure in LAD	0.002	0.95		
No. of stents implanted in mid-RCA	0.004	1.43		
Stenosis in distal RCA	0.02	4.53		
No. of unsuccessful treated segments*	0.03	1.27		
Elevated CK-MB			0.0001	1.73
Increasing age			0.002	1.06
Use of heparin			0.003	2.66
Abnormal hematocrit			0.01	2.56
Intra-aortic balloon pump			0.03	9.44
Anastomosis in distal RCA			0.04	0.4

LAD indicates left anterior descending coronary artery; RCA, right coronary artery.

*Successful treatment: <50% diameter stenosis after balloon angioplasty or <20% diameter stenosis after stented angioplasty by visual assessment.

TABLE 6. One-Year Results: Average Costs and Effectiveness

	Diabetes			Nondiabetes		
	Stent (n=112)	CABG (n=96)	*P*	Stent (n=488)	CABG (n=509)	*P*
Procedural cost, US dollars	7285	11 641	<0.001	6248	10 467	<0.001
Follow-up cost, US dollars	4732	4409	0.096	2972	1953	0.02
Total cost, US dollars*	12 855	16 585	<0.001	10 164	13 082	<0.001
Effectiveness, %†	63.4	84.4	<0.001	76.2	88.4	<0.001

*Total cost indicates sum of procedural, follow-up, and cardiovascular medication costs.
†Effectiveness indicates event-free survival.

appear to have a higher incidence of CVA (6.3%) than the general population (2.4%) treated with CABG.[22] Such findings may highlight the importance of diabetes as an independent risk factor for CVA after CABG, as reported previously.[23]

The 5-year follow-up of the BARI[7] trial, and more recently the 8-year analysis of the EAST trial,[8] have shown a higher mortality rate in diabetic patients with multivessel disease treated with PTCA compared with CABG. In the present study, the incidence of 1-year mortality in the diabetic patients assigned to stented PTCA was twice as high as in those assigned to CABG (6.3% versus 3.1%; P=NS) (Table 4). Although this difference was not statistically significant, it is possible that with longer follow-up and a larger sample size, the difference in mortality rate could achieve statistical significance. In this regard, it is worth noting that the difference in mortality between the CABG- and PTCA-treated patients with diabetes in the EAST trial was not evident after 3 years.[10] The hypothesis that late lesion progression in nontreated coronary segments is an important cause of mortality in diabetic patients with multivessel coronary disease[24,25] may explain the difference in results observed with shorter-term (<3 years) versus longer-term (>5 years) follow-up.

In diabetic patients, the difference in favor of CABG in repeat revascularization was almost twice as great as in the nondiabetic group (21.6% versus 12.4%, respectively). Furthermore, diabetes was an independent risk factor for 1-year MACCE in the stent arm but not in the CABG arm of the ARTS trial. A possible explanation for these findings may be that diabetes has been associated with both increased restenosis[26–28] and late vessel occlusion[29] in stented vessels because of either enhanced neointimal proliferation or vascular thrombosis.[30,31]

Considering that both thrombosis and restenosis may be implicated in the high incidence of repeat revascularization in diabetic patients treated percutaneously, modern adjunctive therapies have been proposed to improve the outcome of this high-risk population. In the EPISTENT trial, the target-vessel revascularization rate of diabetic patients who received a stent plus abciximab was approximately half the rate of patients who received a stent plus placebo.[32] It is also encouraging to note that intravascular radiation therapy has been shown to be effective in the treatment of in-stent restenosis in both diabetic and nondiabetic patients.[33] Finally, stents coated with drugs such as sirolimus are showing very promising results, with essentially no late intimal hyperplasia in either diabetic or nondiabetic patients.[34] These recent encouraging reports may further fuel the debate on the most effective strategy for the treatment of these high-risk patient subsets.

Because of the economic constraints of modern society, physicians also need to consider the cost of each strategy when counseling the diabetic patient with multivessel coronary disease.[35] A strategy of stented angioplasty was less costly than CABG in both diabetic and nondiabetic patients after 1-year follow-up (Table 6). Although CABG resulted in a 21.6% lower rate of repeat intervention at 1 year, the rehospitalization rates were higher in the diabetic patients assigned to surgery because of non-MACCE complications, such as sternal infection, renal insufficiency, heart failure, pulmonary embolism, and gastrointestinal bleeding.

Because technologies continuously evolve, this balance between costs and the outcome achieved is likely to change.

Limitations

Diabetes was not the original focus of the ARTS trial. It is the first prospective, randomized trial, however, comparing stented angioplasty and CABG for the treatment of multivessel coronary disease by contemporary techniques (more complete revascularization in the percutaneous arm with stents and use of arterial conduits in >90% of the cases in the CABG group). This substudy reports on the differences in costs between the patient cohorts but is underpowered to truly assess “cost-effectiveness,” ie, whether the added costs of CABG in diabetics was economically justifiable. We believe, however, that these data will serve as an important frame of reference for clinicians until the results of a large, randomized trial in diabetics can provide a more definitive answer to this problem.

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