Drug-eluting stents versus arterial myocardial revascularization in patients with diabetes mellitus

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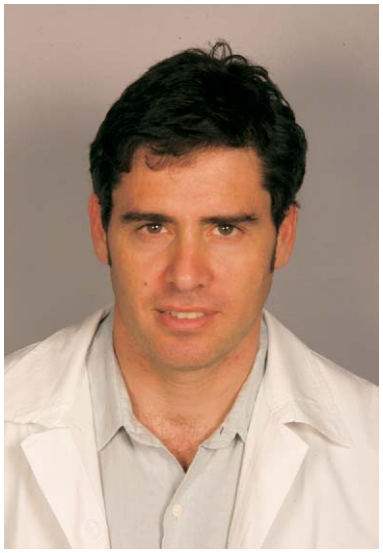

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Objective: The introduction of drug-eluting stents significantly reduced restenosis and reinterventions in patients undergoing percutaneous coronary interventions. This study compares results of Cypher stenting with those of surgical arterial revascularization in patients with diabetes mellitus.

Methods: From May 2002 through May 2005, 523 consecutive diabetic patients underwent myocardial revascularization: 244 underwent percutaneous coronary interventions incorporating drug-eluting stents, and 279 were treated surgically. All single-vessel patients in the surgical group were treated with the left internal thoracic artery, and most multivessel patients were treated with 2 internal thoracic arteries. After propensity score matching, 2 groups (93 patients each) were used to compare the 2 revascularization modalities.

Results: The number of coronary vessels treated per patient was higher in the surgical group (2.72 vs 1.7; $P < .001$). Follow-up ranged between 6 and 42 months (mean, 19 months). Overall mortality (early and late) was 3.2% in the surgical group and 2.2% in the Cypher group ($P = .65$). Two-year angina-free survival and reintervention-free survival (Kaplan-Meier) of the surgical group were 88% and 95%, respectively, compared with 47.8% ($P = .001$) and 83.6% ($P = .01$), respectively, in the percutaneous coronary intervention group. Cox proportional hazards modeling revealed assignment to the Cypher group to be the only predictor of reintervention (hazard ratio, 3.86; 95% confidence interval, 1.25-11.9). Assignment to the Cypher group (hazard ratio, 5.92; 95% confidence interval, 2.96-11.87) and insulin treatment (hazard ratio, 2.06; 95% confidence interval, 1.06-4.02) were independent predictors of angina recurrence.

Conclusions: The midterm clinical outcome of diabetic patients who underwent surgical arterial revascularization is better than that of patients undergoing percutaneous coronary intervention treated with drug-eluting stents.

Ischemic heart disease is a leading cause of death in diabetic patients.[1] Therefore an increasing number of diabetic patients are referred today for surgical or percutaneous revascularization,[2] leading to a significant increase in the prevalence of diabetic patients undergoing coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).[3]

Surgical revascularization of the left anterior descending artery (LAD) with the internal thoracic artery (ITA) in patients with multivessel disease is still the only proved method of improving event-free survival.[4,5] In the subset of patients with diabetes mellitus in the Bypass Angioplasty Revascularization Investigation study,[6,7] which compared PCI with CABG, LAD revascularization with the ITA was found to be an independent predictor of survival. Similar findings were reported later in the subgroup of patients with diabetes in the Arterial Revascularization Therapy Study.[8] In that study 3-year survival of patients treated surgically was significantly better than that of diabetic patients treated with bare-metal stents.

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CI = confidence interval
HR = hazard ratio
ITA = internal thoracic artery
LAD = left anterior descending artery
MACE = major adverse cardiovascular event
MI = myocardial infarction
PCI = percutaneous coronary intervention
TVR = target vessel revascularization

Considerable reduction of restenosis and reintervention rates was recently reported with the introduction of drug-eluting stents (DESs).[9] Improved angiographic and clinical outcome was also reported among diabetic patients.[10,11] We therefore decided to compare the midterm clinical outcome of CABG in diabetic patients with that of PCI incorporating DESs.

Patients and Methods

Five hundred twenty-three consecutive diabetic patients underwent either CABG (n = 279) or Cypher (Cordis Corp, Warren, NJ) implantation (n = 244) between May 2002 and May 2005. The Cypher stent was the only DES available in our centers during the study period.

Adjustment for Patient Selection

The probability (propensity score) that a patient would receive a Cypher stent or undergo CABG, according to the preprocedural variables (all variables included in Table 1) was determined by using a saturated logistic regression model to take into account the different patient profiles.[12] Patients from the Cypher group were then matched with patients from the CABG group according to their propensity score in such a way that the difference between the propensities in each pair of matched patients was less than 10%. This revealed 93 pairs of propensity-matched patients, on whom complete follow-up was performed. Demographic and clinical preprocedural data of the propensity-matched patients are shown in Tables 2 and 3. It can be seen that after matching, patients are more evenly distributed between the 2 groups.

During the study period, selection criteria for surgical intervention versus PCI were mainly technical. In principle, there was a preference to refer patients for surgical intervention for the following reasons:

1. complex type C lesions (calcified coronary arteries, lesion length >20 mm, twisted arteries, or suspicion of a thrombus in an artery) or bifurcation lesion involving a major diagonal or marginal branch;
2. complete occlusion;
3. nonavailability of Cypher stent; or
4. patient's preference.

In the PCI group stent implantation was performed after balloon angioplasty dilatation. All patients received aspirin (325 mg daily) before and after the procedure and clopidogrel (Plavix, Sanofi; a loading dose of 300 mg the day before the procedure and 75 mg daily thereafter). During the procedure, all patients were treated intravenously with heparin. Intravenous platelet glycoprotein IIb/IIIa inhibitors (eptifibatide [Integrilin, Schering-Plough, Kenilworth, NJ] or tirofiban [Aggrastat, Merck, Sharp and Dohme, Whitehouse Station, NJ]) were used only in 10 members of the PCI group. All left anterior descending lesions in the PCI group were treated with DESs. In most patients only one Cypher stent was used for the vessel treated. However, more than one Cypher stent was used if required (eg, long lesion, dissection, or bifurcation). DESs, bare-metal stents, or plain balloon angioplasty were used for non-LAD lesions. Forty-two patients with multivessel disease were treated with 2 or more Cypher stents. Bare stents were used in 18 patients with tortuous or calcified coronary vessels. Percutaneous transluminal coronary angioplasty was used in 8 patients with vessels smaller than 2.25 mm or in patients with focal in-stent restenosis.

TABLE 1. Demographic and clinical preprocedural data collected before matching

	CABG (n = 279)	Cypher (n = 244)	*P* value
Age >70 y	92 (33%)	65 (26.6%)	.288
Female sex	49 (17.6%)	54 (22.1%)	.232
Chronic renal failure	7 (2.5%)	4 (1.6%)	.489
Acute myocardial infarction (7 d)	44 ([illegible])	35 (14.3%)	.650
Ejection fraction <30%	1[illegible]6.5%)	[illegible]5.7%)	.734
Prior PCI	[illegible]5 (19.7%)	74 ([illegible].3%)	.005
In-stent restenosis	[illegible]2.5%)	11 ([illegible]5%)	.211
Emergency	29 ([illegible]4%)	4[illegible].6%)	.000
Intra-aortic balloon pump	11 (2.1[illegible])	[illegible] (0.8%)	.022
Obesity	24 (27.6%)	28 (32.2%)	.508
Left main	83 (29.[illegible]%)	23 (9.4%)	.022
One-vessel disease	6 ([illegible]%)	90 (37%)	
Two-vessel disease	[illegible] (20.4%)	101 (41.4%)	.000
Three-vessel disease	[illegible]16 (77.4%)	52 (21.3%)	
Right coronary artery revascularization	166 (59.9%)	36 (14.8%)	.000
Total occlusion	86 (30.8%)	27 (11.1%)	.000

CABG, Coronary artery bypass grafting; *PCI*, percutaneous coronary intervention, angioplasty or stent.

Fifty-four (58%) of the patients treated surgically were operated on without extracorporeal circulation. All ITAs were dissected as skeletonized vessels and used preferentially for left-sided (LAD and circumflex artery) arterial revascularization. In all patients in the surgical group, ITAs were used for LAD revascularization. In patients with single-vessel disease, we used an in situ left ITA.

The right ITA, either as an in situ graft or as a free graft attached end-to-side to the left ITA (composite T-graft), was used in 74 (79%) patients with multivessel disease. In 17 patients left-sided revascularization was achieved with radial arteries for composite T-grafting.

Right coronary system (posterior descending artery or posterolateral branch of the right coronary artery) revascularization was performed with a saphenous vein graft in 19 patients, the radial artery in 9 patients, the right ITA in 3 patients (distal end of the free graft), and the right gastroepiploic artery in 5 patients.

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TABLE 2. Patient characteristics (after propensity score matching)

Characteristic	CABG (n = 93)	Cypher (n = 93)	P value
Age >70 y	31 (33.3%)	38 (40.9%)	.288
Female sex	19 (20.4%)	24 (25.8%)	.385
Insulin-dependent diabetes mellitus	9 (9.7%)	14 (15.1%)	.265
Hypertension	64 (67.7%)	56 (47.1%)	.285
Hyperlipidemia	56 (60.2%)	56 (60.2%)	1.000
Chronic obstructive pulmonary disease	5 (5.4%)	3 (3.2%)	.470
Chronic renal failure (Cr >1.8)	4 (4.3%)	3 (3.2%)	.700
Peripheral vascular disease	8 (8.6%)	5 (4.5%)	.388
Old myocardial infarction	32 (34.4%)	24 (25.8%)	.201
Acute myocardial infarction (7 d)	15 (16.1%)	11 (11.8%)	.398
Ejection fraction <30%	3 (3.2%)	1 (1.1%)	.312
Prior PCI	38 (40.9%)	26 (28%)	.064
Prior PCI to left anterior descending artery	22 (23.7%)	10 (10.8%)	.211
In-stent restenosis	13 (14%)	7 (7.5%)	.156
Emergency	3 (3.2%)	3 (3.2%)	1.000
Repeat operation	1 (1.1%)	6 (6.5%)	.054
Congestive heart failure	11 (11.8%)	7 (7.5%)	.321
Intra-aortic balloon pump	1 (1.1%)	0 (0%)	
Obesity	24 (40.7%)	35 (37.6%)	

CABG, Coronary artery bypass grafting; *Cr*, creatinine; *PCI*, percutaneous coronary intervention, angioplasty or stent.

TABLE 3. Extent of coronary disease and number of vessels treated*

	CABG (n = 93)	Cypher (n = 93)	P value
Left main	10 (10.8%)	4 (4.3%)	.095
One-vessel disease	3 (3.2%)	5 (5.4%)	
Two-vessel disease	31 (33.3%)	44 (47.3%)	.085
Three-vessel disease	59 (63.4%)	(47.3%)	
Vessels treated			
One-vessel	1 (1.1%)	36 (38.7%)	
Two-vessel	37 (39.8%)	44 (47.3%)	.000
Three or more vessels	55 (59.2%)	13 (14%)	
Right coronary artery revascularization	33 (35.5%)	31 (33.3%)	.758
Circumflex revascularization	88 (94.6%)	37 (39.8%)	.000
Bifurcation lesion	31 (33.3%)	13 (14%)	.002
Total occlusion	28 (30.1%)	6 (6.5%)	.001

CABG, Coronary artery bypass grafting. *Seventy-three (79%) of the 92 patients with multivessel disease were treated with 2 internal thoracic arteries.

Definitions and Data Collection

Patients' data were analyzed according to the Society of Thoracic Surgeons' National Cardiac Surgery database guidelines and definitions. Diabetic patients included patients treated with insulin or oral hypoglycemic agents. Cardiac mortality was defined as death occurring in relation to myocardial infarction (MI), cardiac arrhythmia, out-of-hospital sudden death, or deteriorating congestive heart failure. Undetermined causes of death were regarded as cardiac. Major adverse cardiovascular events (MACEs) were defined as the occurrence of nonfatal MI, the need for repeat revascularization, or cardiac mortality. Target vessel revascularization (TVR) was defined as reintervention in a vessel treated previously with PCI, DES or arterial graft (ITA or radial). Follow-up was obtained by means of telephone questionnaire and from the National Registry database.

Statistical Analysis

Descriptive statistics were performed first, followed by univariate analysis. Continuous variables were compared by using *t* tests, and categoric variables were compared by using χ^2 or Fisher exact tests, as appropriate. Kaplan-Meier curves were used to show freedom from time-related events, and the Cox proportional hazards model was used to identify predictors associated with time-related events. A separate analysis was performed for each time-related event. The time-related events studied were reangina, any reintervention, target vessel reintervention, and MACEs.

Reliability of the Analysis

The bootstrap resampling technique was used to ascertain the reliability of the findings.[13] Patients were drawn at random from the patient pairs with replacement. This was repeated to construct a new data set of 186 observations, which could contain one or more duplicates of patients. This random sampling process was repeated 1000 times to create 1000 differently constituted data sets. We then performed the Cox proportional hazards model on each new dataset and inquired how often each variable in the model would be selected as a risk factor at a *P* value of less than .05. Variables that appeared more than 50% of the time as independent predictors were considered significant predictors.

Results

Demographic and clinical preprocedural and periprocedural data of the 2 groups before matching are displayed in Table 1. After matching, the 2 groups were similar in most preoperative characteristics (Table 2). However, bifurcation lesions and total occlusion were more prevalent in the CABG group (Table 3).

The average number of coronary vessels treated in the CABG and PCI groups was 2.72 ± 0.81 versus 1.75 ± 0.73, respectively ($P < .001$). Despite the fact that the groups had a similar preoperative extent of coronary artery involvement, more patients in the CABG group had revascularization of 3 vessels (59.8%), and more in the Cypher group (38.7% vs 1.1%, $P = .000$) had revascularization of only 1 vessel (Table 3), accounting for incomplete revascularization[14] in 46.2% of the Cypher group compared with 31.2% of the CABG group ($P < .001$). Thirty-day mortality was 1.1% in the CABG group and 0% in the Cypher group ($P = .316$). Early postprocedural unfavorable outcome events in the Cypher group included deterioration of renal function

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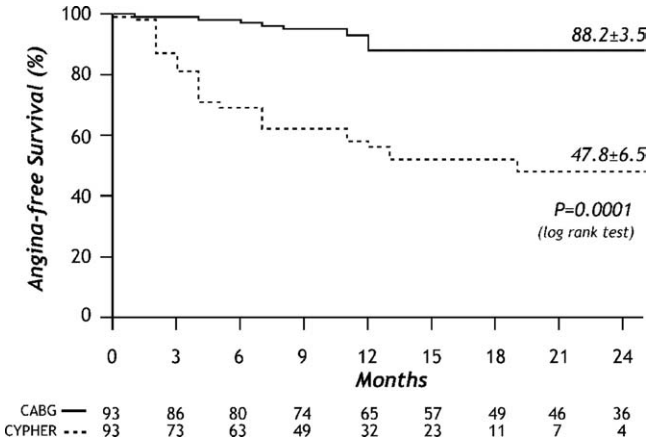

Figure 1. Angina-free survival of the Cypher versus coronary artery bypass grafting *(CABG)* groups (Kaplan-Meier).

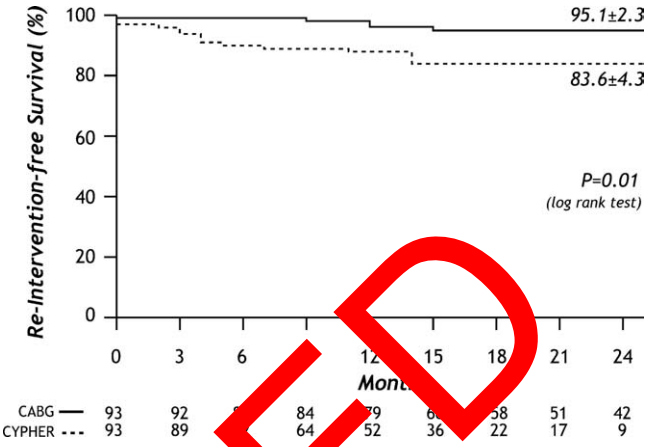

Figure 2. Reinter[illegible]tion-f[illegible]urvival (K[illegible]an-Meier). *CABG*, Coronary artery b[illegible]ass grafting.

(3 [3.4%] patients), leading to chronic dialysis in 1 (1.1%) patient and 2 (2.3%) periprocedural MIs. In the CABG group there were 2 (2.3%) perioperative MIs, 1 (1.1%) stroke, and 1 sternal infection, and 5 (5.7%) patients experienced a temporary deterioration of renal function. Follow-up was 100% complete and ranged between 6 and 42 months (mean, 19 months).

Return of Angina

Angina returned in 43 (46.2%) patients in the Cypher group compared with 12 (12.9%) patients in the CABG group. Two-year angina-free survival (Kaplan-Meier) of patients in the CABG group was 88% compared with 47.8% in the patients in the PCI group ($P = .001$, log-rank test; Figure 1).

Assignment to the Cypher group and preprocedural treatment with insulin were found to be associated with increased risk of early angina return in multivariate analysis (Cox proportional hazards model: assignment to the Cypher group, hazard ratio [HR] = 5.92, 95% confidence interval [CI] = 2.9[illegible]11.[illegible]; insulin treatment, HR = 2.06, 95% CI = 1.06-4.[illegible]2).

In the surgical group multivariate (Cox proportional hazards model) analysis did not identify any specific preoperative (Table 2) or operative (Table 3) characteristics, including the use of the off-pump technique, to be associated with increased risk of reangina. In the Cypher group angina returned in 6 (85.7%) of the 7 patients who underwent PCI because of in-stent restenosis in the LAD. However, in-stent restenosis did not emerge as an independent predictor of reangina in the Cox proportional hazards model.

Reintervention

Thirty-seven patients in the Cypher group and 20 in the CABG group underwent postoperative thallium single photon emission computed tomography, the results of which were found to be positive in 14 (15%) of the Cypher group compared with 2 (2.2%) of the CABG group. Twenty-one of the Cypher group and 9 of the CABG group were referred for coronary angiography.

During the follow-up period, there were 4 (4.3%) reinterventions (2 surgical and 2 PCI) in the CABG group (4.[illegible]%) and 21 (22.6%; 2 surgical and 19 PCI) in the Cypher group. Twelve reinterventions in the Cypher group were to a Cypher-treated vessel, 3 were to a vessel treated previously with a bare-metal stent, 2 were to vessels treated with plain balloon angioplasty, and 4 were in coronary vessels that were not treated in the first PCI.

Two-year reintervention-free survival (Kaplan-Meier) of the patients in the CABG group was 95% compared with 83.6% in the Cypher group ($P = .01$, log-rank test; Figure 2). The Cox proportional hazards model revealed assignment to the Cypher group to be the only independent predictor of reintervention (HR, 3.86; 95% CI, 1.25-11.90).

Separate analysis of risk factors for reintervention in the Cypher group revealed in-stent restenosis in the LAD to be associated with increased risk for reintervention (42.9% vs 11.6% in patients without this risk factor). In-stent restenosis was the only independent predictor for reintervention by using the Cox proportional hazards model (HR, 3.87; 95% CI, 1.07-19.28). None of the preoperative or operative explanatory variables, including the off-pump or on-pump techniques, was associated with increased risk for reintervention in the surgical group.

Target Vessel Reintervention

The purpose of this study was to compare PCI treatment with DESs with surgical treatment with arterial grafts. We therefore defined TVR in the surgical group as a reintervention in a vessel treated previously with an arterial graft (ITA or radial artery).

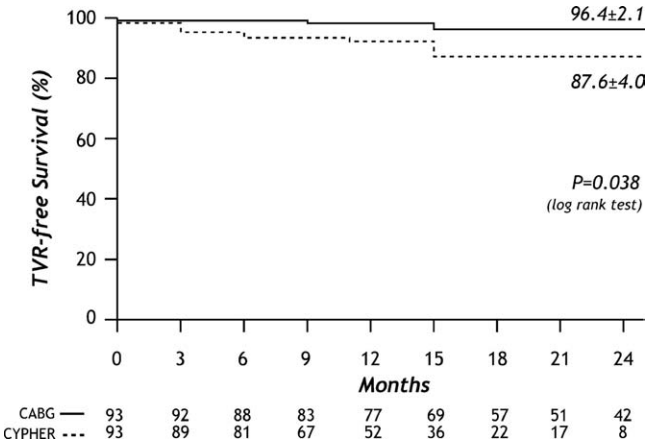

Figure 3. Target vessel revascularization *(TVR)*, Cypher stents versus arterial grafts (Kaplan-Meier).

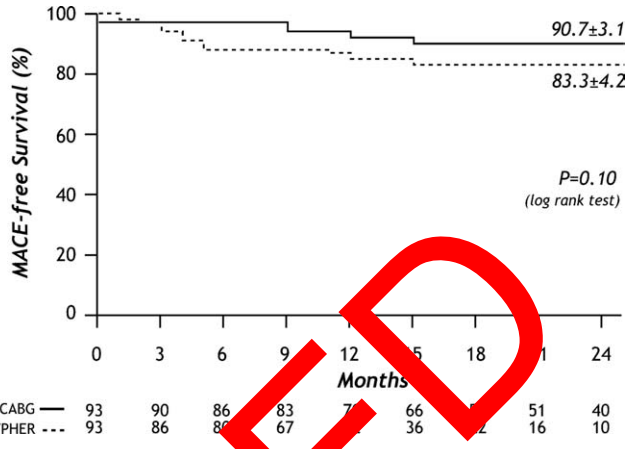

Figure 4. Major adverse cardiovascular event *(MACE)*–free survival (Kaplan-Meier).

There were 12 (12.5%) TVRs in the Cypher group and 3 (3.2%) in the CABG group during the follow-up period. Two-year TVR-free survival (Kaplan-Meier) in the CABG group (95%) was significantly better than that in the Cypher group (87%; $P = .038$, log-rank test; Figure 3).

The Cox proportional hazards model revealed assignment to the Cypher group to be the only independent predictor of TVR (HR, 5.9; 95% CI, 1.35-25.9).

The bootstrap resampling technique showed that assignment to the Cypher group was an independent predictor of TVR in close to 600 of the 1000 analyses performed and was the only significant predictor of TVR, emerging more than 50% of the time.

Major Adverse Cardiovascular Events

During the follow-up period the occurrence of MACEs (cardiac mortality, MI, or reintervention) was higher in the Cypher group (26% [22 events] vs 8.6% [8 events]). There was one late MI in the CABG group, compared with 5 in the Cypher group. However, assignment to the Cypher group was not found to be an independent predictor of MACEs. Moreover, the difference in actuarial occurrence of MACEs between groups did not reach statistical significance ($P = .105$, Figure 4).

The only independent predictor of MACEs using the Cox proportional hazard model was peripheral vascular disease (HR, 3.24; 95% CI, 1.09-9.61).

Congestive heart failure (HR, 6.62; 95% CI, 1.55-20.57) and incomplete revascularization (HR, 4.17; 95% CI, 1-17.54) were independent predictors for MACEs in the surgical group, and in-stent restenosis was the only independent predictor for MACEs in the Cypher group (HR, 6.2; 95% CI, 1.48-26.32).

Discussion

In the present era studies comparing results of CABG and PCI showed similar occurrence of death and MI but higher rates of reintervention and early return of angina in the patients in the PCI group.[15] Comparable long-term survival was demonstrated in most patients, with the exception of diabetics.[6,7,16]

In the Arterial Revascularization Therapy Study similar findings were reported in a subgroup of 207 diabetic patients treated with stents.[8] Survival of diabetic patients treated surgically was better than survival of patients treated with bare-metal stents.

The improved clinical and angiographic outcome reported recently with DESs also included the subset of diabetic patients.[10,11] However, the reported occurrence of MACEs and TVR was still higher in diabetic patients when compared with that seen in nondiabetic patients.

The current report is a retrospective cohort study describing our initial and midterm experience with Cypher stenting in diabetic patients. Results are compared with those of diabetic patients undergoing surgical arterial myocardial revascularization.

Propensity score analysis was used to control for differences in preprocedural patient data. Propensity scores identified 186 patients, 93 for each group, with comparable preprocedural and periprocedural characteristics. After a mean follow-up of 19 months, which is long enough for the development of in-stent restenosis,[17] survival was similar. However, more than 40% of the Cypher-treated patients experienced early return of angina, and only 83% were free of reintervention. Two-year (Kaplan-Meier) angina-free survival and reintervention-free survival of the surgical patients were significantly better (88% and 95% vs 47% and 83%, respectively).

Multivariate analysis with the Cox proportional hazards model defined assignment to the Cypher group to be the only significant predictor of reintervention and TVR and, together with insulin treatment, was also an independent predictor of reangina.

Another important finding is the relatively poor outcome of Cypher stenting in diabetic patients with LAD in-stent restenosis.

The number of patients enrolled is relatively small because of the matching protocol, and important covariates (mainly technical), such as vessel diameter and lesion length, were not included in the analysis. These technical parameters, which are less important in the surgical group, might affect restenosis, reangina, and reintervention in the PCI group. Larger prospective multicenter studies are required to determine their importance in patients selected for PCI or surgical intervention in this evolving era of DESs. Another limitation of this study is the relatively short follow-up period (mean, 19 months). There is growing evidence that DESs might develop delayed thrombosis related to delayed endothelialization, hypersensitivity to the stent polymer, or discontinuation of antiplatelet treatment.[18,19] Longer follow-up that might also reveal statistical significance in MACEs is therefore required.

In conclusion, the midterm clinical outcome of diabetic patients treated surgically is still better than that of patients treated with Cypher stents. However, the reintervention gap[20] between surgical intervention and PCI might be reduced further by more extensive use of DESs in the right coronary artery and circumflex territory and avoiding PCI in diabetic patients with in-stent restenosis in the LAD.

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