

Comparison between Multivessel Stenting with Drug Eluting to the LAD and Bilateral Internal Thoracic Artery Grafting

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ABSTRACT

Background. Reduction of restenosis and reinterventions was reported with drug-eluting stents (Cypher). This study compares results of multivessel Cypher stenting with bilateral internal thoracic artery (BITA) grafting.

Methods. From January 2002 to June 2004, 725 consecutive patients underwent multivessel myocardial revascularization, 95 by 2 or more Cypher stents and 630 by BITA. After matching for age, sex, and extent of coronary artery disease, 2 groups (87 patients each) were used to compare the 2 revascularization modalities.

Results. The 2 groups were similar; however, left main and the use of an intra-aortic balloon pump were more prevalent in the BITA group. The number of coronary vessels treated per patient was higher in the BITA group (2.71 versus 2.24 for BITA and Cypher, respectively; $P = .001$). Mean follow-up was 12 months. Thirty-day mortality was 0 in both groups. There were no late deaths in the BITA group and 2 (2.3%) in the Cypher group (P value was not significant). Angina returned in 29.9% of the Cypher group and 12.6% of the BITA group ($P = .005$). Multivariable Cox analysis revealed percutaneous intervention (PCI) (Cypher group) to be the only independent predictor of angina recurrence (Odds Ratio 2.62, 95% Confidence Interval 1.11-6.17). There were 10 reinterventions (PCI) in the Cypher group compared to 5 in the BITA group. One-year reintervention-free survival (Kaplan-Meier) of the BITA group was 96% compared to 88% in the Cypher group ($P = .015$).

Conclusions. Midterm clinical outcome of surgically treated patients is still better. However, the reintervention gap between surgery and percutaneous interventions was reduced by treating 2 or more coronary vessels with Cypher stents.

INTRODUCTION

The left internal thoracic artery is the graft of choice for myocardial revascularization because of its superior graft patency compared to saphenous vein grafts (SVG) [Barner 1982]. In patients with multivessel disease, surgical revascularization of the left anterior descending with the left internal thoracic artery is the only method proved to improve survival [Loop 1986]. The use of both left and right internal thoracic arteries has shown an additional survival benefit over the use of only 1 internal thoracic artery in combination with vein grafts [Buxton 1998; Lytle 1999].

Previous reports comparing multivessel surgical revascularization with multivessel percutaneous interventions showed that the only advantage of surgery was a lower rate of reinterventions [Serruys 2001; SOS Investigators 2002; Rodriguez 2003; Shirai 2004]. However, percutaneous interventions in these reports included only bare-metal stents, and reinterventions were probably related to a relatively high restenosis rate in the percutaneous intervention group.

Considerable reduction of restenosis and reintervention rates was recently widely reported with the use of drug-eluting stents (DES) [Morice 2003; Moses 2003; Sawhney 2004]. Following the initial reported success of DES for single-vessel disease, more patients with multivessel disease and left anterior descending artery stenosis are currently referred for percutaneous interventions than for coronary artery bypass grafting.

Bilateral skeletonized internal thoracic artery grafting is our preferred method of surgical revascularization of patients with multivessel disease [Lev-Ran 2003]. The purpose of our study, therefore, was to compare medium-term outcome of BITA grafting with multivessel percutaneous interventions incorporating DES.

PATIENTS AND METHODS

Between January 2002 and June 2004, 725 consecutive patients underwent multivessel myocardial revascularization, 630 by BITA and 95 by Cypher stents (Cordis, Miami, FL, USA) for 2 or 3 vessels. Most preoperative characteristics of BITA and Cypher patients were similar. However, BITA patients were older and had an increased prevalence of triple vessel disease (63% versus 41%; $P < .001$).

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Table 1. Extent of Coronary Disease and Number of Vessels Treated*

	Bilateral Internal Thoracic Artery, n = 87 (%)	Cypher, n = 87 (%)	P
Left main	21 (29.1)	3 (3.5)	<.001
3 Vessel disease	45 (51.7)	45 (51.7)	1.0
2 Vessel disease	42 (48.3)	42 (48.3)	1.0
Vessels treated:			
2	38 (43.7)	66 (76)	<.001
3 or more	49 (56.3)	21 (24)	<.001
Revascularization of right coronary artery	27 (31)	47 (54)	.002
Bifurcation lesion	20 (23)	8 (9.2)	.013
Total occlusion	26 (29.9)	10 (11.5)	.003

*Grafts or stents.

To control these differences between surgical and percutaneous intervention patients, we decided to compare results between BITA and Cypher patients after matching for age, sex, and the extent of coronary artery disease. For matching purposes, all vessels with complete occlusion or significant stenosis were regarded as diseased vessels. Patients with left main disease and significant right coronary artery (RCA) stenosis were regarded as 3-vessel disease. On the other hand, left main patients without RCA involvement were regarded as 2-vessel disease (Table 1). Each of the 2 computer-matched groups included 87 patients. Preoperative characteristics of both groups are detailed in Table 2.

During the study period, selection criteria for surgery versus percutaneous interventions were mainly technical. In

principal, there was a preference to refer patients for surgery for the following reasons:

- Comorbid diseases such as diabetes, renal failure, etc.
- In-stent restenosis or thrombosis of a coronary artery.
- Complex type C lesions (calcified coronary arteries, lesion length over 20 mm, twisted arteries, suspicion of a thrombus in an artery).
 - Left main disease.
 - Nonavailability of Cypher, including cases in which the patient was unable to fund a Cypher.
 - Patient's preference.

Acute myocardial infarction (within the previous 48 hours), poor ejection fraction (<25%), calcification or thrombus within the coronary vessel, long lesions (>30 mm), total occlusion, and bifurcation lesions were major criteria for exclusion of patients from the group treated with stents.

During the study period, about 55% of the surgically treated patients were operated on without extracorporeal circulation. In the percutaneous intervention 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-Aventis, New York, NY, USA) (a loading dose of 300 mg the day before the procedure, and 75 mg daily for 3 months thereafter). During the procedure, all patients were intravenously treated with heparin. An intravenous platelet glycoprotein IIb/IIIa inhibitor (Integrilin [eptifibatide; Schering-Plough, Brussels, Belgium] or Aggrastat [tirofiban; Merck, Sharp & Dohme, Haarlem, The Netherlands]) was used in only 8 patients of the percutaneous intervention group. All left anterior descending lesions in the percutaneous intervention

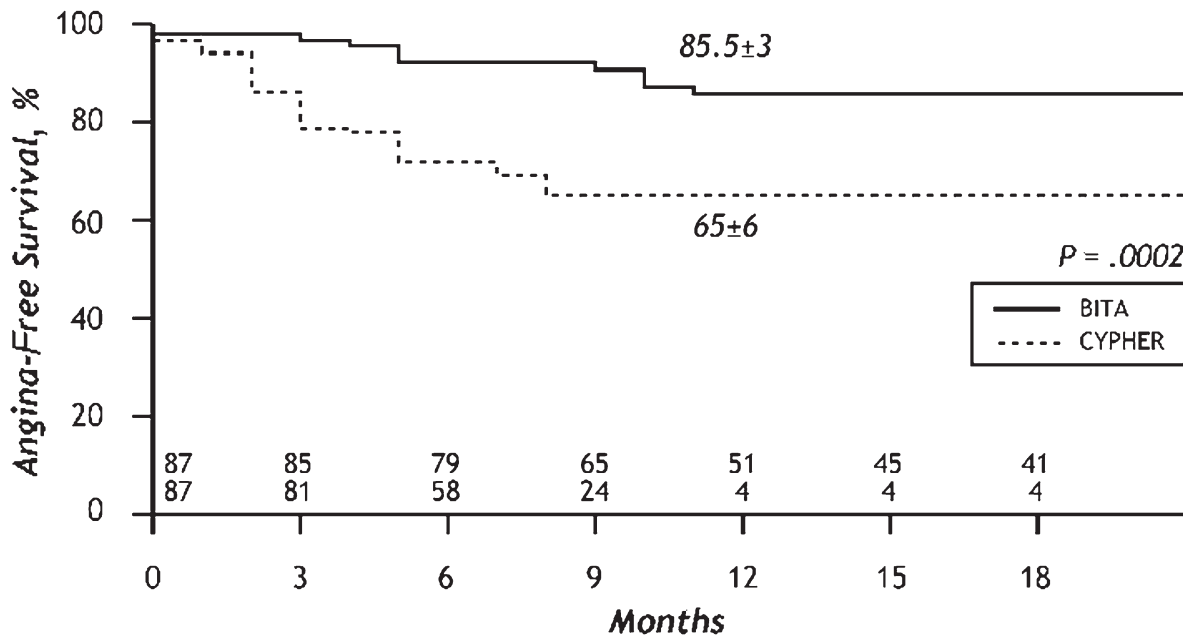


Figure 1. Angina-free survival of Cypher versus bilateral internal thoracic artery groups (Kaplan-Meier).

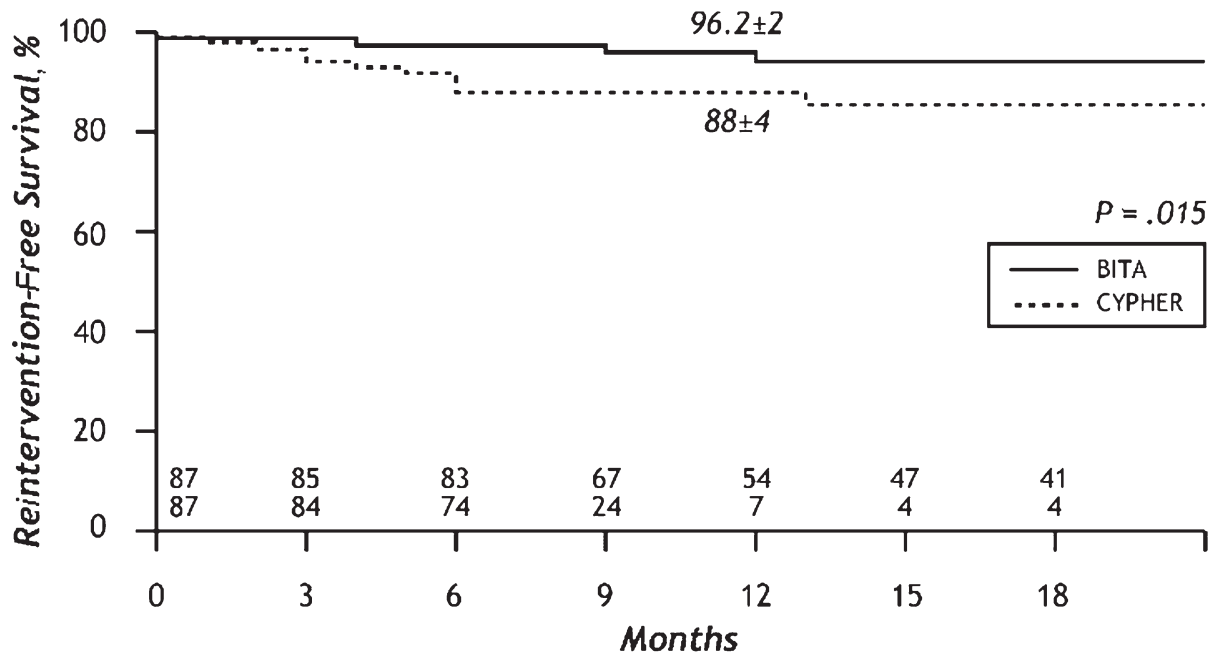


Figure 2. Intervention-free survival of patients undergoing percutaneous interventions with 2 or more Cyphers versus bilateral internal thoracic artery (Kaplan-Meier).

group were treated with DES. In most patients, only 1 Cypher was used for the vessel treated. However, more than 1 Cypher was used if required (long lesion, dissection, bifurcation, etc). Drug-eluting stents, bare-metal stents, or plain balloon angioplasty were used for non-left anterior descending lesions. Bare stents were used in 8 patients with tortuous or calcified coronary vessels. Percutaneous transluminal coronary angioplasty (PTCA) was used in 4 patients with vessels smaller than 2.25 mm, or in patients with focal in-stent restenosis.

In the BITA group, all internal thoracic arteries were dissected as skeletonized vessels and used for left-sided (left anterior descending + circumflex) arterial revascularization. We used the right internal thoracic artery either as an in situ graft or as a free graft attached end-to-side to the left internal thoracic artery (composite T-graft).

Right coronary system (posterior descending artery or posterolateral branch of the right coronary artery) revascularization was performed with SVG in 19 patients, with the radial artery in 4 patients, with the right internal thoracic artery in 2 patients (distal end of the free graft), and with the right gastroepiploic artery in 1 patient.

We treated all BITA patients with a high-dose intravenous infusion of isosorbide dinitrate (Isoket) 4-20 mg/h during the first postoperative 24-48 hours [Gurevitch 1997]. From the second postoperative day, radial artery patients were treated with calcium channel blockers (diltiazem 90-180 mg/day orally).

Statistical Analysis

Data are expressed as mean ± standard deviation or proportions, as appropriate. The χ^2 test and Fisher exact test were used to compare discrete variables. The Cox proportional hazards model was used to evaluate risk factors for

reangina and reintervention. Odds ratio (OR) and 95% confidence interval (CI) were given. Postoperative angina-free survival and reintervention-free survival are expressed by the Kaplan-Meier method, and comparison between groups is made by the log-rank test. All analyses were performed with SPSS 12 software (Chicago, IL, USA).

RESULTS

After matching for age, sex, and extent of coronary artery disease (Table 1), the 2 groups were similar in most preoperative characteristics. However, left main disease (Table 1) and preprocedural use of intra-aortic balloon pump were more prevalent in the BITA group (Table 2). More patients in the BITA group had complete occlusion or a bifurcation lesion (Table 1).

The average number of coronary vessels treated in the BITA and percutaneous intervention groups was 2.7 ± 0.76 versus 2.24 ± 0.43 , respectively ($P = .001$). More patients in the BITA group had revascularization of 3 vessels, and in most of the patients in the Cypher group (76%) only 2 vessels were revascularized (Table 1). Thirty-day mortality was 0% in both groups. In the Cypher group, the only early postprocedural complication was deterioration of renal function, leading to chronic dialysis in 1 patient. In the BITA, there were 3 (3.4%) perioperative myocardial infarctions, 1 (1.1%) stroke, 1 (1.1%) deep sternal wound infection, and 4 (4.6%) revisions for bleeding. Follow-up ranged between 6 and 34 months (mean, 12 months). There were no late deaths in the BITA group and 2 (2.3%) in the Cypher group (P value was not significant). Angina returned in 26 patients (29.9%) of the Cypher group compared to 11 (12.6%) in the BITA group ($P = .005$). Forty-seven of the Cypher group and 52 of

Table 2. Patient Characteristics*

	Bilateral Internal Thoracic Artery, n = 87 (%)	Cypher, n = 87 (%)	P
Age >70	14 (16.1)	14 (16.1)	1.0
Female	6 (6.9)	6 (6.9)	1.0
Diabetes	34 (39.1)	39 (44.8)	.442
Hypertension	52 (59.8)	56 (64.4)	.532
Hyperlipidemia	58 (66.7)	61 (70.1)	.625
Chronic obstructive pulmonary disease	3 (3.4)	4 (4.6)	.700
Chronic renal failure (Cr >1.8)	4 (4.6)	3 (3.4)	.700
Peripheral vascular disease	3 (3.4)	5 (5.7)	.470
Old myocardial infarct	29 (33.3)	28 (32.2)	.872
Acute myocardial infarction (7 days)	7 (8)	8 (9.2)	.787
Ejection fraction <30%	3 (3.4)	0 (0)	.081
Prior intra-aortic balloon pump	4 (4.6)	0 (0)	.043
Prior PCI	26 (29.9)	23 (26.4)	.613
In-stent restenosis (left anterior descending)	4 (4.6)	6 (6.9)	.515
Emergency	5 (5.7)	5 (5.7)	1.000
Repeat operation	0 (0)	2 (2.3)	.155
Congestive heart failure	1 (1.1)	6 (6.9)	.054

*PCI indicates percutaneous coronary intervention angioplasty or stent.

the BITA group underwent postoperative thallium single-photon emission computed tomography scintigraphy, which returned positive results for 13 patients of the Cypher group compared to 5 patients of the BITA group ($P = .046$). During the follow-up period, 15 patients of the Cypher group and 7 patients of the BITA group were referred for coronary angiography. There were 10 (12.5%) reinterventions (percutaneous) in the Cypher group, including 5 to a Cypher-treated vessel, 1 to a vessel previously treated with bare-metal stents, and 5 reinterventions in new coronary lesions. There were 5 (5.7%) reinterventions (percutaneous) in the surgical group ($P = .17$) (Cypher versus BITA).

There was 1 late myocardial infarction in the BITA group. There was 1 late myocardial infarction, and 1 patient had worsening congestive heart failure symptoms in the Cypher group. Two of the 5 reinterventions in the surgical group were in the target vessels, compared to 6 of the 10 reinterventions in the Cypher group: this difference between groups in target vessel reintervention did not reach statistical significance ($P = 0.148$).

One-year angina-free survival (Kaplan-Meier) of the BITA patients was 85.5% compared to 65% in the percutaneous intervention patients ($P = .0002$, log-rank test; Figure 1). After 12 months, BITA patients also had significantly better reintervention-free survival (96.2% versus 88%; $P = .015$, log-rank test; Figure 2). In the BITA group, multivariate (Cox model) and univariate analysis did not identify any specific preoperative (Table 2) or operative (Table 1) characteristics, including the use of off-pump technique and the number of vessels treated, to be associated with increased risk of reangina or reintervention. On the other hand, in the percutaneous intervention group, independent predictors of angina recurrence were 3 vessel disease (OR 5.34, 95% CI 1.75-16.39), total occlusion (OR 5.08, 95% CI 1.55-16.6), and the total

number of Cyphers implanted (OR 2.67, 95% CI 1.17-6.07). Total occlusion (OR 7.99, 95% CI 1.46-43.6) and a higher number of Cypher/patient (OR 5.16, 95% CI 2.08-12.8) were also associated with a higher probability of reintervention.

To determine whether the difference between groups in reangina is affected by the difference in baseline characteristics or the number of vessels treated, we performed multivariate analysis (Cox model), with the patient group (percutaneous interventions or BITA) as an independent variable. We first included the variables to be controlled: the number of vessels treated, left main disease, RCA revascularization, bifurcation lesion, and total occlusion. We then included the treatment group. The Cox model showed that after controlling the above risk factors the only independent predictor of reangina was assignment to the percutaneous intervention group (Cypher group: OR 2.62, 95% CI 1.11-6.17). None of the confounding variables, including patient group, were found to be an independent predictor of reintervention (Cox model).

DISCUSSION

Percutaneous intervention has failed to match the outcome obtained with bypass grafting, primarily because of a greater need for repeat interventions as a result of in-stent restenosis [Serruys 2001; SOS Investigators 2002; Rodriguez 2003; Shirai 2004]. The reported occurrences of restenosis and reinterventions decreased significantly with the introduction of DES [Morice 2003; Moses 2003; Sawhney 2004].

In a recently published study comparing off-pump coronary artery bypass grafting and percutaneous interventions, the initial outcome of percutaneous intervention treatment for multivessel coronary artery disease incorporating 1 Cypher to the left anterior descending artery was satisfactory. However, during a mean follow-up of 18 months, angina

recurrence was significantly higher than the rate of reangina in the matched group of surgically treated patients (31% versus 11%; $P = .001$). Patients in the percutaneous intervention group also required significantly more reinterventions (9.5% versus 2%; $P = .05$) [Herz 2005].

In the above study, most of the percutaneous intervention patients were treated with only 1 Cypher to the left anterior descending artery, and other vessels were treated with bare-metal stents or plain balloon angioplasty. Only 2 of the reinterventions were to a Cypher-treated vessel, and the authors speculated that the use of DES to other vessels with the aim of more complete revascularization with DES might further reduce reangina and reintervention rates in the percutaneous intervention group.

All patients in the current study had multivessel coronary artery disease. All patients in the surgical group underwent revascularization incorporating 2 internal thoracic arteries, and all patients in the percutaneous intervention group had 2 or more of their vessels treated with Cyphers, with the aim of more complete revascularization with DES. Despite significantly higher angina recurrence in the percutaneous intervention group, after a mean follow-up period of 1 year, the reintervention gap between the 2 revascularization modalities was diminished, and the difference in prevalence of reintervention procedures and target vessel reintervention between groups did not reach statistical significance. Moreover, despite better actuarial reintervention-free survival in the BITA group (96% versus 88%; $P = .015$, log-rank test), assignment to the Cypher group was not found to be an independent predictor of reintervention (Cox model).

The separate Cox analysis performed in the percutaneous intervention group showed that many of the preoperative variables regarded in the past to be relative contraindications for percutaneous intervention, with bare-metal stent (diabetes, left main, prior PTCA with in-stent restenosis, bifurcation lesion, etc), were not found in this study to be associated with increased risk of reintervention when using DES [Olivari 2003; Tanabe 2004; Colombo 2005; Silber 2005]. On the other hand, treatment of vessels with total occlusion and treatment of vessels with more than 1 Cypher/vessel (long lesions, dissection, etc) was still associated with increased rate of reintervention. Avoiding treatment of vessels with these technical difficulties (which are known to be associated with increased restenosis rate) might further improve results of percutaneous interventions with DES.

Study Limitations

This study reflects the current treatment practice with the 2 revascularization techniques. The groups were matched for age, sex, and extent of coronary artery disease. However, other 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, may affect restenosis, reangina, and reintervention in the percutaneous intervention group.

Surgical patients usually show more unfavorable coronary morphology (longer lesions, smaller vessel diameter, total occlusion, bifurcation; Table 1), and this fact enhances our

findings of better angina-free and reintervention-free survival in the surgical cohort. Larger prospective multicenter studies are required to determine the importance of these morphologic coronary parameters in patients selected for percutaneous interventions or surgery in this evolving era of DES.

The current study is a retrospective cohort study. The surgical group in our study is easier than and not typical of the kind of patients referred nowadays for surgery. However, the surgical patients' baseline characteristics are similar to those of the percutaneous intervention group, and this was as dictated by the matching protocol. The study findings were strongly supported by the multivariate Cox analysis that was performed to control the major differences between groups (more left main, total occlusion, bifurcation lesions, number of vessels treated in the BITA group, and more cases with RCA revascularization in the Cypher group).

Another limitation of this study is the relatively short follow-up period (mean, 12 months). There is growing evidence that DES may develop delayed thrombosis or restenosis related to delayed endothelialization, hypersensitivity to the stent polymer, or discontinuation of antiplatelet treatment [McFadden 2004; Vimani 2004]. On the other hand, the advantage of arterial revascularization, particularly BITA grafting, has the better patency rate in the long term. Longer follow-up is therefore required.

In conclusion, the reintervention gap [SOS Investigators 2002] between surgery and percutaneous interventions was reduced by treatment of 2 or more coronary vessels with Cypher stents. This could be reduced further by better patient selection based on known angiographic criteria for each of the 2 revascularization modalities.

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