Initial Impact of Drug-Eluting Stents on Coronary Artery Bypass Grafting

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SUMMARY

The impact of drug-eluting stents (DES) on the characteristics and operative results of patients referred for coronary artery bypass grafting (CABG) was studied. We reviewed data from isolated CABG patients 24 months before (group A, $n = 134$) and 24 months after (group B, $n = 98$) the introduction of DES for clinical use at Teikyo University Hospital in Tokyo. Group B patients were significantly older than those of group A (66 ± 9 versus 69 ± 9 years old). The number of diseased vessels was significantly larger in group B (2.5 ± 0.6 versus 2.7 ± 0.5) and left main trunk disease decreased in group B (27% versus 17%). Preoperative IABP support was more frequent in group B (9% versus 17%) and beating heart surgery was significantly more frequent in group B (26% versus 59%). The number of grafts was similar in the 2 groups (3.2 ± 1.4 versus 3.0 ± 1.1). The operative mortality rates were 0.7% and 4.1% in group A and B, respectively. Incomplete revascularization followed by postoperative percutaneous coronary intervention (PCI) was performed in 11% and 12%, respectively, and all the patients survived surgery. The operative mortality rates for arrested heart and beating heart surgery were 2% and 2%, respectively. In conclusion, after the introduction of DES, more clinically ill patients were referred to CABG. Combination therapy consisting of CABG and PCI (Hybrid) may be a treatment of choice in critical patients. (Int Heart J 2007; 48: 455-461)

Key words: Drug-eluting stent, Cypher, Coronary artery bypass grafting, Percutaneous coronary intervention

DRUG-ELUTING stent (DES) implantation has recently been demonstrated to markedly reduce the incidence of restenosis and repeat revascularization in selected patients.¹⁻³⁾

The introduction of DES to clinical use has had an impact not only on the number of patients for coronary artery bypass grafting (CABG), but also on treatment strategies for coronary artery disease (CAD). With respect to the characteristics of patients referred for surgery, shifts in the CABG group towards more impaired LV function and more 3-vessel disease were observed.⁴⁾

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Event-free survival was still better for patients treated with CABG than patients treated with percutaneous coronary intervention (PCI), although patients treated with drug-eluting stents had a 25% relative risk reduction in the rates of death, myocardial infarction, and target lesion revascularization compared with patients treated with bare-metal stents.⁵⁾ The most appropriate treatment remains a matter of debate for patients in general, and especially in patients with severe ischemia. The impact of DES on PCI using DES on the overall clinical management of revascularization remains unknown. The aim of this study was to investigate the impact of DES in clinical practice. We evaluated CABG patients in the 24 months preceding the introduction of DES in our hospital and also during the first 24 months of DES use.

METHODS

The use of drug-eluting stents (Cypher; Johnson & Johnson-Cordis unit, Cordis Europe NV, Roden, The Netherlands) was commenced in earnest in September 2004 at Teikyo University Hospital in Tokyo. We have compared the data for CABG patients operated on beginning 24 months before full implementation of DES use (September 2002 to August 2004: group A) with the data from those up until 24 months after full implementation of DES (September 2004 to August 2006: group B). The number of CABG patients was 134 in group A and 98 in group B. The male to female ratios were 103/31 in group A and 69/29 in group B. Complete revascularization was performed in most of the cases, however, incomplete revascularization followed by PCI (Hybrid therapy) was selected in particularly critical patients. Drug-eluting stents were used in 15 out of 800 (1.8%) PCI patients during the pre-DES period and in 529 out of 907 (58.3%) patients in the DES period.

Statistical analysis was performed using SAS version 5.0 software (SAS Institute, Inc, Cary, NC). Continuous data are expressed as the mean $\pm$ standard deviation (SD). Student's *t*-test and the chi-square test were used for statistical analysis and a *P* value of less than 0.05 was considered to be significant.

RESULTS

The number of CABG patients was reduced by 27% (from 134 to 98) in the DES period. The mean age of group B was 69 ± 9 years old, which was significantly ($P < 0.05$) older than group A (66 ± 9 years). The mean cardiothoracic rate values were similar in both groups. There were no differences between the groups in the preoperative prevalence rates of risk factors such as hypertension, hyperlipidemia, diabetes mellitus, or smoking. There were no differences between the

Table I. Patient Demographics

	Group A	Group B
Period	Sept. 2002 to August 2004	Sept. 2004 to August 2006
Number of patients	134	98
Age (years)	66 ± 9*	69 ± 9*
Male/female	103/31	69/29
Cardiothoracic rate	52 ± 6	52 ± 5
Risk factors/complications		
Hypertension	70%	75%
Hyperlipidemia	46%	57%
Diabetes mellitus	43%	49%
Current smoker	45%	45%
Renal insufficiency	27%	33%
Cerebral disease	20%	13%
Liver disease	8%	5%

*: $P < 0.05$ versus group A.

Table II. Preoperative Coronary Artery Disease

	Group A ($n = 134$)	Group B ($n = 98$)
Preoperative condition		
ACS	52%	61%
Stable angina	48%	39%
History of PCI	31%	28%
Number of diseased vessels	2.5 ± 0.6	2.7 ± 0.5*
Single vessel	8%	2%
Double vessel	38%	31%
Triple vessel	54%	67%
LMT disease	27%	17%
Preoperative IABP	9%	17%

* : $P < 0.05$ versus group A.

ACS indicates acute coronary syndrome; PCI, percutaneous coronary artery intervention; LMT, left main trunk; and IABP: intra-aortic balloon pumping.

groups in the preoperative prevalence rates of complications such as renal insufficiency, cerebral disease, or liver disease (Table I). Preoperatively, the conditions of the patients could be described as acute coronary syndrome in 52% of the group A patients and 61% of the group B patients. Thirty-one percent of the group A patients and 28% of the group B patients had a past history of PCI. The number of diseased vessels was significantly larger in group B than in group A (2.7 ± 0.5 versus 2.5 ± 0.6). In group B, the percentage of patients with triple ves-

sel disease increased slightly (54% versus 67%, NS) and the prevalence of left main trunk disease decreased slightly (27% versus 17%, NS). The incidence of preoperative intra-aortic balloon pumping (IABP) support was slightly higher in group B (9% versus 17%, NS) (Table II).

Emergency or urgent operations were performed in 22% of group A patients and 28% of group B patients. Beating heart surgery was significantly more frequent in group B (26% versus 59%, $P < 0.01$). The number of grafts was similar in both groups (3.2 ± 1.4 versus 3.0 ± 1.1 , NS). Complete revascularization was performed in 119 (89%) group A patients and in 87 (88%) group B patients. Incomplete revascularization followed by PCI (Hybrid therapy) was performed in 15 (11%) group A patients and in 12 (12%) group B patients. The surgical mortality rate was 0.7% in group A and 4.1% in group B (NS). The mortality rate after emergency or urgent surgery was 3.4% in group A and 11% in group B, and 0% in group A and 3.6% in group B after beating heart surgery. The mortality rate after arrested heart surgery was 1% and 4.8% in groups A and B, respectively, and 0.8% and 4.6% after complete revascularization, respectively ($P < 0.1$). All Hybrid therapy patients survived in both groups (Table III).

Table III. Operative Procedure and Results

	Group A (<i>n</i> = 134)	Group B (<i>n</i> = 98)
Timing of operation		
Emergency/urgent	22%	28%
Scheduled	78%	72%
Operation		
Heart beating	26%	59%**
Arrested	74%	41%
Number of grafts	3.2 ± 1.4	3.0 ± 1.1
Revascularization		
Complete	119 (89%)	87 (88%)
Incomplete (Hybrid)	15 (11%)	12 (12%)
Operative mortality		
Total	1 (0.7%)	4 (4.1%)
Emergency/urgent	1/29 (3.4%)	3/27 (11%)
Scheduled	0/105	1/71 (1.4%)
Beating	0/35	2/56 (3.6%)
Arrested	1/99 (1%)	2/42 (4.8%)
CABG only	1/119 (0.8%)	4/87 (4.6%)
Hybrid therapy	0	0

** $P < 0.01$ versus group A.

Hybrid therapy: combination therapy consisting of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI).

DISCUSSION

Drug-eluting stents have had a great impact on the treatment of coronary artery disease. According to some publications,⁶⁾ recent and ongoing progress will make bypass surgery largely obsolete within the next several years. The number of CABG decreased after the availability of DES, with the actual reduction volume ranging from 14% to 21%.^{7,8)} In our study, the number of CABG patients was reduced by 27% after the full implementation of DES. According to an angiographic evaluation by Powell and colleagues,⁹⁾ up to 46% of current CABG patients may ultimately undergo conversion to DES treatment. There were no significant changes in the preoperative prevalence of risk factors and complications in our patients referred for CABG. According to the report by Cohn, *et al*,¹⁰⁾ however, CABG has proven effective for CAD patients with diabetes or chronic total occlusion, and for these cases, surgery remains an important treatment option.

The most critical factors in the selection of DES treatment are the location and the number of diseased coronary vessels. Two major issues in the selection of treatments are left main trunk disease (LMT) and multivessel disease. These two diseases have been the main targets of CABG for some time. Chieffo and coworkers¹¹⁾ reported that there was no difference in the degree of protection against death, stroke, myocardial infarction, and revascularization between PCI with DES and CABG for LMCA disease. However, Kappetein and colleagues¹²⁾ reported that in patients with multivessel or left main disease, CABG remains the dominant revascularization strategy. According to controlled trials of percutaneous intervention versus coronary bypass, a meta-analysis has shown a significant survival advantage for CABG, and the current therapy for multivessel disease patients has resulted in a relative excess mortality of as much as 46% in patients with initial stenting compared with patients with initial CABG.¹³⁾ The advantages of PCI are its less invasiveness and safety, however, coronary perforation during PCI is associated with significant morbidity and mortality.¹⁴⁾ Thus, the appropriate target selection of PCI lesions is still indispensable in the DES era.

Off-pump coronary bypass grafting is one of the less invasive surgical treatments available when undertaking DES intervention. In left anterior descending artery disease including multivessel disease, the mid-term clinical outcome of OPCAB in patients with CAD, including multivessel disease, was better than that for PCIs with only one DES used in patients with similar extents of CAD.¹⁵⁾ Angina returned in 31% of patients in the DES group and in 11.2% of the patients in the OPCAB group ($P = 0.001$). In our series, the operative results of Hybrid treatment were excellent with no mortality. Vassiliades, *et al*¹⁶⁾ recommended an integrated coronary revascularization strategy that combines minimally invasive

left internal thoracic artery to left anterior descending coronary artery anastomosis with DES implantation to non-left anterior descending coronary artery lesions. Hybrid revascularization is currently reserved for particularly high-risk patients or those with favorable anatomic variants, largely because of the emergence of off-pump coronary artery bypass grafting, which permits more complete multi-vessel revascularization with low morbidity in high-risk groups.¹⁷⁾

According to recent reports, significant problems concerning DES treatment have become apparent. The major concern is late angiographic stent thrombosis (LAST),^{18,19)} and the relation of LAST and antiplatelet therapy discontinuation has been discussed.²⁰⁾ In addition, the occurrence of coronary artery aneurysm has been reported.²¹⁾ DES is definitely an effective instrument for CAD treatment, however, it is not a magic wand. Further discussions on the biological mechanisms and clinical implications of DES are necessary.

In conclusion, after the introduction of DES, more clinically ill patients were referred to CABG. Combination therapy consisting of CABG and PCI (Hybrid) should be a treatment of choice in critically ill patients. Defining the role of DES versus CABG for coronary revascularization will require more understanding of the long-term outcomes of DES compared with CABG.

REFERENCES

1. Sousa JE, Costa MA, Abizaid AC, *et al.* Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation* 2001; 104: 2007-11.
2. Morice MC, Serruys PW, Sousa JE, *et al.* A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; 346: 1773-80.
3. Ozcan T, Cin VG, Yurtas M, *et al.* Angiographic and clinical outcome following sirolimus-eluting stent (cypher) implantation. *Int Heart J* 2007; 48: 11-23.
4. van Domburg RT, Lemos PA, Takkenberg JJ, *et al.* The impact of the introduction of drug-eluting stents on the clinical practice of surgical and percutaneous treatment of coronary artery disease. *Eur Heart J* 2005; 26: 675-81.
5. Palmerini T, Marzocchi A, Marrozzini C, *et al.* Comparison between coronary angioplasty and coronary artery bypass surgery for the treatment of unprotected left main coronary artery stenosis (the Bologna Registry). *Am J Cardiol* 2006; 98: 54-9.
6. Baim DS. New devices for percutaneous coronary intervention are rapidly making bypass surgery obsolete. *Curr Opin Cardiol* 2004; 19: 593-7.
7. Liddicoat JR, De La Torre R, Ho KK, *et al.* Initial impact of drug-eluting stents on coronary artery bypass graft surgery. *Ann Thorac Surg* 2006; 81: 1239-42.
8. Ferreira AC, Peter AA, Salerno TA, Bolooki H, de Marchena E. Clinical impact of drug-eluting stents in changing referral practices for coronary surgical revascularization in a tertiary care center. *Ann Thorac Surg* 2003; 75: 485-9.
9. Powell BD, Rihal CS, Bell MR, Zehr KJ, Holmes DR Jr. Anticipated impact of drug-eluting stents on referral patterns for coronary artery bypass graft surgery: a population-based angiographic analysis. *Mayo Clin Proc* 2004; 79: 769-72.
10. Cohn WE. Surgical coronary revascularization remains relevant in the era of stents. *Curr Opin Cardiol* 2004; 19: 589-92. (Review)

11. Chieffo A, Morici N, Maisano F, *et al.* Percutaneous treatment with drug-eluting stent implantation versus bypass surgery for unprotected left main stenosis: a single-center experience. *Circulation* 2006; 113: 2542-7.
12. Kappetein AP, Dawkins KD, Mohr FW, *et al.* Current percutaneous coronary intervention and coronary artery bypass grafting practices for three-vessel and left main coronary artery disease. Insights from the SYNTAX run-in phase. *Eur J Cardiothorac Surg* 2006; 29: 486-91.
13. Guyton RA. Coronary artery bypass is superior to drug-eluting stents in multivessel coronary artery disease. *Ann Thorac Surg* 2006; 81: 1949-57. (Review)
14. Shirakabe A, Takano H, Nakamura S, *et al.* Coronary perforation during percutaneous coronary intervention. *Int Heart J* 2007; 48: 1-9.
15. Moshkovitz Y, Mohr R, Braunstein R, *et al.* Revascularization of left anterior descending coronary artery in patients with single and multivessel disease: comparison between off-pump internal thoracic artery and drug-eluting stent. *Chest* 2005; 128: 804-9.
16. Vassiliades TA Jr, Douglas JS, Morris DC, *et al.* Integrated coronary revascularization with drug-eluting stents: immediate and seven-month outcome. *J Thorac Cardiovasc Surg* 2006; 131: 956-62.
17. Murphy GJ, Bryan AJ, Angelini GD. Hybrid coronary revascularization in the era of drug-eluting stents. *Ann Thorac Surg* 2004; 78: 1861-7. (Review)
18. Daemen J, Wenaweser P, Tsuchida K, *et al.* Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 2007; 369: 667-78.
19. Luscher TF, Steffel J, Eberli FR, *et al.* Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. *Circulation* 2007; 115: 1051-8. (Review)
20. Yang J, Wang N, Zhang X, *et al.* Late angiographic stent thrombosis in a drug-eluting stent that occurred 20 months after premature discontinuation of clopidogrel administration. *Int Heart J* 2006; 47: 707-13.
21. Luthra S, Tatoulis J, Warren RJ. Drug-eluting stent-induced left anterior descending coronary artery aneurysm: repair by pericardial patch - where are we headed? *Ann Thorac Surg* 2007; 83: 1530-2.