ELSEVIER

International Journal of Cardiology 123 (2007) 34–42

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Comparison of bypass surgery with drug-eluting stents for diabetic patients with multivessel disease ☆

Michael S. Lee [a,*], Faizi Jamal [b], Gautam Kedia [b], Gilbert Chang [b], Nikhil Kapoor [b], James Forrester [b], Lawrence Czer [b], Raymond Zimmer [a], Michele DeRobertis [b], Alfredo Trento [b], Raj R. Makkar [b]

[a] *University of California, Los Angeles School of Medicine, Los Angeles, California, United States*
[b] *Cedars-Sinai Medical Center, Los Angeles, California, United States*

Received 30 June 2006; received in revised form 21 October 2006; accepted 11 November 2006
Available online 12 February 2007

Abstract

Background: This retrospective study of prospectively collected data compared coronary artery bypass graft (CABG) surgery to drug-eluting stenting (DES) in diabetic patients with multivessel coronary artery disease (CAD). Prior randomized trials and clinical studies have suggested that CABG may be the preferred revascularization strategy in diabetic patients with multivessel CAD. Data are limited regarding the impact of DES vs. CABG on clinical outcomes.
Methods: We included 205 consecutive diabetic patients who underwent either CABG ($n=103$) or DES ($n=102$). The primary clinical end points were freedom from major adverse cardiac events (MACE) at 30 days and 1 year.
Results: Baseline characteristics were similar between both groups. At 1 year, the mortality rate was similar in the CABG and DES group (8% vs. 10%, $p=0.6$) but the MACE rate was lower in the CABG group (12% vs. 27%, $p=0.006$) due to less repeat revascularization with CABG (3% vs. 20%, $p<0.001$). Stroke occurred only in the CABG group (4% vs. 0%, $p=0.04$). Angiographically-documented stent thrombosis after DES occurred in 3%. Presentation with acute myocardial infarction (hazard ratio [HR], 2.26, 95% CI, 1.13 to 4.55) and DES (HR, 2.4, 95% CI, 1.23 to 4.77) were positive independent predictors, whereas therapy with a statin was a negative independent predictor of MACE (HR, 0.40, 95% CI, 0.21 to 0.76).
Conclusions: Bypass surgery was associated with less MACE primarily due to the higher repeat revascularization rate with DES and is therefore superior to DES despite more extensive CAD in CABG patients.

Keywords: Drug-eluting stent; Diabetes mellitus; Coronary artery bypass surgery; Multivessel disease

1. Introduction

Diabetic patients who undergo either coronary artery bypass graft (CABG) surgery [1, 2] or percutaneous coronary intervention (PCI) [3, 4] have higher perioperative mortality rates compared to non-diabetic patients. While less invasive, PCI may not provide complete revascularization. Although the Emory Angioplasty versus Surgery Trial (EAST) demonstrated no significant difference in survival between surgical and percutaneous revascularization, the Bypass Angioplasty Revascularization Investigation (BARI) demonstrated a clear survival advantage at 5 years in the diabetic patients randomized to CABG and at 7 years in the surgical revascularization group [5–8]. The Arterial Revascularization Therapies Study (ARTS) and other smaller trials have reported that diabetic patients treated with bare metal stents had a greater frequency and severity of in-stent restenosis compared with non-diabetic patients [9–14]. Combined

☆ No financial support was received.
* Corresponding author. Tel.: +1 310 825 7129; fax: +1 310 794 2116.
E-mail address: michaelslee@pol.net (M.S. Lee).

0167-5273/$ - see front matter © 2007 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2006.11.103

endpoint analysis also found that CABG provided superior outcomes in diabetic patients [9, 14]. These results have led to the suggestion that CABG is the preferred mode of revascularization in diabetic patients with multivessel coronary artery disease (CAD). However, these trials used either angioplasty alone or bare metal stents. With the widespread use of DES and adjunctive pharmacotherapy, comparison of this newer strategy with CABG in diabetic patients with multivessel CAD is indicated particularly since subgroup analysis of recent trials suggests that PCI with sirolimus-eluting stents (Cypher, Cordis, Johnson and Johnson Corp, Miami, Florida) and paclitaxel-eluting stents (Taxus, Boston Scientific Corp., Natick, Massachusetts) may decrease the in-stent restenosis rate when compared to bare metal stents in diabetic patients [15–17].

While the value of randomized trials is unquestioned, an important limitation is that they eliminate the majority of patients treated and the decision process among physicians that typically occurs in clinical practice. Thus, our analysis is the first report to compare the safety and efficacy of DES to CABG in diabetic patients with multivessel CAD, where patient distribution was determined by clinical judgment among cardiologists and cardiac surgeons.

2. Methods

2.1. Study population

Since April 2003, 103 diabetic patients with multivessel CAD underwent CABG without concomitant valve surgery, and 102 diabetic patients with multivessel CAD underwent DES at Cedars-Sinai Medical Center. Patient demographic, medical, and procedural data were recorded in a computerized cardiovascular database. The assignment to CABG or DES was made on the basis of clinical judgment among cardiologists and cardiac surgeons. The assignment to treatment involved balancing a spectrum of factors, which were weighted differently in each individual patient. Among these factors were extent of CAD, the feasibility of achieving complete revascularization, age, prior surgery, current cardiac function, co-morbidities, specific details of coronary anatomy, general health, pulmonary function, current smoking history, risk of anticoagulation, and likelihood of compliance to continuing clopidogrel therapy. In general, patients with focal disease that was amenable to percutaneous revascularization underwent DES whereas patients with long diffuse disease where complete revascularization could not be accomplished with DES were referred for CABG.

The primary clinical end points were freedom from major adverse cardiac (death, myocardial infarction, and repeat revascularization) events (MACE) at 30 days and 1 year. The secondary clinical end points were procedure-related complications including stroke, post-procedural bleeding, pneumonia, permanent pacemaker implantation, thoracocentesis, renal failure requiring hemodialysis, atrial fibrillation, and ventricular tachycardia/ventricular fibrillation. We included patients with myocardial infarction, including those with myocardial infarction, left ventricular dysfunction, renal or hepatic disease, and patients who required non-cardiac surgery. Multivessel PCI was defined as PCI in two or more major epicardial coronary arteries (right, left anterior descending, left circumflex arteries or left main) or one major artery and a branch originating from another major epicardial artery supplying different myocardial regions. Diabetic patients were further classified as non-insulin-dependent, which included patients treated with diet and oral hypoglycemic agents but no insulin, and insulin-dependent, which included patients treated with insulin regardless of other therapies. This study was approved by the Cedars-Sinai Medical Center Institutional Review Board.

2.2 DES

The choice of a sirolimus-eluting stent or paclitaxel-eluting stent and antithrombotic agent was made by the operator. Stent deployment was routinely performed using an initial inflation of 12–16 atm. Intravascular ultrasound was used at the discretion of the operator. Glycoprotein IIb/IIIa antagonists and intra-aortic balloon pump were used if clinically indicated. All patients received aspirin (325 mg/day) indefinitely and a loading dose of 300 mg of clopidogrel. Clopidogrel was continued for at least 3 months. Cardiac enzymes were not routinely measured unless there was a clinical suspicion of ischemia, and therefore was not a designated outcome of the study.

2.3 CABG

Complete revascularization, using a left internal mammary artery for revascularization of the left anterior descending coronary artery, was attempted whenever possible. Standard operative techniques for on-pump CABG for patients were used, including standard cardiopulmonary bypass, moderate hypothermia, and cold potassium cardioplegia (crystalloid or blood) for myocardial protection. Off-pump CABG was performed using mechanical stabilization (Octopus I and II; Medtronic, Inc, Minneapolis, Minnesota) and intravascular shunting of the target coronary arteries. Whenever feasible, Y or T grafts were used to avoid partial aortic clamping when performing proximal anastomoses. Cardiac enzymes were not measured routinely unless there was a clinical suspicion of ischemia.

2.4. Definitions

A myocardial infarction was defined as ischemic symptoms associated with cardiac enzyme elevation ≥ 3 times the upper limit of the normal value. A stroke was defined as an acute onset of a neurologic deficit that persisted for at least 24 h. Each stroke was diagnosed by a neurologist. Lesions were defined according to the American College of Cardiology/American Heart Association classification [18]. Stent thrombosis was defined as an acute coronary syndrome

with angiographically-documented partial or complete occlusion in a previously successfully stented artery or occurrence of sudden cardiac death. Subacute stent thrombosis was defined as thrombosis occurring after the end of DES through 30 days. Late stent thrombosis was defined as thrombosis occurring more than 30 days after DES.

The Parsonnet score was used to stratify the risk of death at 30 days in patients undergoing cardiac surgery [19,20]. A Parsonnet score >15 identified patients at high-risk for surgical mortality.

2.5. Quantitative angiographic analysis

Quantitative coronary analysis was performed on all cineangiograms off-line in a core laboratory using the QCA-CMS (CMS-MEDIS Medical Imaging Systems, Nuenen, The Netherlands) by a single experienced observer without any prior knowledge of clinical outcomes. Paired cine frames of 2 orthogonal views in the end-diastolic frames showing the stenosis in its most severe projection were selected. The lesion length in total occlusions was assessed from collateral filling whenever possible and from the lesion length visible after first balloon dilatation.

2.6. Statistical analysis

Continuous variables were presented as mean±SD and were compared in the CABG and DES groups by Student's *t* test or the Wilcoxon rank sum test (Wilcoxon when the distributions showed evidence of non-normality). The Fisher exact test was used to determine the significance of group differences in categorical variables. For MACE, the event time was the number of days from the initial procedure to the first event. Time to death and time to MACE were censored at 365 days. Event times for myocardial infarction, repeat revascularization, and cerebrovascular events were censored at the day of death or at 365 days (as appropriate). Survival curves were generated by the Kaplan–Meier method, and group differences were assessed by the log-rank test. Multivariable Cox proportional hazards models were created with the use of baseline clinical and angiographic characteristics and procedure-related variables in order to identify independent predictors of death and MACE. All statistical tests were 2-tailed, and a significance level of 0.05 was used throughout. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina) and SPSS version 10 (SPSS Inc., Chicago, Illinois).

Table 1
Baseline Clinical Characteristics

	CABG	DES	*p*-value
	n=103	*n*=102	
Age (yrs±SD)	68±10	67±13	0.55
Male (%)	65	66	>0.9
Diabetes mellitus			0.65
Insulin-dependent (%)	25	22	
Non-insulin-dependent (%)	78	80	
Hypertension (%)	90	89	>0.9
Hypercholesterolemia (%)	74	74	>0.9
Current smoking (%)	15	16	>0.9
Chronic renal insufficiency (Cr≥1.5 mg/dL)	17	20	0.57
Previous stroke (%)	10	10	>0.9
Clinical presentation			0.10
Stable angina (%)	48	42	
Unstable angina (%)	36	41	
Myocardial infarction (%)	17	17	
Ejection fraction (%±SD)	52±10	51±15	0.64
Previous myocardial infarction (%)	17	23	0.57
Parsonnet score (mean±SD)	15.7±8.8	16.8±10.7	0.29
Patients with Parsonnet score >15(%)	45	47	0.73
Patients with bifurcation lesions (%)	41	34	0.31
Patients with CTO (%)	14	9	0.28

CABG=coronary artery bypass graft surgery; Cr=creatinine; CTO=chronic total occlusion; PCI=percutaneous coronary intervention; SD=standard deviation.

Table 2
Baseline angiographic characteristics

	CABG	DES	*p*-value
Vessel territory with stenosis (% of patients)			
LM	29.1	9.8	<0.001
LAD	92.2	71.6	<0.001
LCX	79.6	65.7	0.03
RCA	75.7	60.8	0.03
ACC/AHA lesion type C[a]	91/239 (38.1%)	79/295 (26.8%)	0.007
Target vessel diameter			
LM (mm)	3.94±0.67	3.90±0.67	0.53
LAD (mm)	2.92±0.68	3.01±0.77	0.19
LCX (mm)	2.54±0.60	2.90±0.81	0.005
RCA (mm)	2.87±0.70	3.15±0.86	0.014
Lesion length			
LM (mm)	8.98±3.26	9.73±3.16	0.53
LAD (mm)	19.19±11.25	15.52±7.25	0.004
LCX (mm)	13.75±7.72	14.12±5.95	0.83
RCA (mm)	23.80±12.54	15.27±6.66	<0.001

LAD=left anterior descending artery; LCX=left circumflex artery; LM=left main coronary artery; RCA=right coronary artery.
[a] A type C lesion was defined according to the criteria of the Modified American College of Cardiology/American Heart Association (ACC/AHA) lesion classification.

3. Results

3.1. Baseline characteristics

Baseline clinical and demographic characteristics are listed in Table 1. The two groups were well matched clinically. There were 25 (24%) insulin-dependent and 78 (76%) non-insulin-dependent diabetic patients in the CABG group. There were 22 (22%) insulin-dependent and 80 (78%) non-insulin-dependent diabetic patients in the DES group. There were no significant differences in the mean Parsonnet scores between the CABG group (15.7±8.8) and DES group (16.8±10.7, $p=0.4$). There was no significant difference in the proportion of patients with bifurcation lesions (41% vs.

34%, $p=0.31$) and chronic total occlusions (14% vs. 9%, $p=0.28$) in the CABG and DES group, respectively.

Baseline angiographic data are presented in Table 2. Patients in the CABG group had more involvement of left main, left anterior descending, left circumflex, and right coronary arteries. Patients in the CABG group also had more type C lesions (38.1% vs. 26.8%, $p=0.007$). Patients in the CABG group had smaller left circumflex (2.54±0.60 mm vs. 2.90±0.81 mm, $p=0.005$) and right coronary artery (2.87±0.70 mm vs. 3.15±0.86 mm, $p=0.014$) diameters. Patients in the CABG group also had longer lesions in the left anterior descending (19.19±11.25 mm vs. 15.52±7.25 mm, $p=0.004$) and right coronary arteries (23.80±12.54 mm vs. 15.27±6.66 mm, $p<0.001$).

3.2. Procedural outcomes

Procedural characteristics are presented in Table 3. Among patients allocated to CABG, off-pump CABG was performed in 21% of cases, and a mean of 3.0±0.9 grafts per patient were used. An internal mammary graft to the left anterior descending artery was used in 97% of CABG patients. Nine patients (9%) underwent DES with hemodynamic support with intra-aortic balloon pump counterpulsation, and 5 patients (5%) with the TandemHeart percutaneous left ventricular assist device (CardiacAssist Inc., Pittsburgh, Pennsylvania). Seventy-seven patients (75%) underwent DES with sirolimus-eluting stents and 11 patients (11%) with paclitaxel-eluting stents. Fourteen patients (14%) were treated with a combination of sirolimus-eluting stents and paclitaxel-eluting stents. A mean of 2.8±1.0 stents were implanted with a total stent length of 51.9±24.6 m. The majority of patients were anticoagulated with unfractionated heparin (94%). Glycoprotein IIb/IIIa antagonists were used in 26% of the PCI cases.

Table 3
Procedural characteristics for CABG and DES

CABG	
Off-pump CABG (%)	21
Grafts per patient	3.0±0.9
IMA-to-LAD graft (%)	97
DES	
No. of vessels treated	2.1±0.3
No of stents implanted	2.8±1.0
No. of diseased vessels stented	
2 (%)	89
3 (%)	11
Stent type	
Cypher (%)	75
Taxus (%)	11
Cypher and Taxus (%)	14
Total stent length (mm)	51.9±24.6
Guidance with IVUS (%)	14
Hemodynamic support with IABP (%)	9
TandemHeart percutaneous LVAD (%)	5
Glycoprotein IIb/IIIa antagonists (%)	26

IABP=intra-aortic balloon pump; IMA=internal mammary artery; IVUS=intravascular ultrasound; LAD=left anterior descending artery; LCX=left circumflex artery; LVAD=left ventricular assist device.

Table 4
Procedural and 30-Day outcomes

	CABG	DES	*p*-value
	n=103	*n*=102	
MACE (%)	8	5	0.40
Death (%)	5	3	0.48
Myocardial infarction[a] (%)	2	2	>0.9
Repeat revascularization (%)	1	3	0.32
Stroke (%)	3	0	0.08
VT/VF (%)	4	0	0.04
Requirement for permanent pacemaker (%)	8	0	0.004
Renal failure requiring dialysis (%)	3	1	0.32
Repeat surgery for bleeding (%)	5	NA	
Cardiac tamponade (%)	2	0	0.16
In-hospital length of stay (days±SD)	8.4±6.3	3.0±4.8	<0.001

MACE=major adverse cardiac event; VF=ventricular fibrillation; VT=ventricular tachycardia.

[a] Only post-hospitalization and/or clinical myocardial infarction as cardiac enzymes were not drawn serially after revascularization.

3.3. 30-day outcomes

The 30-day clinical outcomes are summarized in Table 4. The MACE rate was 8% in the CABG group and 5% in the DES group ($p=0.40$). Stroke occurred only in patients treated with CABG (3% vs. 0%, $p=0.08$) but there were no significant differences in mortality (5% vs. 3%, $p=0.48$) and myocardial infarction (2% vs. 2%, $p>0.9$). The cause of death in CABG patients included low cardiac output syndrome in 3 patients, pneumothorax, and sepsis. One patient in the DES group died due to iatrogenic left main coronary artery dissection.

One CABG patient underwent emergent PCI on the second postoperative day for a ST-segment elevation myocardial infarction secondary to the occlusion of a saphenous vein graft that was anastomosed to the posterior descending artery. Three patients underwent repeat revascularization in the DES group. Two of these patients had subacute thrombosis, and one patient underwent repeat DES because of recurrent chest pain and distal stent stenosis that was not addressed after the initial PCI.

There was also a spectrum of secondary adverse events in the CABG group. Five patients (5%) required repeat thoracotomy for bleeding (2 for cardiac tamponade), 4 patients (4%) developed postoperative pneumonia, 8 patients (8%) required permanent pacemaker implantation, 8 patients (8%) developed pleural effusions requiring thoracocentesis, 3 patients (3%) developed renal failure requiring hemodialysis, 22 patients (21%) developed atrial fibrillation, and 4 patients (4%) developed ventricular tachycardia/ventricular fibrillation.

No patient in the PCI group underwent emergent CABG for failed DES, required permanent pacemaker implantation, developed a cardiac tamponade requiring pericardiocentesis, or had vascular complications such as major hematoma requiring surgery or need for vascular repair at the access

Table 5
One-year outcomes

	CABG	DES	*p*-value
	n=103	*n*=102	
MACE (%)	12	27	0.006
Death (%)	8	10	0.6
Myocardial infarction[a] (%)	2	8	0.1
Repeat revascularization (%)	3	20	<0.001
Stroke (%)	4	0	0.04

[a] Only post-hospitalization and/or clinical myocardial infarction as cardiac enzymes were not drawn serially after revascularization.

site. One patient was admitted with acute pulmonary edema, non-ST-segment myocardial infarction, and required hemodialysis after DES.

The mean hospital length of stay was 8.4±6.3 days after CABG and 3.0±4.8 days after DES ($p<0.001$).

3.4. One-year follow-up

One-year clinical outcomes are presented in Table 5. The MACE rate was 12% in the CABG group and 27% in the DES group ($p=0.006$) (Fig. 1). There were no significant differences between the CABG and DES group in death (8% vs. 10%, $p=0.6$) and myocardial infarction (2% vs. 8%, $p=0.1$).

Between 31 days and 1 year, there were 7 deaths in the DES group, 2 of which were cardiac-related (one from congestive heart failure secondary to severe mitral regurgitation and one sudden death possibly due to stent thrombosis) and 5 were non-cardiac-related (2 from sepsis, one from head trauma after a fall, one from lung cancer, and one from intra-abdominal bleeding after surgery).

Between 31 days and 1 year, there were 6 patients in the DES group who had myocardial infarction. One patient had late stent thrombosis on day 260. Another patient had an acute infero-posterior wall myocardial infarction due to a thrombotic occlusion of a left circumflex artery that had not previously been stented. The remaining 4 patients had myocardial infarction due to in-stent restenosis.

Repeat revascularization was performed less often after CABG than after DES (3% vs. 20%, $p<0.001$). Repeat revascularization in the DES group was performed because of stent thrombosis (3/20 patients, 15%), in-stent restenosis (12/20 patients, 60%), and non-culprit lesion progression (5/20 patients, 25%). Of the 20 patients in the DES group who had repeat revascularization, 17 underwent repeat PCI, and 3 underwent CABG. All 3 patients in the CABG group who underwent repeat revascularization underwent DES.

Stroke occurred only in the CABG group (4% vs. 0%, $p=0.04$). One patient developed upper extremity hemiparesis, confusion, dysphagia and pneumonia and died on postoperative day 27. Another patient developed several episodes of expressive aphasia and dysphagia secondary to multiple acute infarcts confirmed on magnetic resonance imaging on day 204 which resolved on hospital discharge. Another patient developed right-sided hemiataxia postoperatively and was admitted to in-patient rehabilitation for two weeks. The postoperative course was complicated by recurrent pleural effusion requiring decortication and pleurodesis. Another patient developed dysarthria postoperatively and was admitted to in-patient rehabilitation after CABG for 13 days.

3.5. Incidence of stent thrombosis

Three patients (3%) who presented with acute myocardial infarction had documented stent thrombosis and were treated with repeat PCI, even though they were being treated with clopidogrel at the time of stent thrombosis. Two patients treated with sirolimus-eluting stents had stent thrombosis and one patient treated with a paclitaxel-eluting stent had stent thrombosis. Two patients had subacute thrombosis on days 3 and 8, respectively, and one patient had late thrombosis on day 260. Three patients had sudden cardiac death and had possible stent thrombosis. An 88 year-old female with a Parsonnet score of 51, severe congestive heart failure, severe mitral regurgitation, end-stage renal disease on hemodialysis, and an aortic abdominal aneurysm who was turned down for CABG after surgical consultation died 8 days after undergoing DES with 5 stents. An 81 year-old female with a Parsonnet score of 41, severe congestive heart failure, acute renal failure, severe peripheral vascular disease which required vascular surgery 2 days after DES with the TandemHeart percutaneous left ventricular assist device, and turned down for CABG after surgical consultation died suddenly at day 10. A 59 year-old male with a history of a myocardial infarction and congestive heart failure died suddenly at 270 days after PCI with 2 drug-eluting stents.

3.6. Predictors of intermediate MACE and death

The following variables were entered into a stepwise multivariable Cox proportional hazards model for MACE: age, sex, insulin-dependent diabetes mellitus, Parsonnet score,

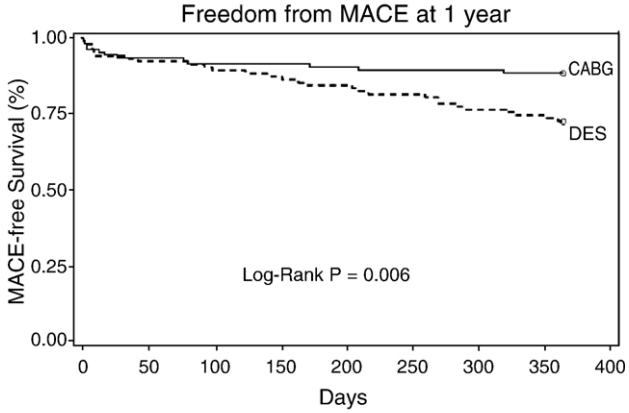

Fig. 1. Kaplan–Meier estimates of freedom from MACE at 1 year. MACE=major adverse cardiac events including death, myocardial infarction, and repeat revascularization.

ejection fraction, chronic renal insufficiency, myocardial infarction, peripheral vascular disease, use of statin, and type of revascularization (CABG or DES). The Cox proportional hazards regression model demonstrated that independent predictors for MACE were presentation with acute myocardial infarction (hazard ratio [HR], 2.26, 95% CI, 1.13 to 4.55) and DES (HR, 2.4, 95% CI, 1.23 to 4.77). Therapy with a statin was a negative independent predictor for MACE (HR, 0.40, 95% CI, 0.21 to 0.76). The Cox proportional hazards regression model demonstrated that independent predictors for death were the ejection fraction (HR, 0.97, 95% CI, 0.94 to 1.00) and Parsonnet score (HR, 1.08; 95% CI, 1.03 to 1.12).

4. Discussion

The most important result of our study is that despite more complex lesions, smaller vessel size, and longer lesions, CABG was associated with less MACE in diabetic patients with multivessel CAD. This result is primarily due to the increased need for repeat revascularization in the DES group. Thus, although DES reduces the rates of revascularization compared to bare metal stenting, the revascularization rate still remained a critical endpoint in our study. Bypass surgery was associated with a higher incidence of stroke and other important adverse post operative events.

It has been generally accepted that CABG is the preferred revascularization strategy in diabetic patients with multivessel CAD. This conclusion has been based upon the results of the 5-year follow-up of the BARI trial [6] and the 8-year analysis of the EAST [8], in which a significantly higher mortality rate occurred in the PCI group. Similarly, ARTS reported that the 1-year mortality was twice as high (6.3% vs. 3.1%, p=NS) in diabetics assigned to PCI [9]. Our results are more consistent with bare metal stent studies in which clinical judgment rather than randomization was used to distribute patients to the two treatment arms. In the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) trial and the BARI registry, there was no significant difference in long-term mortality [21–23]. In ARTS II [24], subgroup analysis of the diabetic subgroup suggested that the one year major adverse cardiac and cerebrovascular event rate in DES patients (15.7%) was similar to that in the patients treated with CABG in ARTS I (14.6%). However, this comparison is severely limited as ARTS II was a non-randomized trial where operators chose patients for DES in an attempt to match already known outcomes from the CABG cohort of ARTS I. Our data demonstrates that DES was associated with increased 1-year MACE suggesting introduction of current DES technology is not adequate in reducing revascularization in diabetic patients to match CABG.

The one year mortality in our study (8% with CABG and 10% with DES) was higher than has been reported in other trials. The excessive number of deaths in the DES group that occurred between day 31 and 1 year are concerning. However, there were only 2 cardiac-related deaths, one of which was caused by severe mitral regurgitation and the other death that was sudden, possibly related to stent thrombosis. In ARTS II [25], these values were 3.1% and 2.5%. These differences reflect the inclusion of high-risk patients (mean Parsonnet score in the CABG group, 15.7±8.8, and DES group, 16.8±10.7). In the randomized trials patients with left ventricular dysfunction, recent myocardial infarction, previous stroke, severe hepatic or renal disease, and those who required surgery (i.e. carotid endarterectomy and peripheral vascular surgery) were excluded. Our study included all such patients. Thus, while randomized trials provide unbiased data for rigorous statistical comparisons, our data is more representative of the outcomes that are likely to be obtained by high quality clinical programs, providing additional insight for health policy analysis.

Compared to CABG, the principal limitation of PCI with bare metal stents is the need for repeat revascularization, especially in diabetic patients [21, 26, 27]. In ARTS [26], this difference in one year repeat revascularization was striking: 22.3% for PCI vs. 3.1% for CABG. In our study, this difference persisted as DES failed to demonstrate any difference in repeat revascularization (DES, 20% vs. CABG 3%, $p<0.001$). These results are consistent with the higher repeat revascularization rates seen in the diabetic cohort in ARTS II (DES, 12.5% vs. CABG, 4.1%) [24] and represent the principal limitation of the DES strategy. In-stent restenosis was accountable for 12 of the 20 cases of repeat revascularization and 4 of the 6 cases of myocardial infarction between 31 days and 1 year. The two other cases of myocardial infarction in the DES group were attributable to late stent thrombosis and thrombotic occlusion of an artery that was previously not intervened upon. Bypass surgery may therefore be superior to DES in preventing myocardial infarction as longer-term follow-up is achieved because it is not associated with stent restenosis and thrombosis, and arterial or venous grafts may protect from potentially fatal consequences of atherosclerotic progression and plaque rupture [28, 29].

Progressive atherosclerosis is responsible for repeat revascularization in a significant number of diabetic patients [30, 31]. Progression of non-stented lesions was the reason for revascularization in 28% of patients in our study. Most obstructive lesions occur within the proximal 6 cm of epicardial arteries, the coronary artery segment that is usually bypassed by a graft [31]. Thus, in BARI, approximately 50% of the survival benefit observed with CABG was due to an 8-fold reduction in mortality in diabetic patients who sustained a Q-wave myocardial infarction. Furthermore, CABG provides more complete revascularization. Stented patients in ARTS with less complete revascularization were more likely to require subsequent CABG [32].

An important adverse event in the DES group in our study was the 3% angiographically-documented stent thrombosis rate. If we include patients who had sudden cardiac death from no identifiable cause, the stent thrombosis rate increases to 6%. Four of these events occurred within 30 days, and 2 of these events occurred after 30 days. All 3 patients with angiographically-documented stent thrombosis were

being treated with dual antiplatelet therapy. This rate is higher than the stent thrombosis rate of 1.3% reported by Iakovou et al in 2229 consecutive patients treated with DES [33]. In addition to diabetes, key predictors of stent thrombosis were renal failure, bifurcation lesions, and low ejection fraction, and for subacute thrombosis, stent length. In the Intracoronary Stenting and Angiographic Results—Do Diabetic Patients Derive Similar Benefits from Paclitaxel-Eluting and Sirolimus-Eluting Stents (ISAR-DIABETES) trial [34], only one patient (0.4%) had stent thrombosis, although this study excluded high-risk patients with acute myocardial infarction, left main coronary artery stenosis, and in-stent restenosis. In the Diabetes and Sirolimus-Eluting Stent (DIABETES) trial [35], where patients were treated with clopidogrel for one year, there was no incidence of stent thrombosis in the 80 patients treated with sirolimus-eluting stents. However, the Argentine Randomized Trial of Coronary Stents versus Bypass Surgery (ERACI) III trial reported a stent thrombosis rate of 3.1% in the 225 patients with multivessel CAD treated with DES at 1 year [36]. The patients in our study who experienced stent thrombosis each had 2 or more key predictors for stent thrombosis. In the 4 patients with subacute thrombosis, the average stent length was 55.8 mm. Five of the 6 patients with stent thrombosis had left ventricular dysfunction, 3 of the patients had renal failure, and 2 of the patients had bifurcation lesions. Our results suggest the immediate need for studies that assess whether more aggressive antiplatelet therapy might decrease the stent thrombosis rate in diabetic patients undergoing multivessel DES. Lee et al. [37] reported that triple antiplatelet therapy with aspirin, clopidogrel or ticlopidine, and cilostazol appeared to be more effective in preventing thrombotic complications after stenting without an increased risk of side effects compared with dual antiplatelet therapy. This regimen might be safely applied in diabetic patients who undergo multivessel DES.

The incidence of stroke at one year in the CABG group was 4%. This rate of cerebrovascular events is compared to that of diabetic patients who underwent CABG in ARTS at one year follow-up (6.3%) [26], and the 2–3% rate commonly reported in the non-diabetic population [38]. This increased risk may reflect impaired autoregulation of the cerebrovasculature as well as diffuse atherosclerosis of the aortic, carotid, and cerebral arteries as well as our inclusion of higher-risk patients than those in randomized trials. Given the more advanced atherosclerosis observed in the CABG group, it is not unexpected that more strokes were observed in this group. Although only one of the patients who underwent off-pump CABG had a stroke, Cheng et al [39] reported no benefit of off-pump CABG on stroke. Perioperative stroke was an independent predictor of death in patients who underwent CABG [40]. One patient who had a stroke died from pneumonia.

We also found a significant rate of important but less serious complications in our CABG patients. Repeat thoracotomy for bleeding, postoperative pneumonia, permanent pacemaker implantation, pleural effusions requiring thoracocentesis, renal failure requiring hemodialysis, atrial fibrillation, or ventricular tachycardia/ventricular fibrillation occurred in 53% of our CABG population, compared to 1% in the DES group. These complications contributed to more than double the length of stay in our CABG patients compared to our DES patients. Some of these complications were as serious and as expensive as rehospitalization for repeat revascularization, but are not included in the primary composite endpoint, an illustration of the difficulty inherent in drawing a conclusion from a single composite endpoint composed of events with markedly different impact on patient welfare.

4.1. Limitations

Our study has several important limitations. Most important is that our current follow-up period is only one year. Since DES is a recent development, in longer follow-up this strategy may not match the superior long-term clinical outcomes of a left internal mammary to the left anterior descending artery graft, which has a patency rate of more than 90% at 10 years and improves survival and freedom from further cardiovascular events [41, 42]. This outcome is suggested by several studies that show CABG superiority emerges only after 5 to 6 years [43]. This study was non-randomized, observational, uncontrolled, and without specific protocols, and therefore limits any direct comparisons of the two methods of revascularization. The rate of myocardial infarction may be underestimated because cardiac enzymes and electrocardiograms were not routinely obtained in patients after revascularization. This may have underestimated the real incidence of myocardial infarction in the diabetic patients, especially in the DES group, who may have had silent infarcts. The restenosis rate after DES in diabetic patients with multivessel CAD remains undefined because late systematic angiography was not performed in all of our patients. Only 26% of patients who underwent DES received glycoprotein IIb/IIIa antagonists even though a pooled analysis of Evaluation of c7E3 Fab for Prevention of Ischemic Complications (EPIC), Evaluation in PTCA of Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG), and Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trials of 1462 diabetic patients demonstrated that treatment with abciximab reduced one year mortality and myocardial infarction [44]. Patients were subjected to a large treatment bias as patients who had focal disease usually underwent DES while patients who had more extensive CAD including longer lesions, smaller vessels, and more complex disease underwent CABG.

4.2. Conclusions

Bypass surgery was associated with less MACE in diabetic patients with multivessel CAD at one year follow-up, primarily due to the higher repeat revascularization rate with DES and is therefore superior to DES despite more

extensive CAD in CABG patients. The ongoing Future Revascularization in Patients With Diabetes Mellitus: Optimum Management of Multivessel Disease (FREEDOM), Coronary Artery Revascularisation in Diabetes (CARDIA), Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D), and the Veterans Administration trials will provide further insights on the optimal revascularization strategy in diabetic patients with multivessel CAD to provide a basis for re-evaluation of treatment guidelines for revascularization in the DES era. Our study, although less scientifically rigorous, may provide important insight into the results that are likely to be obtained in actual clinical practice.

Acknowledgement

We thank James Mirocha for providing statistical support for this manuscript.

References

[1] Thourani VH, Weintraub WS, Stein B, et al. Influence of diabetes mellitus on early and late outcome after coronary artery bypass grafting. Ann Thorac Surg 1999;67:1045–52.
[2] Smith LR, Harrell Jr FE, Rankin JS, et al. Determinants of early versus late cardiac death in patients undergoing coronary artery bypass graft surgery. Circulation 1991;84(5 Suppl):245–53.
[3] Stein B, Weintraub WS, Gebhart SP, et al. Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. Circulation 1995;91:979–89.
[4] Kip KE, Faxon DP, Detre KM, Yeh W, Kelsey SF, Currier JW. Coronary angioplasty in diabetic patients. The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. Circulation 1996;94:1818–25.
[5] The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary artery bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med 1996;335: 217–25.
[6] Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). Circulation 1997;96:1761–9.
[7] The BARI Investigators. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. J Am Coll Cardiol 2000;35:1122–9.
[8] King III SB, Kosinski AS, Guyton RA, Lembo NJ, Weintraub WS. Eight year mortality in the Emory Angioplasty vs. Surgery Trial (EAST). J Am Coll Cardiol 2000;35:1116–21.
[9] Abizaid A, Kornowski R, Mintz GS, et al. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. J Am Coll Cardiol 1998;32:584–9.
[10] Ho KKL, Senerchia C, Rodriguez O, Chauhan MS, Kuntz RE. Predictors of angiographic restenosis after stenting: pooled analysis of 1197 patients with protocol-mandated angiographic follow-up from 5 randomized stent trials. Circulation 1998;98(Suppl I):I362.
[11] Kobayashi Y, De Gregorio J, Kobayashi N, et al. Stented segment length as an independent predictor of restenosis. J Am Coll Cardiol 1999;34:651–9.
[12] Elezi S, Kastrati A, Pache J, et al. Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. J Am Coll Cardiol 1998;32:1866–73.
[13] Schofer J, Schluter M, Rau T, Hammer F, Haag N, Mathey DG. Influence of treatment modality on angiographic outcome after coronary stenting in diabetic patients: a controlled study. J Am Coll Cardiol 2000;35:1554–9.
[14] Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117–24.
[15] Moussa I, Leon MB, Baim DS, et al. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients With de novo Coronary Artery Lesions) substudy. Circulation 2004;109: 2273–8.
[16] Abizaid A, Costa MA, Blanchard D, et al. Sirolimus-eluting stents inhibit neointimal hyperplasia in diabetic patients. Insights from the RAVEL Trial Eur Heart J 2004;25:107–12.
[17] Hermiller JB, Raizner A, Cannon L, et al. Outcomes with the Polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus. J Am Coll Cardiol 2005;45:1172–9.
[18] Ryan TJ, Faxon DP, Gunnar RM, et al. Guidelines for percutaneous transluminal coronary angioplasty: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). Circulation 1988;78:486–502.
[19] Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. Circulation 1989;79(suppl I):I-3-I-12.
[20] Bernstein AD, Parsonnet V. Bedside estimation of risk as an aid for decision-making in cardiac surgery. Ann Thorac Surg 2000;69: 823–8.
[21] Sedlis SP, Morrison DA, Lorin JD, et al. Percutaneous coronary intervention versus coronary bypass surgery for diabetic patients with unstable angina and risk factors for adverse outcomes with bypass: outcome of diabetic patients in the AWESOME randomized trial and registry. J Am Coll Cardiol 2002;40:1555–66.
[22] Feit F, Brooks MM, Sopko G, et al. Long-term clinical outcome in the Bypass Angioplasty Revascularization Investigation Registry: comparison with the randomized trial. Circulation 2000;101:2795–802.
[23] Detre KM, Guo P, Holubkov R, et al. Coronary revascularization in diabetic patients: a comparison of the randomized and observational components of the Bypass Angioplasty Revascularization Investigation (BARI). Circulation 1999;99:633–40.
[24] Morice M.C. ARTS II-1-year follow-up. Presented at: EuroPCR 2005; May 24, 2005; Paris, France.
[25] Serruys PW. Arterial revascularization therapies study part II of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. J Am Cardiol Coll 2005;45:7A.
[26] Abizaid A, Costa MA, Centemero M, et al. 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. Circulation 2001;104:533–8.
[27] SOS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomized controlled trial. Lancet 2002;360:959–70.
[28] Fitzgibbon GM, Kafka HP, Leach AJ, et al. Coronary artery bypass graft fate and patient outcome: angiographic follow-up of 5065 grafts related to survival and reoperation in 1388 patients during 25 years. J Am Coll Cardiol 1996;28:616–26.
[29] Tatoulis J, Buxton BF, Fuller JA, Royce AG. Total arterial coronary revascularization: techniques and results in 3220 patients. Ann Thorac Surg 1999;68:2093–9.
[30] Mathew V, Holmes DR. Outcomes in diabetics undergoing revascularization: the long and the short of it. J Am Coll Cardiol 2002;40: 424–7.
[31] Kuntz R. Importance of considering atherosclerosis progression when choosing a coronary revascularization strategy: the diabetes-percutaneous transluminal coronary angioplasty dilemma. Circulation 1999;99: 847–51.
[32] Van den Brand MJ, Rensing BJ, Morel MA, et al. The effect of completeness of revascularization on event-free survival at one year in the ARTS Trial. J Am Coll Cardiol 2002;87:947–50.

[33] Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.
[34] Dibra A, Kastrati A, Mehilli J, et al. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. N Engl J Med 2005;353:663–70.
[35] Sabaté M, Jiménez-Quevedo P, Angiolillo DJ, et al. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the Diabetes and Sirolimus-Eluting Stent (DIABETES) trial. Circulation 2005;112: 2175–83.
[36] Rodriguez AE, Mieres J, Fernandez-Pereira C, et al. Coronary stent thrombosis in the current drug-eluting stent era: insights from the ERACI III trial. J Am Coll Cardiol 2006;47:205–7.
[37] Lee SW, Park SW, Hong MK, et al. Triple versus dual antiplatelet therapy after coronary artery stenting: impact on stent thrombosis. J Am Coll Cardiol 2005;46:1833–7.
[38] Borst C, Grunderman PF. Minimally invasive coronary artery bypass grafting: an experimental perspective. Circulation 1999;99:1400–3.
[39] Cheng W, Denton TA, Fontana GP, et al. Off-pump coronary surgery: effect on early mortality and stroke. J Thorac Cardiovasc Surg 2002;124: 313–20.
[40] Dacey LJ, Likosky DS, Leavitt BJ, et al. Perioperative stroke and long-term survival after coronary bypass graft surgery. Ann Thorac Surg 2005;79:532–6.
[41] Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary artery bypass graft fate and patient outcome: angiographic follow-up of 5065 grafts related to survival and reoperation in 1388 patients during 25 years. J Am Coll Cardiol 1996;28:616–26.
[42] Tatoulis J, Buxton BF, Fuller JA, Royse AG. Total arterial coronary revascularization: techniques and results in 3220 patients. Ann Thorac Surg 1999;68:2093–9.
[43] Niles NW, McGrath PD, Malenka D, et al. Survival of patients with diabetes and multivessel coronary artery disease after surgical or percutaneous coronary revascularization: results of a large regional prospective study: Northern New England Cardiovascular Disease Study Group. J Am Coll Cardiol 2001;37:1008–15.
[44] Bhatt DL, Marso SP, Lincoff AM, Wolski KE, Ellis SG, Topol EJ. Abciximab reduced mortality in diabetics following percutaneous coronary intervention. J Am Coll Cardiol 2000;35:922–8.