Table 2. Baseline Characteristics of Patients When Sub-Grouped by Numbers of Coronary Risk Factors

Coronary risk factors	Risk 0	Risk 1	Risk 2	Risk 3	Risk 4
No. of patients	11	25	59	50	18
Characteristics					
Age (years)	52.4±16.5	68.8±11.6	65.9±11.3	68.6±8.4	65.6±8.0
Gender (M/F)	4/7	10/15	33/26	27/23	17/1
Brinkman index	0	91.0±216.9	251.7± 369.8	538.8 ± 629.4	1,126±521.7
BMI (kg/m^2)	22.8±1.8	22.6±2.4	23.8±3.8	24.0±3.7	24.8±4.2
Waist circumference (cm)	77.8±8.4	81.6±9.1	84.3±10.8	87.3±10.6	89.9±11.2
SBP (mmHg)	114.9±9.0	125.4±15.3	122.2±23.5	127.1±21.1	135.8±13.4
DBP (mmHg)	65.5±6.5	68.3±9.8	67.0±15.1	65.8±9.4	67.4±6.3
Blood chemistry					
TC (mg/dl)	178.3± 20.0	198.8±46.2	206.2±42.7	195.2±44.4	205.3±46.9
TG (mg/dl)	80.8±19.3	110.3±42.6	150.9±81.9	134.4±60.3	173.7±57.2
HDL-C (mg/dl)	67.3±18.1	58.0±14.2	54.8±21.7	51.7±15.6	44.2±11.3
LDL-C (mg/dl)	97.6±17.5	120.1±36.6	128.0±32.5	118.8±32.7	132.5±40.0
HbA$_{1c}$ (%)	5.1±0.2	5.3±0.3	5.5±1.0	6.3±1.1	6.9±0.8
FPG (mg/dl)	86.9±9.3	93.0±7.6	101.4±20.2	114.7±32.2	120.7±37.6
IRI (μU/ml)	4.5±1.2	4.4±1.6	8.4±8.2	10.7±11.7	8.2±5.1
HOMA-IR	0.98±0.34	0.98±0.38	2.06±2.11	2.94±3.17	2.37±1.59
hs-CRP (mg/dl)	0.66±0.73	0.46±1.09	0.55±0.95	0.64±1.39	0.38±0.78
Left ventricular function					
LVEF (%)	62.2±8.1	60.0±9.3	52.4±12.2	56.1±9.3	51.5±6.4
Medication (%)					
β-blockers	9.1	32.0	37.3	38.0	61.1
Ca-blockers	9.1	28.0	39.0	46.0	16.7
ACEI	0	12.0	18.6	14.0	33.3
ARB	0	32.0	44.1	56.0	50
Nitrates	9.1	12.0	25.4	36.0	38.9
Statins	0	8.0	32.2	48.0	55.6
Oral antidiabetics and insulin	0	0	11.9	54.0	88.9
Aspirins	18.2	48.0	47.5	52.0	88.9
Diuretics	18.2	8.0	30.5	34.0	27.8
Underlining diseases (%)					
Coronary artery disease	27.3	40.0	61.0	84.0	94.4
Arrhythmia	63.6	32.0	11.9	8.0	5.6
Valvular disease	9.1	4.0	13.6	0	0
Hypertension	0	24.0	13.6	8.0	0
Risk factors (%)					
Hypertension	0	52.0	64.4	86.0	100
Diabetes mellitus	0	0	18.6	68.0	100
Hyperlipidemia	0	28.0	80.0	84.0	100
Smoking	0	20.0	37.3	68.0	100

Data are mean±SEM.
IRI, immunoreactive insulin; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitive C-reactive protein; LVEF, left ventricular ejection fraction. Other abbreviations see in Table 1.

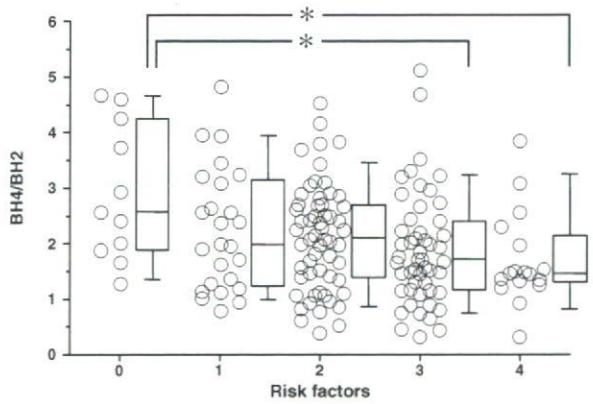

Figure 2. Relationship between the plasma tetrahydrobiopterin/7,8–dihydrobiopterin (BH4/BH2) ratio and the total number of coronary risk factors. A box-and-whisker plot shows the relationship between the plasma BH4/BH2 ratio and the total number of coronary risk factors. For each value of the coronary risk factors, the lines within the boxes represent median values; the upper and lower lines of the boxes represent the 25th and 75th percentiles, respectively, and the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively. *P<0.05.

than 2 risk factors showed significant reductions compared with that in those without risk factors (P<0.05) (**Figure 2**). As to the presence of each single risk factor examined, age, sex, and the Brinkman Index, which represents the severity of a smoking habit, showed a weak but significant negative correlation with the plasma BH4/BH2 ratio (β=–0.259, P=0.0009, β=–0.207 P=0.0084, and β=–0.251, P=0.0014, respectively). In the stepwise regression model, age and sex showed a significant negative correlation with the plasma BH4/BH2 ratio. There was no correlation between the Brinkman Index and the BH4/BH2 ratio. In addition, there were no correlations between the Log CRP levels and the BH4/BH2 ratio in the simple and multiple stepwise regression analyses. We then examined whether the BH4/BH2 ratio was associated with FMD, independently of risk factors. Multivariate analyses using stepwise regression models were carried out to analyze the relationships between FMD and risk factors including age, sex, abdominal circumference, BMI, Brinkman index, BP, HbA$_{1c}$, FPG, HOMA-IR, TC, LDL-C, HDL-C, Log CRP and/or the BH4/BH2 ratio and medications such as calcium channel blockers, angiotensin converting-enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB) and statins. As demonstrated in

Table 3. Multiple Stepwise Regression Analysis of Variables Significantly Associated With FMD

	β	SE	F	P value
Model 1				
Age	−0.306	0.020	10.539	<0.001
Sex	−0.303	0.351	10.670	<0.001
Log CRP	−0.235	0.259	6.538	<0.001
HbA_{1c}	−0.189	0.161	4.092	<0.001
		Multiple R^2=0.254		
Model 2				
BH4/BH2 ratio	0.438	0.157	24.892	<0.001
Age	−0.270	0.018	9.597	<0.001
Sex	−0.220	0.330	6.126	<0.001
		Multiple R^2=0.357		

Model-1 includes age, sex, abdominal circumference, BMI, Brinkman index, BP, HbA_{1c}, FPG, HOMA-IR, TC, LDL-C, HDL-C, LogCRP and each medication such as Ca-blocker, ACEI, ARB and statin as independent variables.
Model 2 includes age, sex, abdominal circumference, BMI, Brinkman index, BP, HbA_{1c}, FPG, HOMA-IR, TC, LDL-C, HDL-C, LogCRP, each medication such as Ca-blocker, ACEI, ARB, statin and BH4/BH2 as independent variables.
FMD, flow-mediated vasodilatory; β, standardized regression coefficient; SE, standard error; R, multiple correlation coefficient; BH4, tetrahydrobiopterin; BH2, 7,8–dihydrobiopterin; BP, blood pressure. Other abbreviations see in Tables 1,2.

Table 4. Multiple Regression Analysis of the BH4/BH2 Ratio and Numbers of Risk Factors Significantly Associated With FMD

	β	SE	P value
BH4/BH2	0.558	0.131	<0.001
Risk factor numbers	−0.147	0.128	0.0259

Abbreviations see in Table 3.

Table 5. Comparison of Parameters at the Basal Levels Before Treatment in Stain-Treated and Non-Stain Treated Groups

	Statin-treated	Non-statin treated	P value
No. of patients	23	21	
Characteristics			
Age (years)	67.1±6.9	64.3±11.3	NS
Gender (M/F)	15/8	12/9	
SBP (mmHg)	127.4±16.3	120.6±18.0	NS
DBP (mmHg)	67.7±9.8	69.1±9.5	NS
Blood chemistry			
TC (mg/dl)	229.4±30.5	226.6±42.5	NS
TG (mg/dl)	146.9±67.9	158.4±101.5	NS
HDL-C (mg/dl)	53.2±20.4	56.0±14.6	NS
LDL-C(mg/dl)	153.4±26.2	142.2±28.8	NS
HbA_{1c} (%)	5.9±1.3	5.9±1.3	NS
FPG (mg/dl)	107.8±31.2	109.5±34.0	NS
BH4 (ng/ml)	2.03±0.93	1.75±0.53	NS
BH2 (ng/ml)	1.15±0.39	1.05±0.39	NS
BH4/BH2	1.96±1.06	1.96±0.94	NS
Ultrasonography			
FMD (%)	4.71±1.80	4.82±2.18	NS
NMD (%)	16.3±4.2	16.4±2.6	NS
Underlining diseases (%)			
Coronary artery disease	87.0	52.4	
Arrhythmia	8.7	14.3	
Valvular disease	0	9.5	
Hypertension	4.3	23.8	
Risk factors (%)			
Hypertension	65.2	47.6	
Diabetes mellitus	30.4	38.1	
Hyperlipidemia	87.0	71.4	
Smoking	39.1	47.6	

Data are mean±SEM.
NMD, nitroglycerin-mediated vasodilation. Other abbreviations see in Tables 1,3.

Table 3, the BH4/BH2 ratio was associated with FMD, independently of these risk factors. Furthermore, after adjusting the number of risk factors, the BH4/BH2 ratio was also associated with FMD independently (**Table 4**).

Table 5 shows the basal clinical characteristics of patients assigned to the atorvastatin protocol. Before treatment, there were no differences in blood chemistry including plasma pteridine levels and FMD value between the statin-treated and control groups. Stain treatment for 3 months did not change these parameters, the only exception being the

Table 6. Multiple Stepwise Regression Analysis Between the Change of FMD (ΔFMD) and the Changes of Parameters

	β	SE	F	P value
ΔBH4/BH2	0.455	0.363 Multiple R^2=0.207	5.468	<0.001

Table 6 includes ΔBP, ΔHbA1c, ΔFPG, ΔTC, ΔTG, ΔLDL-C, ΔHDL-C and ΔBH4/BH2 as independent variables. Abbreviations see in Tables 1–3.

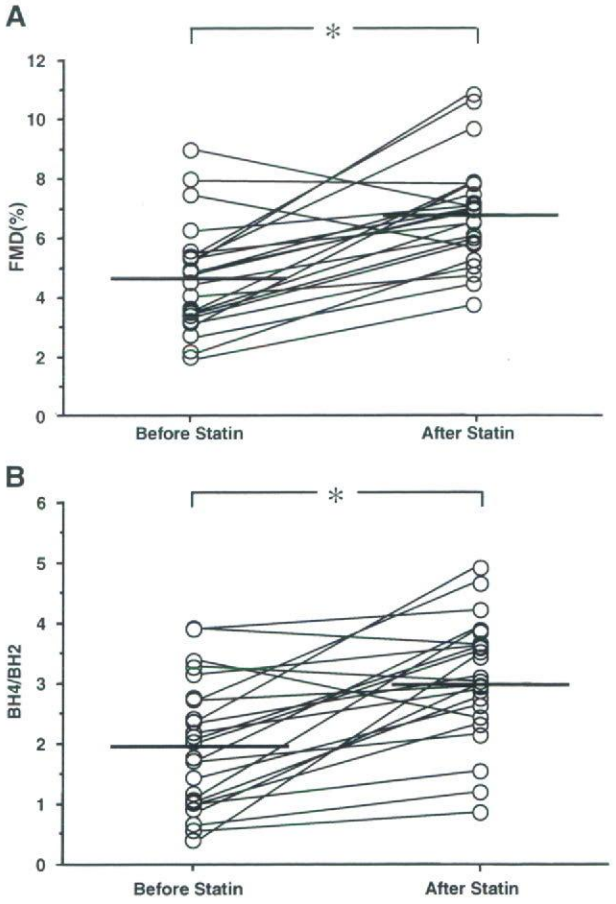

Figure 3. Effects of statin treatment on flow-mediated vasodilatation (FMD, **A**) and the plasma tetrahydrobiopterin/7,8–dihydrobiopterin (BH4/BH2) ratio (**B**). Statin treatment improved FMD. Along with these changes, the plasma BH4/BH2 ratio increased in most patients, with the exception of a few patients in whom improvement of FMD was minimal. The bars show mean values. *P<0.05.

plasma lipid profiles. TC decreased from 229.4±30.5 to 187.3±24.3 (mg/dl), and LDL-C from 153.4±26.2 to 109.4±26.5 (mg/dl) by atorvastatin treatment. In the control group, there were no significant changes in parameters (as shown in **Table 5**) during the 3-month observation period. And as for FMD, statin treatment improved FMD (6.81±1.80%, P<0.05) (**Figure 3A**). Along with these changes, the plasma BH4/BH2 ratio increased in most patients, with the exception of a few patients in whom improvement of FMD was minimal (2.99±1.01, P<0.05) (**Figure 3B**). In contrast, in the control group who did not receive statin treatment, both FMD and the plasma BH4/BH2 ratio remained unchanged during the 3 months (4.71±1.59% and 1.87±0.78, respectively). We then assessed the relationship between ΔFMD and the ΔBH4/BH2 ratio by using multiple stepwise regression analysis including ΔBP, ΔHbA1c, ΔFPG, ΔTC, ΔTG, ΔLDL-C, ΔHDL-C and ΔBH4/BH2 as independent variables. As shown in **Table 6**, we found a significant correlation between the ΔFMD and the ΔBH4/BH2.

Discussion

In the present study, we examined plasma pteridine levels and endothelial function via the brachial artery FMD in patients with various cardiovascular disorders including coronary artery disease. We demonstrated that the extent of FMD was correlated with plasma pteridine levels. In association with a reduction in FMD, plasma BH4 levels decreased, BH2 levels increased and subsequently the BH4/BH2 ratio decreased. Particularly, the plasma BH4/BH2 ratio showed a strong positive correlation with FMD. The plasma BH4/BH2 ratio was negatively correlated with the total numbers of coronary risk factors. In addition, we showed that, in patients with multiple coronary risk factors, treatment with statins improved FMD in association with an increase in plasma BH4/BH2 ratio.

Among various factors produced by endothelial cells, NO produced by eNOS is most important in the control of endothelial function, and EDR is caused by eNOS-derived NO. NO is generated from the conversion of L-arginine to L-citrulline by the enzymatic action of a NADPH-dependent NO synthase, which requires Ca^{2+}/calmodulin, FAD, FMN, and BH4 as cofactors. Although recently a catheter-type NO sensor has been extensively experimented with to measure NO synthase directly in animal models, it is difficult to apply in human studies[23,24] EDR has been used to assess the endothelial function, and clinically is most commonly evaluated by FMD in the brachial artery. Many experimental and human studies have demonstrated that coronary risk factors are associated with impaired endothelial function, which represents the reduced eNOS-derived NO bioactivity in vessels.

Among various mechanisms responsible for the impaired EDR, the increased breakdown of NO by superoxide is important. In vessels, a variety of enzymes, including NADPH oxidase and xanthine oxidase, produce superoxide. Recently, it has been revealed that eNOS itself produces superoxide when there is a relative deficiency of its essential cofactor, BH4[21,25] In the presence of sub-optimal levels of BH4, electrons flowing from the reductase domain to the hem is diverted to molecular oxygen rather than to L-arginine, and thereby production of superoxide occurs[26] BH4 is a molecular target for oxidative stress, and ROS such as peroxynitrite oxidizes BH4 to its oxidative form, BH2[15,27,28] Under conditions with elevated oxidative stress, it is assumed that BH4 levels decrease and its oxidative form, BH2, increases in the endothelium[28] It is well known that the presence of atherosclerosis as well as coronary risk factors is associated with elevated oxidative stress. In the present study, therefore, oxidative stress is closely linked to impaired endothelial function, although the precise role of eNOS-derived superoxide was not elucidated.

Before this present study, a few clinical studies examined plasma levels of pteridine in patients with cardiovascular disorders[18,29,30] In patients with chronic renal failure, it was shown that the plasma BH4/BH2 ratio was reduced in association with the severity of renal failure and that there was a positive correlation between the BH4/BH2 ratio and creatinine clearance[18] Shinozaki et al showed that the plasma BH4/BH2 ratio was reduced in patients with insulin resistance[29] They also demonstrated that the maximum coronary dilation induced by acetylcholine was positively correlated with insulin sensitivity and the plasma BH4/BH2 ratio. In the present study, we demonstrated that the plasma BH4/BH2 ratio was positively correlated with FMD in the brachial artery in patients with various cardiovascular disorders. Our finding is partly in accordance with the study of Shinozaki et al[29] and extended the importance of plasma pteridine measurements on the evaluation of ED. The present finding most likely indicates that plasma pteridine levels, particularly the BH4/BH2 ratio, can be used as a biomarker to evaluate ED.

Plasma BH2 levels increased, whereas BH4 levels did not change, in association with the increment of total numbers of coronary risk factors. Subsequently, the BH4/BH2 ratio significantly decreased as the numbers of coronary risk factors increased. It is very likely that the increased oxidative stress in the presence of coronary risk factors resulted in the oxidation of BH4 and an increase in BH2. Reduction of the plasma BH4/BH2 ratio might, therefore, represent the increased levels of oxidative stress. Although it is widely accepted that oxidative stress serves to impair endothelial function, only a limited numbers of studies have demonstrated the correlation between the plasma markers of oxidative stress, such as TBARS and oxLDL, and the extent of FMD in clinical studies[31,32] In the preliminary study, we did not find correlations between plasma TBARS or 8-iso PGF2α levels and the plasma BH4/BH2 ratio or FMD (%) (data not shown). Although the source of plasma pteridine has not been clarified yet, it is assumed that plasma levels of pteridine reflect endothelial pteridine metabolism because the endothelium is directly in contact with blood and is the major site for formation of peroxynitrite that oxidizes BH4. Therefore, it is possible that the plasma BH4/BH2 ratio can serve as a more sensitive and specific marker of oxidative stress on the endothelium than commonly used plasma markers such as TBARS and 8-iso PGF2 , which are markers of total oxidative stress in a whole body. To prove this hypothesis, further studies will be required to investigate this.

Our finding is in contrast to that by Antoniades et al, who found no association between plasma pteridine levels and endothelial function in isolated vessels (saphenous veins or internal mammalian arteries) obtained from patients at the time of bypass surgery[30] They also described that plasma pteridine levels are linked to systemic inflammation, because they found the association between plasma total pteridine levels and plasma CRP levels. The divergent results might be explained by the difference in patients' profiles. In our study, which is different from their study, most patients were not the subjects for coronary intervention, and CRP levels were relatively low. In their study, there were wide variations in plasma total pteridine, BH4 and BH2 levels, which are likely influenced by systemic inflammation rather than local vascular redox status. In our study, however, we did not find such a variation in plasma BH4 or BH2 levels, although our HPLC methods does not permit us to measure total pteridine. Therefore, it is likely that the plasma BH4/BH2 ratio can be used as a marker of endothelial function in the absence of overt systemic inflammation.

As a limitation of the present study, most patients recruited were taking various medications that could modify endothelial function and oxidative stress. Although all medications were stopped at least 12 h prior to the study, their influence on the endothelial function and plasma pteridine metabolism probably did not disappear completely. In addition, we did not find a correlation between the Brinkman index and FMD. This might be related to the examinations performed during hospital admission when patients were not smoking cigarettes. However, our present study findings represented the overall relationship between FMD and plasma pteridine levels, and demonstrated the usefulness of plasma pteridine measurement to assess ED in the clinical situation, where many subjects were most likely taking medication.

In conclusion, the present study suggested that plasma pteridine levels, particularly the BH4/BH2 ratio, were associated with ED in the absence of recognizable systemic inflammation. The present study findings were obtained using a relatively small number of patients with heterogeneity, and, therefore, further studies conducted with a larger population will be needed to ascertain whether BH4/BH2 can be used as a marker of ED, and to address the issue of whether the measurement of the BH4/BH2 ratio serves as a useful tool in determining a therapeutic strategy for vascular disorders based on the improvement of endothelial function.

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Disclosure

We have no conflicts of interests.

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SHORT REPORT

Inoue Stent-Graft Implantation for Thoracoabdominal Aortic Aneurysm Involving the Visceral Arteries

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Purpose. *To assess the efficacy of the Inoue stent-graft placement for thoracoabdominal aortic aneurysm (TAAA).*
Methods. *Patients with TAAA underwent Inoue stent-graft placement with single branched stent-graft in 4 patients, straight graft in 3 patients and double branched stent-graft in 1 patient. Half the patients required additional open surgical revascularizations of involved visceral arteries (Hybrid procedures).*
Results. *Stent-grafts were deployed successfully in all patients. One patient with Hybrid procedure developed major complications, required haemodialysis and died in hospital. In another patient the post-operative CT scan demonstrated a type I endoleak, but this had resolved by 3 months.*
Conclusion. *Inoue stent-grafting for TAAA with or without adjunctive open surgical revascularization is feasible.*

Keywords: Endvascular repair; Thoracoabdominal aneurysm; Inoue stent-graft.

Introduction

Several centres have described the feasibility of a hybrid endovascular approach for TAAA, with surgical reconstruction of visceral arteries.[1] Alternatively visceral perfusion can be preserved using either fenestrated or branched stent-grafts.[2] The purpose of this study was to assess the feasibility of Inoue stent-graft placement for TAAA.

Patients and Methods

Between March 2003 and December 2006, endovascular repair using Inoue stent-grafts, was undertaken in 8 patients with TAAAs at Kyoto University Hospital, Japan. All patients gave their informed consent in conformance with protocols approved by the institutional review board of the hospital.

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Patient characteristics are given in Table 1. Endovascular repair, using Inoue branched stent-grafts, was achieved in 4 patients (Branched group). However, the remaining 4 patients required open surgical revascularization of visceral arteries before stent-graft placement (Hybrid group).

Each Inoue stent-graft was custom made for the individual patient. Three kinds of Inoue stent-grafts were used in this study, straight, single branched and double branched stent-grafts (Fig. 1A). The implantation technique has been described previously[3,4] (Fig. 1B).

The coeliac artery (CA), superior mesenteric artery (SMA), and bilateral renal arteries (RAs) were reconstructed in 3 patients. One further patient underwent a combination of open surgical reconstruction and double branched stent-graft implantation (Case 8). The patient had chronic aortic dissection with a patent false lumen; the CA and SMA originated from a common coeliomesenteric trunk (CMT). The origin of the CMT and left RA was from the true lumen, but the right RA originated from the false lumen. Since the insertion of the branched graft to the right RA was difficult, the right RA was revascularized surgically.

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Table 1. Patient characteristics

Case number	Group	Age, Sex	Risk for open replacement	Aneurysm etiology	Crawford type	Aneurysm size	Involved visceral arteries	Adjunctive Procedure, Procedure time (minutes)	Stent-graft type, Procedure time (minutes)	Total Procedure time (minutes)	Complications	Hospital stay (days)	Follow-up period (months)	Events in the follow-up	Sac size change
1	Branched	78, M	None	Degenerative	I	63	CA	None	Single branched, 267	267	None	11	3	None	Stable
2	Branched	79, M	COPD	Degenerative	I	51	CA, SMA	Coil embolization of the CA, 255	Single branched, 255	350	None	19	24	Occlusion of the branched section to the SMA	Stable
3	Branched	78, M	IP	Degenerative	I	64	CA, SMA	Coil embolization of the CA, 195	Single branched, 195	320	Lymphorrhea	39	17	None	Stable
4	Branched	38, M	None	Chronic aortic dissection	I	49	CA, SMA	Coil embolization of the CA, 180	Single branched, 180	360	Gastric ulcers	36	15	None	Reduced
5	Hybrid	82, F	High age	Pseudoaneurysm, ruptured	III	83	CA, SMA, Lt. RA, Rt. RA	Bypass placement (CA, SMA, Rt. RA, Lt. RA), 130	Straight, 130	582	None	72	20	None	Reduced
6	Hybrid	77, F	None	Degenerative, ruptured	II	82	CA, SMA, Lt. RA, Rt. RA	Bypass placement (CA, SMA, Rt. RA, Lt. RA), 580	Straight, 580	819	Pneumonia, Renal damage	313	10	Death***	Stable
7	Hybrid	63, F	None	Chronic aortic dissection	II	65	Lt. SCA, CA, SMA, Lt. RA, Rt. RA	Bypass placement (CA, SMA, Rt. RA, Lt. RA), 510	Straight, 510	1093	Type I endoleak**	59	10	Disappearance of the initial endoleak	Reduced
8	Hybrid	40, M	None	Chronic aortic dissection	II	45	Celiomesenteric trunk*, Lt. RA, Rt. RA	Bypass placement (Rt. RA), 395	Double branched, 395	585	None	35	13	None	stable

M, Male; F, Female; Lt., Left; Rt., Right.
High age was defined as over 79 years.
* A common origin of the CA and SMA.
** The endoleak was from the distal attachment site, and dissolved 3 months after the stent-graft placement.
*** The cause of death was unrelated to the stent-grafting.

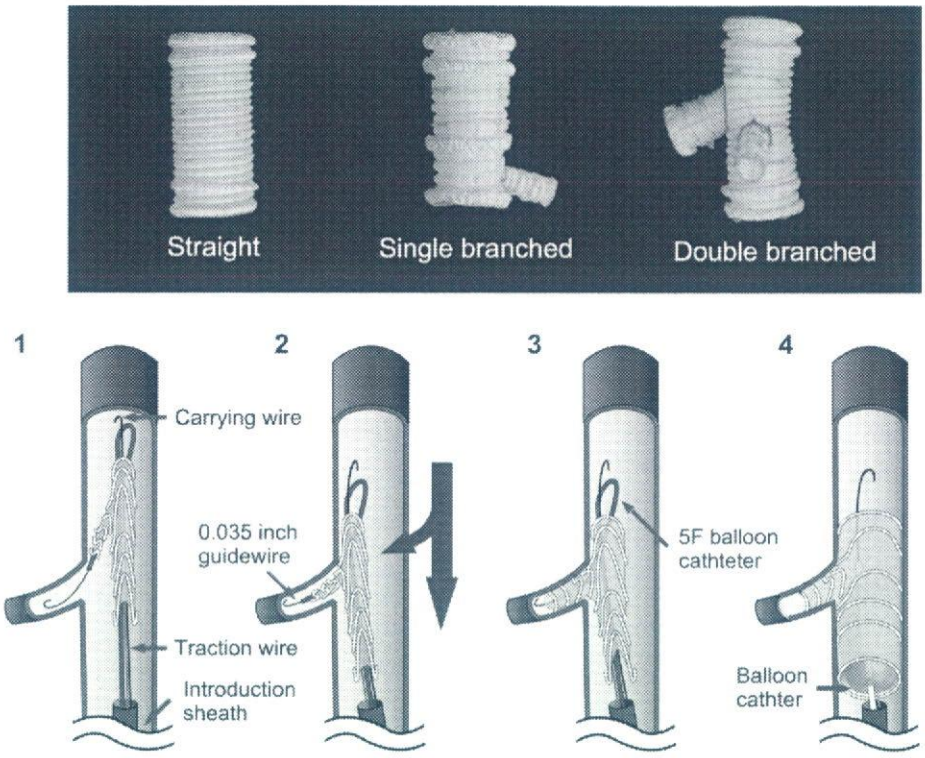

Fig. 1. Three kinds of the Inoue stent-graft for TAAA were used in this study. The straight graft was used in 3 patients (Case 5, 6 and 7), the single branched graft in 4 patients (Case 1–4), the double branched graft in 1 patient (Case 8). A. Single branched stent-graft implantation technique. 1. The folded stent-graft is delivered to the thoracoabdominal aorta through the introduction sheath using the carrying wire and traction wire. The 0.035-inch guidewire is selectively advanced to the target visceral artery through the 5F balloon catheters attached to the branched section. 2. The branched section is steered into the target visceral artery by pulling back the traction wire attached to the distal end of the aortic section. 3. The folded aortic section and the branched section are unfolded. The branched section is dilated by the 5F balloon catheter. 4. The aortic section is dilated by the custom made balloon catheter inserted thorough the introduction sheath.

The CMT and left RA were reconstructed using the Inoue double branched stent-graft. Three patients underwent deliberate coverage of the CA by the stent-graft to provide an adequate proximal landing zone and as prophylaxis against type II endoleak, as described previously.[3]

Results

The initial and follow-up results are summarized in Table 1; average follow-up period was 14 ± 7 months (rang, 3–24 months).

In the 4 patients requiring surgical revascularization of visceral arteries, 13/15 arteries were revascularized using open surgery and 2 arteries were reconstructed by the double branched stent-graft implantation, initial patency rate of 92% (12/13).

Three patients underwent prophylactic coil embolization of the CA.[5] One patient developed multiple gastric ulcers 2days after coil embolization (Case 4), which resolved after treatment with oral proton pump inhibitors. The procedure time for the coil embolization was 133 ± 43 minutes (range 95–180 minutes).

All the stent-grafts were deployed successfully. Average procedure time was 314 ± 164 minutes (range 130–580 minutes). In one patient (Case 6), the bypass graft to the right RA occluded and since the patient developed severe bacterial pneumonia and renal dysfunction, hemodialysis was required resulting in a prolonged hospital stay of 313 days: this patient died in hospital due to gastrointestinal bleeding. Median hospital stay was 40 days (range 11–313 days). Postoperative CT scans demonstrated an endoleak from the distal attachment site in one patient (Case 7), but this appeared to have resolved at 3 month follow up.

Significant sac size shrinkage was achieved in three patients (38%). Sac enlargement and stent-graft

migration were not observed. One branched section to the SMA occluded silently 6 months after the procedure.

Discussion

Implantation of Inoue branched stent-grafts in the thoracoabdominal aorta requires the following conditions. 1) The thoracoabdominal aorta is not severely tortuous. 2) The visceral artery does not have severe stenosis, calcification, dissection, mural thrombus or kinking, with a diameter of more than 5 mm. 3) The angle between thoracoabdominal aorta and visceral artery is less than 90°. 4) The visceral arteries do not originate from the aneurysm. 5) The procedure is conducted electively, since at 3 days is required for graft construction. In this manner, we have used the Inoue branched stent-graft only to treat successfully TAAA, either with or without adjunctive surgical revascularization of visceral arteries.

Conflict of interest

Dr. Kanji Inoue holds all patents of the Inoue stent-graft. The Inouestent-graft have been developed and made by Dr. Kanji Inoue.

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Long-Term Outcomes of Coronary-Artery Bypass Graft Surgery Versus Percutaneous Coronary Intervention for Multivessel Coronary Artery Disease in the Bare-Metal Stent Era

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Background—Observational registries comparing coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) have reported long-term survival results that are discordant with those of randomized trials.

Methods and Results—We conducted a multicenter study in Japan enrolling consecutive patients undergoing first CABG or PCI between January 2000 and December 2002. Among 9877 patients enrolled, 5420 (PCI: 3712, CABG: 1708) had multivessel disease without left main involvement. Because age is an important determinant when choosing revascularization strategies, survival analysis was stratified by either age ≥75 or <75 years. Analyses were also performed in other relevant subgroups. Median follow-up interval was 1284 days with 95% follow-up rate at 2 years. At 3 years, unadjusted survival rates were 91.7% and 89.6% in the CABG and PCI groups, respectively (log rank $P=0.26$). After adjustment for baseline characteristics, survival outcome tended to be better after CABG (hazard ratio for death after PCI versus CABG [HR], 95% confidence interval [CI]: 1.23 [0.99-1.53], $P=0.06$). Adjusted survival outcomes also tended to be better for CABG among elderly patients (HR [95%CI]: 1.37 [0.98-1.92] $P=0.07$), but not among nonelderly patients (HR [95% CI]: 1.09 [0.82-1.46], $P=0.55$). Unadjusted and adjusted survival outcome for CABG and PCI were not significantly different in any subgroups when elderly patients were excluded from analysis.

Conclusions—In the CREDO-Kyoto registry, survival outcomes among patients <75 years of age were similar after PCI and CABG, a result that is consistent with those of randomized trials. (***Circulation*. 2008;118[suppl 1]:S199–S209.**)

Key Words: coronary artery disease ■ percutaneous coronary intervention ■ coronary stent ■ coronary artery bypass graft (CABG) surgery ■ long-term outcome

Randomized controlled trials comparing coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) in the bare-metal stent era generally showed similar survival rates up to 5 years.[1-7] However, a recent report from New York's cardiac registries involving 59|314 patients demonstrated higher risk-adjusted survival rates at three years with CABG in all clinical and anatomic subgroups studied.[8] Similarly, an analysis from the Northern New England Registry revealed better survival with CABG among patients with triple-vessel disease.[9]

These conflicting observations between randomized trials and registries have raised much controversy, and the reasons for this discrepancy have not yet been well addressed. To further understand relative survival outcomes of CABG and

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PCI, we evaluated long-term outcomes of patients undergoing coronary revascularization in a large-scale multicenter registry in Japan.

Methods

Study Population

The CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome Study in Kyoto) is a multicenter registry in Japan enrolling consecutive patients undergoing first PCI or CABG and excluding those patients with acute myocardial infarction within a week before index procedure. The relevant review boards or ethics committees in all 30 participating centers (Table 1) approved the research protocol. Because of retrospective enrollment, written informed consent was not obtained from the patients; however, 73 patients were excluded because of their refusal to participate in the study when contacted for follow-up. This strategy is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor and Welfare of Japan.

Between January 2000 and December 2002, 9877 patients were identified to have undergone either CABG (2999 patients) or PCI (6878 patients) without prior history of coronary revascularization. Patients were enrolled from 21 centers for CABG (median number of patients from each center: 100 [19 to 550, interquartile range 57 to 199]), and from 30 centers for PCI (median number of patients from each center: 129 [16 to 1760, interquartile range 74 to 237]), respectively. Four hundred eighty-four patients undergoing concomitant valvular, left ventricular, or major vascular operation were excluded from the current analysis. Patients with disease of the left main coronary artery (PCI 165 patients, CABG 742 patients) and with single-vessel disease (PCI 3001 patients, CABG 65 patients) were excluded. Therefore, the study group comprised 5420 patients with multivessel coronary artery disease undergoing first coronary revascularization (PCI: 3712 patients, CABG: 1708 patients).

Data Collection and Definitions

Demographic, angiographic, and procedural data in both groups were collected from hospital charts or databases in each center by independent clinical research coordinators (Appendix) according to prespecified definitions. Follow-up data were obtained from hospital charts or by contacting patients or referring physicians.

Baseline clinical characteristics, such as myocardial infarction, heart failure, diabetes, hypertension, current smoker status, atrial fibrillation, chronic obstructive lung disease, and malignancy were regarded as present when these diagnoses were recorded in the hospital charts. Stroke at baseline included asymptomatic stroke detected by noninvasive imaging modalities. Peripheral vascular disease was regarded to be present when carotid, aortic, or other peripheral vascular disease were being treated or scheduled for surgical or endovascular interventions.

Elderly patients were defined as those patients ≥75 years of age. Left ventricular ejection fraction (LVEF) was measured either by contrast left ventriculography or echocardiography. Patients with LVEF ≤40% were regarded as having left ventricular dysfunction. Chronic kidney disease was regarded as present when creatinine clearance estimated by Cockcloft-Gould formula was less than 60 mL/min. Anemia was defined as blood hemoglobin level less than 12 g/dL.

An independent clinical events committee adjudicated events. Death was regarded as cardiovascular in origin unless obvious noncardiovascular causes could be identified. Any death during the index hospitalization was regarded as cardiovascular death. Myocardial infarction was adjudicated according to the definition in the Arterial Revascularization Therapy Study.[1] Within 1 week of the index procedure, only Q-wave myocardial infarction was adjudicated as myocardial infarction. Stroke at follow-up was defined as symptomatic stroke.

Statistical Analyses

After the descriptive statistics, we used Kaplan-Meier estimates to plot the percentage of patients in each group who died for any reason; data on patients who lost follow-up were censored. The log-rank test was used to identify significant differences in unadjusted survival rates. To determine the baseline risk factors for mortality, we conducted Log-rank tests for the following 30 potential variables: age, gender, body mass index, emergency procedure, prior myocardial infarction, congestive heart failure, stroke, peripheral arterial disease, atrial fibrillation, chronic obstructive pulmonary disease, malignancy, hypertension, diabetes without insulin therapy, diabetes with insulin therapy, hemodialysis, chronic kidney disease, anemia, current smoker status, LVEF, total occlusion, proximal LAD disease, triple vessel disease, and use of medications such as statins, aspirin, thienopyridines, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, and nitrates. All continuous variables were dichotomized for fitting proportional assumption according to the predetermined clinical contexts. We plotted log (time) versus log [-log (survival)] stratified by each significant risk factor and evaluated whether the plotted lines were parallel.[10] Those variables for which probability values were less than 0.05 in univariate analyses and proportional assumptions were generally fair were included in the multivariable analysis. We developed multivariable Cox proportional hazard models that controlled for significant risk factors while testing for significant differences in long-term survival between the 2 groups of patients undergoing CABG or PCI.

Analysis of treatment-related differences in long-term survival was stratified whether or not the patients have 5 prespecified risk factors, including triple vessel disease, diabetes, left ventricular dysfunction, proximal LAD disease, and elderly. The same factors used for analysis of the total cohort were incorporated in the multivariable models for subgroup analyses.

All analyses were conducted by the 2 physicians (Takeshi Kimura and Takeshi Morimoto) with the use of SAS software version 9.1 (SAS Institute Inc) and S-Plus version 7.0 (Insightful Corp) and all reported probability values were 2-sided. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

Baseline Characteristics

Baseline characteristics of the patients in the 2 groups are shown in Table 2. The PCI group included more elderly patients, particularly those ≥80 years of age. Although malignancy was more often found in the PCI group, the CABG group generally included more high-risk patients, such as those with left ventricular dysfunction, heart failure, prior myocardial infarction, diabetes, stroke, and anemia. However, mean EuroSCORE values were similar between the PCI and the CABG groups.

Regarding the complexity of coronary artery anatomy, the CABG group included more complex patients, such as those with triple-vessel disease, involvement of proximal LAD, and total occlusion. Patients in the CABG group underwent more complete revascularization as indicated by the number of vessels revascularized.

In the PCI group, bare-metal stents were used in 85% of patients. None of the patients received drug-eluting stents. Directional and rotational coronary atherectomy was used in 2% and 7% of patients, respectively. In the CABG group, internal mammary artery graft was used in 95% of patients. Forty-three percent of CABG operations were performed without cardiopulmonary bypass.

Medications such as statins, aspirin, thienopyridines, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, and nitrates were more frequently used in the PCI group than in the CABG group. Blood pressure and HbA1c level were significantly higher in the PCI group than in the CABG group.

Survival Outcome

Clinical follow-up were completed in 98% at 1 year, and 95% at 2 years. The median follow-up interval was 1319 days in the CABG group (interquartile range, 994 to 1642) and 1266 days in the PCI group (interquartile range, 933 to 1567).

In the total patient population, unadjusted survival outcomes were not different between the CABG and PCI groups (hazard ratio for death after PCI versus CABG [HR], 95% confidence interval [CI]: 1.11 [0.93-1.32], $P=0.26$; Table 3). Operative mortality in the CABG group evaluated at 30 days was only 1.1% as compared with 0.8% in the PCI group. At 3 years, unadjusted survival rates were 91.7% and 89.6% in

Table 2. Baseline Characteristics

	PCI (n=3712)	CABG (n=1708)	*P* Value
Age, y	68.1±9.9 (11–96)	66.9±9.4 (11–89)	0.0001
≥75 years	27%	21%	0.0001
≥80 years	12%	6%	0.0001
Female	30%	29%	0.17
Body mass index	23.8±3.3	23.6±3.2	0.04
Ejection fraction	62.1±13.6	59.4±14.5	0.0001
<40%	8%	12%	0.0001
Heart failure	15%	25%	0.0001
Functional class 3/4	5%	6%	0.17
Prior myocardial infarction	26%	38%	0.0001
Atrial fibrillation	6%	5%	0.13
Diabetes	43%	48%	0.0002
Insulin treated	9%	14%	0.0001
Oral drug treated	20%	21%	0.24
HbA1c	7.3±1.5	7.0±1.3	0.0002
Hypertension	73%	71%	0.1
Blood pressure			
Systolic	138.4±22.2	131.1±19.9	0.0001
Diastolic	75.6±13.3	71.4±11.8	0.0001
Current smoker	28%	25%	0.04
Stroke	17%	23%	0.0001
Peripheral vascular disease	6%	8%	0.046
Chronic pulmonary disease	2%	2%	0.86
Malignancy	8%	6%	0.0048
Chronic kidney disease	42%	45%	0.049
Dialysis	4%	5%	0.13
Anemia	25%	35%	0.0001
Emergency procedure	5%	4%	0.1
EuroSCORE	3.7±2.4	3.7±2.5	0.74
Triple vessel disease	38%	80%	0.0001
Proximal LAD disease	74%	94%	0.0001
Total occlusion	34%	53%	0.0001
Treatment of ≥2 Vessels	43%	95%	0.0001
No. of target vessels	1.5±0.6	2.6±0.5	0.0001
Medication at hospital discharge			
Statins	33%	21%	0.0001
Aspirin	89%	81%	0.0001
Thienopyridines	76%	11%	0.0001
ACE-I	27%	12%	0.0001
ARB	16%	10%	0.0001
β-blockers	22%	10%	0.0001
Calcium channel blockers	60%	61%	0.56
Nitrates	72%	46%	0.0001

ACE-I indicates angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

the CABG and PCI groups, respectively (log rank $P=0.26$) (Figure 1).

Survival rates at 3 years were similar in patients with Euro SCORE below or equal to median (3 points; CABG 96.1% versus PCI 95.6%, log rank $P=0.77$). However, survival rates at 3 years tended to be better for CABG in patients with EuroSCORE above median (CABG 87.5% versus 83.1%, log rank $P=0.06$).

By multivariable analysis, 14 independent predictors of all-cause mortality were identified, including age ≥75 years, chronic kidney disease, hemodialysis, history of heart failure, chronic obstructive lung disease, malignancy, anemia, periph-

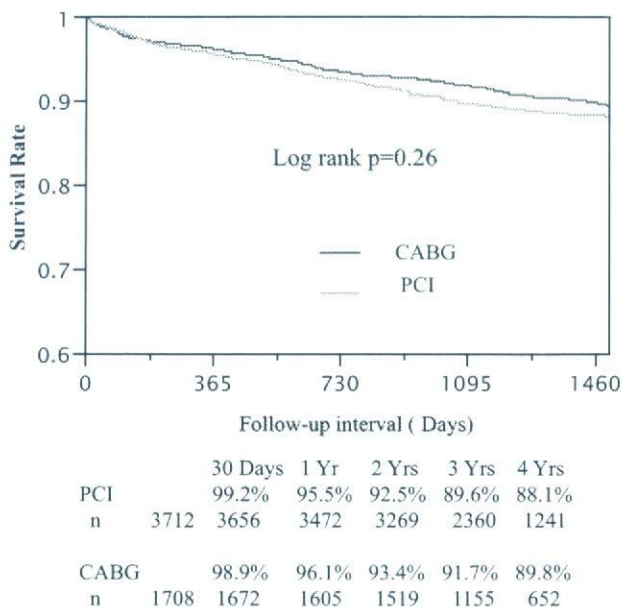
Table 3. Hazard Ratios for Death After PCI as Compared With That After CABG in Prespecified Subgroups

	No. of Patients (Event/Total)		Hazard Ratio (95% CI)		Interaction
	CABG	PCI	Unadjusted *P*	Adjusted *P*	*P* Value
All patients	181/1708	423/3712	1.11 (0.93–1.32) 0.26	1.23 (0.99–1.53) 0.06	
Triple vessel disease	153/1366	195/1412	1.29 (1.04–1.59) 0.02	1.09 (0.85–1.41) 0.5	0.7
Double vessels disease	28/342	228/2300	1.23 (0.83–1.83) 0.29	1.37 (0.89–2.12) 0.15	
Diabetes	95/824	227/1592	1.3 (1.02–1.65) 0.03	1.38 (1.02–1.86) 0.04	0.003
Nondiabetes	86/883	196/2117	0.96 (0.75–1.24) 0.77	1.09 (0.8–1.49) 0.6	
Diabetes/Insulin	36/243	61/338	1.28 (0.85–1.94) 0.24	1.18 (0.7–2.0) 0.53	0.57
Diabetes/Noninsulin	59/581	166/1254	1.37 (1.01–1.85) 0.04	1.46 (1.0–2.14) 0.05	
Diabetes/Triple vessel disease	83/693	108/667	1.44 (1.08–1.92) 0.01	1.14 (0.8–1.63) 0.46	0.41
Diabetes/Double vessel disease	12/131	119/925	1.45 (0.8–2.62) 0.22	1.88 (0.95–3.74) 0.07	
LVEF ≤40%	31/195	60/273	1.56 (1.01–2.41) 0.046	1.94 (1.12–3.34) 0.02	0.054
LVEF >40%	140/1430	286/3050	0.97 (0.8–1.19) 0.8	1.16 (0.91–1.47) 0.24	
Proximal LAD	173/1608	324//2729	1.14 (0.95–1.37) 0.17	1.21 (0.96–1.52) 0.11	0.8
No proximal LAD	8/100	99/983	1.3 (0.63–2.67) 0.48	1.31 (0.58–2.95) 0.51	
Age ≥75	65/367	222/1003	1.29 (0.98–1.7) 0.07	1.37 (0.98–1.92) 0.07	0.61
Age <75	116/1341	201/2709	0.88 (0.7–1.1) 0.27	1.09 (0.82–1.46) 0.55	

eral vascular disease, stroke, left ventricular dysfunction, body mass index ≤25.0, diabetes with insulin, absence of statin use, and use of angiotensin converting enzyme inhibitors.

When treatment modalities (CABG/PCI) were incorporated into this multivariable model, survival outcomes tended to be better after CABG (HR [95% CI]: 1.23 [0.99-1.53], $P=0.06$; Table 3).

Survival outcomes were compared in the prespecified high-risk subgroups. Even in high-risk patients, such as those with diabetes or triple-vessel disease, PCI was frequently chosen in this registry (66% and 51% of patients with diabetes and triple-vessel disease, respectively). CABG was associated with significantly better unadjusted-survival outcomes in patients with triple-vessel disease, diabetes, and left ventricular dysfunction (Table 3). After adjustment for baseline characteristics, the CABG group had significantly better survival outcomes in patients with diabetes, but not in patients with triple-vessel disease (Table 3).



		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		99.2%	95.5%	92.5%	89.6%	88.1%
n	3712	3656	3472	3269	2360	1241
CABG		98.9%	96.1%	93.4%	91.7%	89.8%
n	1708	1672	1605	1519	1155	652

Figure 1. Unadjusted Kaplan-Meier survival curves among all patients.

Influence of Age on the Survival Outcome After PCI and CABG

Because age is an important determinant in coronary revascularization strategy choice, survival analyses were stratified by age with a prespecified cut-off value of 75 years.

Survival outcomes favored CABG in patients ≥75 years of age (adjusted HR [95% CI]: 1.37 [0.98-1.92], $P=0.07$), but not in patients <75 years of age (adjusted HR [95% CI]: 1.09 [0.82-1.46], $P=0.55$) (Tables 3 and 4 and Figures 2 and 3). The magnitudes of the differences in survival rates between the CABG and PCI groups in patients ≥75 years of age were greater in the high-risk subgroups of triple-vessel disease, diabetes and left ventricular dysfunction (Table 4 and Figures 4 and 5).

In patients ≥75 years of age, unadjusted rates for all-cause mortality at 3 years were 13.3% and 20.7% in the CABG and PCI groups, respectively (log rank $P=0.07$). Rates of noncardiovascular and cardiovascular death tended to be higher in the PCI group. This trend for excessive noncardiovascular death rates in the PCI group was not observed in patients <75 years of age (Figures 2 and 3).

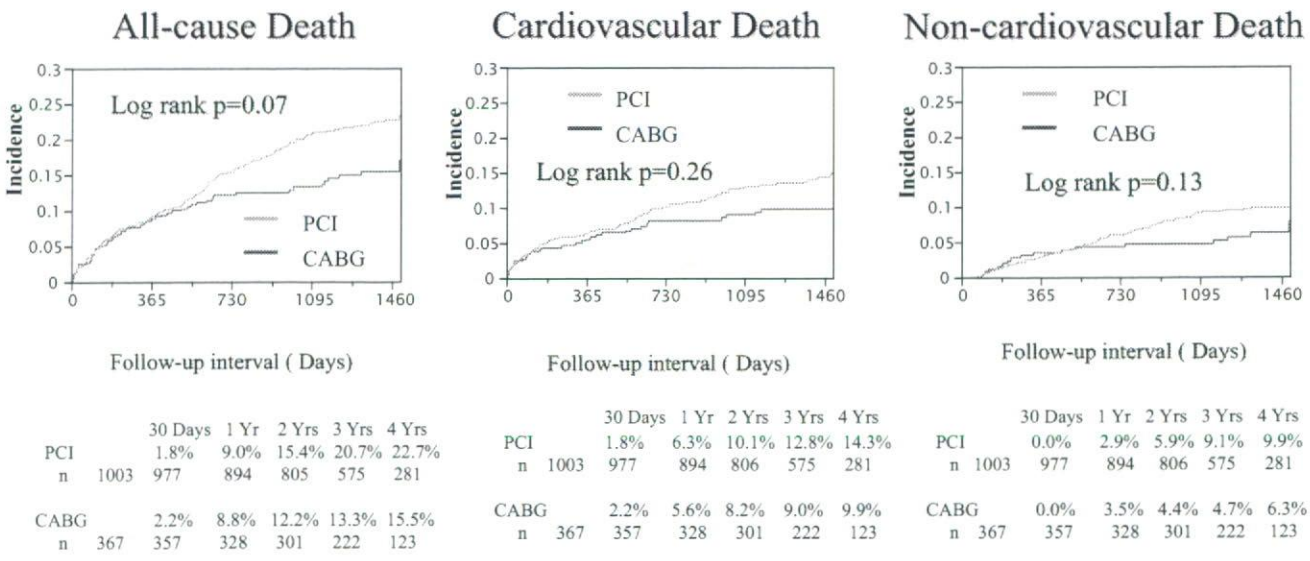
In patients <75 years of age, no differences between the 2 treatment modalities were apparent in either unadjusted or adjusted survival outcomes in any of the high-risk subgroups of triple-vessel disease, diabetes and left ventricular dysfunction (Table 4 and Figures 4 and 5).

Table 4. Hazard Ratios for Death After PCI as Compared With That After CABG in Prespecified Subgroups According to Age

	No. of Patients (Event/Total)		Hazard Ratio (95% CI)		Interaction
	CABG	PCI	Unadjusted *P*	Adjusted *P*	*P* Value
A. Age ≥75					
Triple vessel disease	54/297	119/429	1.6 (1.16–2.21) 0.004	1.29 (0.88–1.9) 0.2	0.81
Double vessels disease	11/70	103/574	1.22 (0.65–2.27) 0.54	1.32 (0.64–2.74) 0.46	
Diabetes	27/153	109/383	1.73 (1.13–2.63) 0.01	1.85 (1.1–3.12) 0.02	0.002
Nondiabetes	38/214	113/620	1.04 (0.72–1.5) 0.85	1.14 (0.72–1.8) 0.59	
Diabetes/insulin	6/32	23/73	1.58 (0.64–3.88) 0.32	2.16 (0.78–6.01) 0.14	0.82
Diabetes/noninsulin	21/121	86/310	1.73 (1.07–2.79) 0.03	1.75 (0.94–3.24) 0.08	
Diabetes/triple vessel disease	24/130	59/178	1.84 (1.15–2.96) 0.01	1.36 (0.75–2.46) 0.31	0.18
Diabetes/double vessel disease	3/23	50/205	2.47 (0.77–7.95) 0.13	7.29 (1.45–36.6) 0.02	
LVEF ≤40%	9/33	38/92	1.9 (0.92–3.95) 0.08	2.94 (1.09–7.95) 0.03	0.23
LVEF >40%	50/309	143/785	1.14 (0.82–1.57) 0.44	1.27 (0.87–1.85) 0.22	
B. Age <75					
Triple vessel disease	99/1069	76/983	0.86 (0.64–1.16) 0.33	0.92 (0.64–1.32) 0.65	0.27
Double vessels disease	17/272	125/1726	1.17 (0.7–1.94) 0.55	1.37 (0.79–2.37) 0.26	
Diabetes	68/671	118/1209	1.00 (0.74–1.34) 0.99	1.21 (0.83–1.78) 0.33	0.26
Nondiabetes	48/669	83/1497	0.79 (0.55–1.12) 0.18	0.99 (0.64–1.54) 0.97	
Diabetes/insulin	30/211	38/265	1.06 (0.66–1.72) 0.8	0.89 (0.46–1.72) 0.73	0.56
Diabetes/noninsulin	38/460	80/944	1.07 (0.73–1.59) 0.73	1.36 (0.82–2.24) 0.23	
Diabetes/triple vessel disease	59/563	49/489	1.02 (0.7–1.48) 0.94	0.98 (0.61–1.59) 0.95	0.45
Diabetes/double vessel disease	9/108	69/720	1.11 (0.55–2.22) 0.78	1.44 (0.65–3.2) 0.37	
LVEF ≤40%	22/162	22/181	0.95 (0.52–1.71) 0.86	1.26 (0.58–2.73) 0.56	0.34
LVEF >40%	90/1121	143/2265	0.8 (0.62–1.04) 0.1	1.08 (0.79–1.48) 0.61	

Other Cardiovascular End Points

Event-free rates from other cardiovascular end points are shown in Figure 6. The rate of freedom from myocardial infarction was significantly higher after CABG as compared with that after PCI. The incidences of myocardial infarction were similar at 30 days in the 2 groups. The 2 event-free curves for myocardial infarction diverged between 30 days and 1 year (incidences of myocardial infarction: 0.3% and 1.6% in the CABG and PCI groups, respectively). On the other hand, the incidences of myocardial infarction between 1 year and 3 years were similar in both groups (1.4% and 1.5% in the CABG and PCI groups, respectively).

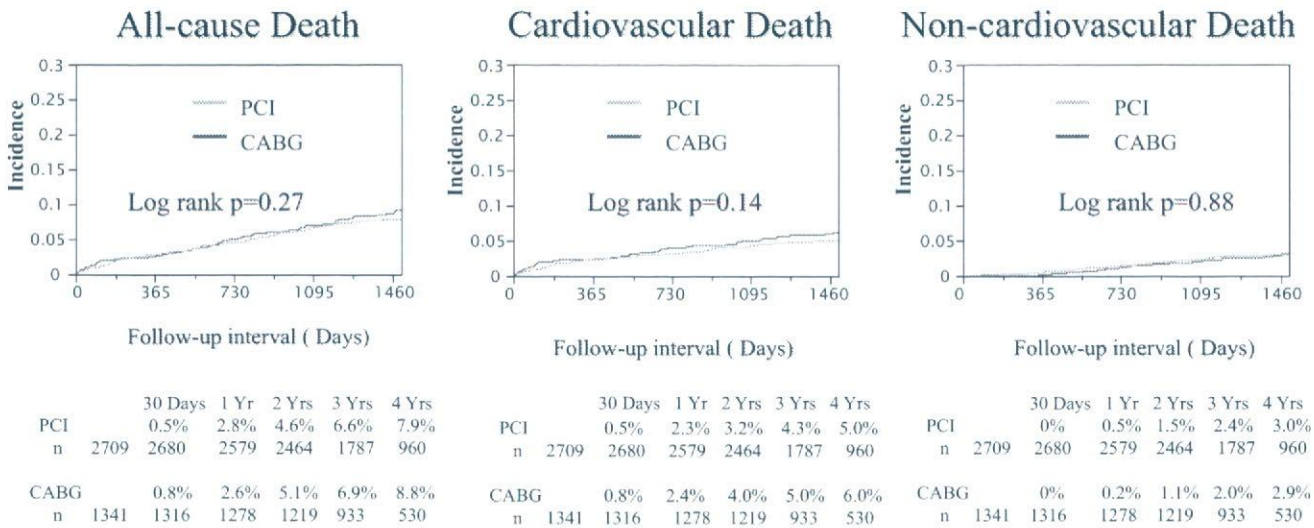


		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		1.8%	9.0%	15.4%	20.7%	22.7%
n	1003	977	894	805	575	281
CABG		2.2%	8.8%	12.2%	13.3%	15.5%
n	367	357	328	301	222	123

		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		1.8%	6.3%	10.1%	12.8%	14.3%
n	1003	977	894	806	575	281
CABG		2.2%	5.6%	8.2%	9.0%	9.9%
n	367	357	328	301	222	123

		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		0.0%	2.9%	5.9%	9.1%	9.9%
n	1003	977	894	806	575	281
CABG		0.0%	3.5%	4.4%	4.7%	6.3%
n	367	357	328	301	222	123

Figure 2. Cumulative incidence of all-cause death, cardiovascular death, and noncardiovascular death among patients with age ≥75.



		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		0.5%	2.8%	4.6%	6.6%	7.9%
n	2709	2680	2579	2464	1787	960
CABG		0.8%	2.6%	5.1%	6.9%	8.8%
n	1341	1316	1278	1219	933	530

		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		0.5%	2.3%	3.2%	4.3%	5.0%
n	2709	2680	2579	2464	1787	960
CABG		0.8%	2.4%	4.0%	5.0%	6.0%
n	1341	1316	1278	1219	933	530

		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		0%	0.5%	1.5%	2.4%	3.0%
n	2709	2680	2579	2464	1787	960
CABG		0%	0.2%	1.1%	2.0%	2.9%
n	1341	1316	1278	1219	933	530

Figure 3. Cumulative incidence of all-cause death, cardiovascular death, and noncardiovascular death among patients with age <75.

The rates of freedom from stroke were significantly higher after PCI versus CABG, a difference driven by a relatively higher rate of periprocedural stroke in the CABG group (1.8% and 0.2% in the CABG and PCI groups, respectively, at 30 days).

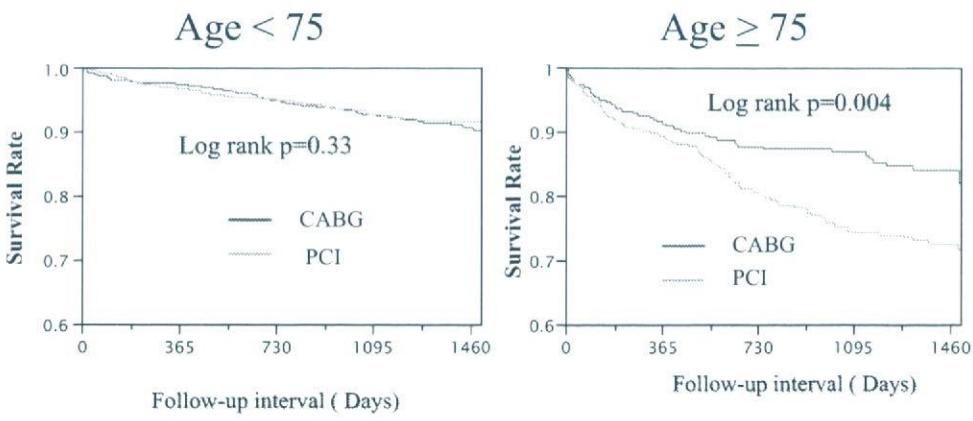
The rates of freedom from death, myocardial infarction, and stroke were similar between the 2 groups (87.8% and 86.8% in the CABG and PCI groups, respectively, at 3 years, log rank $P=0.63$).

The rate of freedom from any revascularization procedures was strikingly lower in the PCI group. At 3 years, only 51.7% of patients in the PCI group were free from any revascularization procedures as compared with 90.2% of patients in the CABG group. The rates of target-lesion revascularization in the PCI group were 33.4%, 35.9% and 37% at 1, 2, and 3 years, respectively. The rate of crossover to CABG in the PCI group was 7.2% at 3 years.

Discussion

The discrepancy in outcomes between randomized controlled trials and registries comparing PCI with CABG is commonly ascribed to usual enrollment in the former of very selected low-risk patients with multi vessel coronary artery disease who are suitable for PCI, a feature that limits the ability to generalize conclusions to many high-risk patient categories in real-world clinical practice.

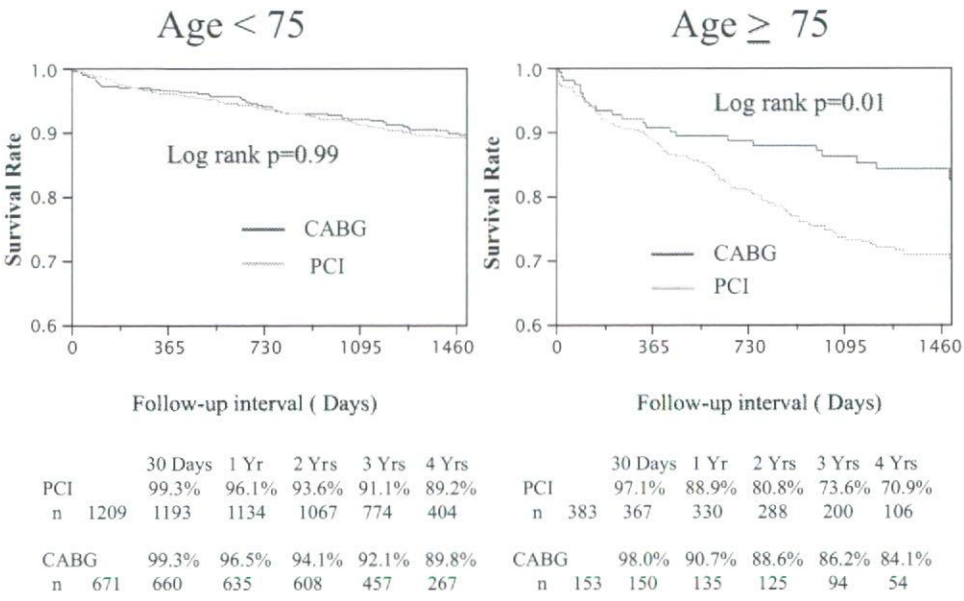
Our current analysis of CREDO-Kyoto registry data demonstrated both similar and discrepant results to those of other large-scale registries.[8,9] Although we also observed trends for better survival outcomes after CABG among overall and diabetic patient populations, in contrast to prior registries, adjusted survival outcomes were not significantly different in patients with triple-vessel disease. Differences in the practice pattern might be related to this discrepancy. Only 14% and 10% of patients with triple



		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		99.6%	96.7%	95.0%	92.6%	91.6%
n	983	971	927	880	641	337
CABG		99.2%	97.4%	94.8%	92.6%	90.8%
n	1069	1050	1021	975	751	427

		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		97.7%	89.4%	80.5%	74.6%	72.5%
n	429	419	379	331	240	120
CABG		97.6%	91.1%	87.6%	86.8%	84.0%
n	297	288	265	242	181	97

Figure 4. Unadjusted Kaplan-Meier survival curves according to age in patients with triple vessel disease.



		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		99.3%	96.1%	93.6%	91.1%	89.2%
n	1209	1193	1134	1067	774	404
CABG		99.3%	96.5%	94.1%	92.1%	89.8%
n	671	660	635	608	457	267

		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		97.1%	88.9%	80.8%	73.6%	70.9%
n	383	367	330	288	200	106
CABG		98.0%	90.7%	88.6%	86.2%	84.1%
n	153	150	135	125	94	54

Figure 5. Unadjusted Kaplan-Meier survival curves according to age in patients with diabetes.

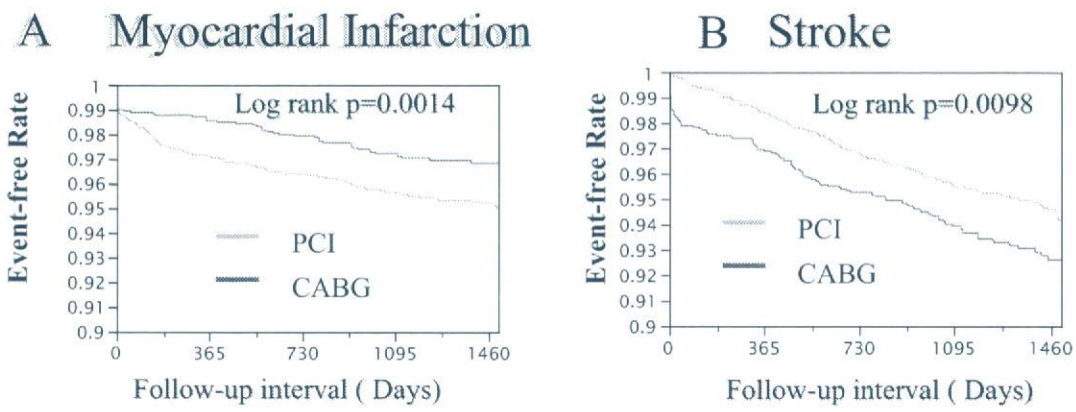
vessel disease were treated by PCI in the New York's cardiac registries and the Northern New England registry, respectively, an observation that is consistent with current guidelines that generally recommend CABG in patients with triple-vessel disease.[11,12] However, when CABG is the preferred treatment choice for triple-vessel disease patients, it is possible that the proportion of patients who have comorbidities that preclude choice of CABG would increase in the PCI group. Therefore, the practice pattern in Japan, which is reflected by the choice in the CREDO-Kyoto registry of PCI in 51% of patients with triple-vessel disease, may provide a more appropriate environment to compare PCI with CABG in this subgroup.

Age is an important determinant when considering the choice between CABG and PCI. We observed better survival rate in the CABG group in patients ≥75 years of age, especially in the high risk subgroups such as triple vessel disease and diabetes. Excellent outcome could be achieved by contemporary CABG even in elderly patients. Complex coronary anatomy in elderly patients might be more adequately managed by CABG. However, one could argue this result could be attributable to patient selection bias. Consistent with the latter argument, although better survival after CABG in elderly patients was also reported in the APPROACH registry,[13] the AWESOME randomized trial demonstrated similar survival outcomes in patients ≥70 years of age.[14] In real-world clinical practice, it is likely that elderly patients with significant comorbidities tend to be more often referred for PCI because of its less invasive nature. The trend for excessive noncardiovascular mortality observed among elderly patients who underwent PCI in this study is suggestive of patient selection bias. This trend for excessive noncardiovascular mortality in the PCI group was not seen in patients <75 years of age. Considering the potential presence of profound patient selection bias in the elderly population, it would be appropriate to exclude elderly patients when attempting observational comparisons between CABG and PCI. In the current analyses, unadjusted and adjusted survival rates of CABG and PCI were not different in any of the anatomic and clinical subgroups when elderly patients were excluded from analyses.

In this study, diabetes did not influence survival among nonelderly patients with triple vessel disease, which is an important difference with current guideline and prior studies.[8,9,11,12] This finding might relate to the characteristics of patients with diabetes in our population. Only a quarter of the diabetic patients in this study were insulin-treated diabetes. However, we could not find out any difference in terms of relative survival outcome for CABG as compared with PCI between diabetic patients with or without insulin use.

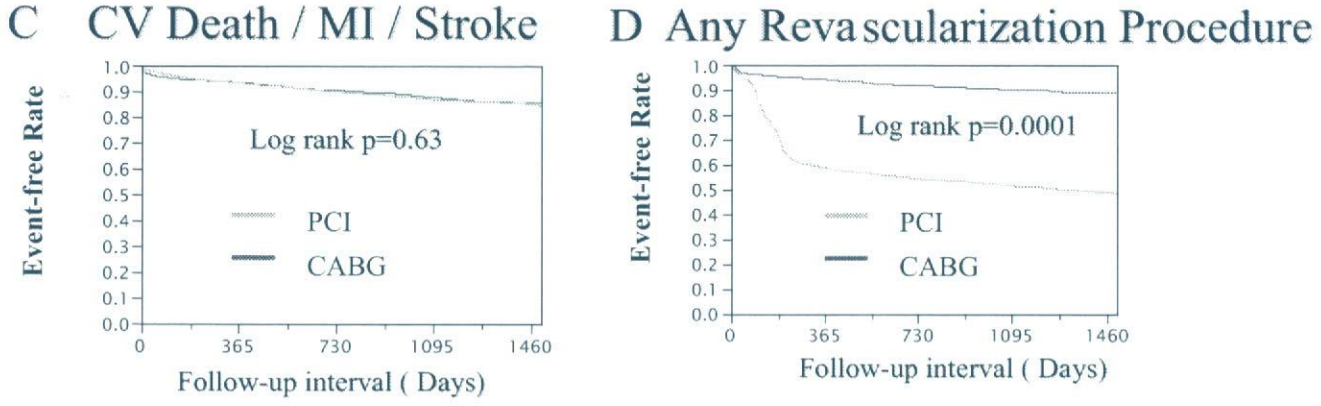
Another important issue regarding comparisons between CABG and PCI using observational study data are the fact that patients undergoing CABG are more likely to be subjected to extensive scrutiny for comorbidities. Underestimation of comorbidities in the PCI group could lead to results favoring CABG when multivariable analysis is performed to adjust for confounding factors.

Long-term follow-up studies to compare revascularization strategies have the inherent limitation that rapid technical and technological improvements often render the tested strategies obsolete by the time results are available. Although in the current study surgical practices and outcome rates (at least one internal mammary graft in 95% of patients, 43% off-pump procedures, and a 30-day survival rate of 98.8%) were comparable to contemporary ones, contemporary PCI procedures have already shifted from bare-metal to drug-eluting stenting with variable penetration rates. The striking efficacy of drug-eluting stents in preventing both clinical and angiographic restenosis[15,16] has led to a rapid expansion of PCI use particularly for patients with complex multivessel disease; however, improvement of survival has not yet been reported with use of drug-eluting stents.[17] In the ARTS-2 study, survival rates at 3 years were not significantly different



		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		98.7%	97.1%	96.4%	95.6%	95.2%
n	3712	3615	3392	3175	2272	1192
CABG		98.9%	98.6%	97.9%	97.2%	96.8%
n	1708	1656	1584	1493	1130	639

		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		99.8%	98.4%	96.8%	95.5%	94.6%
n	3712	3650	3433	3198	2290	1199
CABG		98.2%	96.9%	95.3%	93.9%	92.6%
n	1708	1644	1568	1467	1105	624



		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		97.9%	93.3%	89.9%	86.8%	85.1%
n	3712	3609	3356	3108	2206	1152
CABG		96.4%	93.4%	90.3%	87.8%	85.4%
n	1708	1629	1549	1446	1085	611

		30 Days	1 Yr	2 Yrs	3 Yrs	4 Yrs
PCI		96.1%	58.8%	54.4%	51.7%	48.7%
n	3712	3520	2043	1781	1215	625
CABG		97.0%	94.2%	91.6%	90.2%	88.7%
n	1708	1628	1515	1397	1045	592

Figure 6. Unadjusted event-free survival curves for myocardial infarction (panel A), stroke (panel B), cardiovascular death/myocardial infarction/stroke (panel C), and any coronary revascularization procedure (panel D).

among the 3 groups of ARTS-2, ARTS-1 CABG, and ARTS-1 PCI, initial advantage with sirolimus-eluting stent appeared to be diminished at 3 years of follow-up (Serruys PW, MD, unpublished data, 2007). Furthermore, the pooled analysis of the pivotal randomized trials of the sirolimus-eluting stents suggested excessive mortality in diabetic patients treated with the sirolimus-eluting stents as compared with those treated with bare-metal stents.[18] These observations underscore the need for longer-term follow-up of patients with multivessel coronary artery disease treated with drug-eluting stents. When we expand the indications of PCI to more complex subsets of patients by using drug-eluting stents, we should at least confirm that PCI in high risk patients using bare metal stents did not impair the long-term survival as compared with CABG.

Results regarding cardiovascular endpoints other than mortality also deserve some discussion. Although incidences of myocardial infarction were clearly lower after CABG versus PCI, the excess of myocardial infarction in the PCI group was only seen within 1 year after the index procedure. Besides progression of new lesions, abrupt closure, stent thrombosis and restenosis are among the mechanisms of myocardial infarction in this particular time period. Myocardial infarction secondary to these causes might be largely preventable by future development of better drug-eluting stents and improved use and availability of existing and novel adjunctive pharmacology. It is noteworthy that the incidences of myocardial infarction beyond one year were similar in both groups, although this observation needs confirmation with longer-term follow-up.

Restenosis had been the major drawback of PCI using bare-metal stent. Extremely high rate of repeated revascularization procedures in this study might be largely attributable to expanded use of PCI for more complex subsets of patients and high rate of angiographic follow-up in the Japanese clinical practice. However, the advent of drug-eluting stents have already markedly ameliorated the problems related to restenosis in real world clinical practice.[19]

There are several important limitations of this study. As compared with prior observational studies,[8,9] the sample size was not large enough to detect small differences in survival rates between the CABG and PCI groups. Although the definition of elderly patients was prespecified and seems clinically reasonable, the cut-off value of 75 years of age is arbitrary. Although variations in the frequencies of some anatomic factors such as numbers of diseased vessels, involvement of proximal LAD, and presence of total occlusions were adjusted for comparative analyses, our conclusions might not be applicable to those patients with other anatomic complexities, such as diffuse disease, heavy calcification or bifurcation that were not evaluated in this study. Furthermore, important medications, statins in particular, to prevent cardiovascular events are obviously underused. More optimal use of medications might have changed the long-term outcome of both CABG and PCI. Finally, the baseline characteristics such as age, body mass index, and prevalence of diabetes in the current population were markedly different from prior studies.[8,9] Although it is beyond the scope of the current article to discuss on the contribution of these demographic features to the different outcome in comparison to prior studies, we should admit that differences in racial, cultural, and socioeconomic factors might hinder generalization of the conclusions of this study outside Japan. Relatively low rate of recurrent coronary events in the Japanese population demonstrated in the REACH registry might have favorable influence on survival outcome after PCI.[20]

Despite the abovementioned study limitations, we would conclude that for patients with multivessel coronary artery disease, survival outcomes were similar among those who underwent either CABG or PCI with bare-metal stents in real-world clinical practice in Japan, when elderly patients are excluded from analysis.

Appendix

List of Clinical Research Coordinators

Kumiko Kitagawa, Hiromi Yoshida, Misato Yamauchi, Asuka Saeki, Chikako Hibi, Emi Takinami, Izumi Miki, Miya Hanazawa, Naoko Okamoto, Sachiko Maeda, Saeko Minematsu, Saori Tezuka, Yuki Sato, Yumika Fujino, Hitomi Sasae, Rei Fujita, Ayu Motofusa, Takami Hiraoka, Ayumi Yamamoto, Miho Hayashikawa, Yoko Fujiki.

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Disclosures

None.

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