TABLE 4. Multivariable analysis: Predictors of graft occlusion (FitzGibbon B or O)

Variable	OR	95% CI	*P* value
Age > 75 y	1.37	0.98-1.90	.064
Female sex	1.24	0.91-1.68	.183
NYHA class ≥ 3	0.89	0.60-1.35	.592
Recent MI (<90 d)	1.25	0.82-1.91	.301
LVEF < 50%	0.79	0.56-1.12	.181
CRF	0.67	0.34-1.33	.253
Hypertension	0.93	0.69-1.25	.627
Hypercholesterolemia	1.07	0.79-1.44	.668
Diabetes mellitus	1.06	0.79-1.40	.712
Left main disease	0.72	0.53-0.96	.028
Extracardiac arteriopathy	0.86	0.61-1.22	.401
Previous cardiac surgery	1.25	0.57-2.75	.580
Emergency	0.88	0.48-1.61	.683
First 100 cases	1.00	0.58-1.73	.995
Recipient coronary			
Stenosis > 75%	0.71	0.53-0.93	.013
Diameter < 1.5 mm	1.62	1.24-2.11	<.001
No. of anastomoses	1.04	0.89-1.21	.618
Conduit			
LITA	Reference		
RITA	0.75	0.45-1.26	.275
GEA	1.16	0.57-2.38	.684
SVG	1.37	0.78-2.40	.275
Radial artery	0.70	0.20-2.48	.579
Territory			
LAD	Reference		
LCx	1.06	0.69-1.61	.805
RCA	0.88	0.48-1.60	.668
Grafting technique			
Sequential graft	0.69	0.51-0.94	.018
Composite graft	1.61	0.98-2.62	.058
Endarterectomy	1.96	0.62-6.24	.254

OR, Odds ratio; *CI,* confidence interval; *NYHA,* New York Heart Association; *MI,* myocardial infarction; *LVEF,* left ventricular ejection fraction; *CRF,* chronic renal failure; *LITA,* left internal thoracic artery; *RITA,* right internal thoracic artery; *GEA,* gastroepiploic artery; *SVG,* saphenous vein graft; *LAD,* left anterior descending; *LCx,* left circumflex; *RCA,* right coronary artery.

In 1604 consecutive patients who underwent OPCAB, 89% received systematic catheter-based angiography before discharge. GEE logistic analysis was performed to identify the independent predictors of graft failure, and percent stenosis diameter (>75%), recipient coronary diameter (<1.5 mm), sequential graft, and left main disease were found to be predictors.

Percent Stenosis Diameter

When arterial grafts are used to bypass a low-grade stenosis, competitive flow may increase from the native coronary vessel.[18] Several authors also noted an association between decreased severity of stenosis and frequency of the string sign.[11] Miwa and colleagues[19] reported that the string sign of patent radial arteries was a consequence of competitive flow. The current authors and Desai and colleagues[15] have speculated that arterial remodeling to maintain shear stress against the endothelium in the setting of low flow may lead to graft failure.

Recipient Coronary Diameter

Desai and colleagues[15] noted that the distal run-off was strongly correlated with the size of the distal target vessel. Similar to percent stenosis diameter, recipient coronary diameter is deemed to influence the flow through the bypass conduits. Grafting small target vessels may be more technically demanding, especially on the beating heart. On the basis of the results of the subanalysis of each conduit (Table 5), an internal thoracic artery conduit could be expected to have excellent patency for the left coronary arteries even with small target-vessel size.

Sequential Graft

Sequential graft was revealed to be a determinant of graft patency. The primary advantages of this technique include a higher blood flow through the sequential graft than through the individual graft.[20] Intraoperative velocity studies showed a higher velocity of blood flow in the sequential graft.[21] Although a sequential graft may be technically difficult in OPCAB surgery, several authors have reported excellent results.[22]

Left Main Disease

The reason why left main disease served as a protective factor for graft patency was not identified from this retrospective study. When the study cohort was divided as to the sides of the coronary arteries grafted (left or right), left main disease was associated with graft patency in the left coronary arteries, not in the RCAs (data not shown). This result may imply that left main disease, in addition to percent stenosis diameter, decreased the risk of competitive flow. It is also conceivable that patients who have significant left main disease are good candidates for not only CCAB[23] but also OPCAB surgery. However, noncritical, isolated left main stenosis may cause competitive flow. Relationships between graft patency in OPCAB surgery and left main disease (eg, ostial, mid-shaft, and noncritical lesions) need to be evaluated in the future.

Subanalysis: Left Internal Thoracic Artery

In our subanalyses, less severe percent stenosis diameter was associated with LITA graft failure. Doppler studies suggested that severity of stenosis is associated with flow and size of the LITA graft.[18] However, adaptive shrinkage of the arterial conduits may be reversible as the native coronary stenosis progresses.

Subanalysis: Gastroepiploic Artery

Recipient coronary diameter influenced the patency of the GEA. The GEA may be more susceptible to having

ACD

TABLE 5. Subanalysis of each conduit

Variable	LITA			RITA			GEA			SVG		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Recipient coronary												
Stenosis > 75%	0.61	0.40-0.94	.025	0.77	0.45-1.31	.331	0.91	0.93-2.11	.826	0.96	0.53-1.73	.878
Diameter < 1.5 mm	1.14	0.71-1.82	.591	1.65	0.98-2.80	.061	2.37	1.08-5.20	.032	2.36	1.32-4.19	.004
Territory												
LAD	Reference			1.22	0.66-2.25	.531	—	—	—	—	—	—
LCx	0.85	0.37-1.97	.706	Reference			4.39	1.66-11.61	.003	1.25	0.70-2.26	.449
RCA	—	—	—	—	—	—	Reference			Reference		
Grafting technique												
Sequential graft	0.99	0.59-1.67	.968	0.94	0.53-1.69	.845	0.33	0.15-0.70	.004	0.76	0.41-1.40	.375
Composite graft	—	—	—	0.86	0.44-1.72	.676	—	—	—	1.46	0.64-3.30	.369
Endarterectomy	—	—	—	—	—	—	—	—	—	3.45	0.75-15.88	.111

LITA, Left internal thoracic artery; *RITA*, right internal thoracic artery; *GEA*, gastroepiploic artery; *SVG*, saphenous vein graft; *OR*, odds ratio; *CI*, confidence interval; *LAD*, left anterior descending; *LCx*, left circumflex; *RCA*, right coronary artery.

a contractile response in the low-flow situation than the LITA because of their different histologic characteristics.[24] We preferentially used the GEA grafts for the RCA system with severe stenosis (>75%). This may partly explain the reason why recipient coronary diameter, not percent stenosis diameter, influenced GEA patency. On the other hand, a sequential graft seems advantageous with GEA grafts, as shown in the subanalysis (Table 5). This technique may help increase the graft flow.

The LCx system was associated with graft failure. In our experience, by harvesting in a skeletonized fashion, the GEA grafts could reach the LCx in some cases. The higher failure rate of this configuration may be attributed to spasm of the distal portion of the GEA and tension on the graft. We have abandoned this configuration and adopted the SVG and the RITA for mild and severe lesions of the LCx, respectively.

Subanalysis: Saphenous Vein Graft

SVG failure was associated with smaller recipient coronary diameter. Goldman and colleagues[16] reported that the smaller diameter of the recipient vessel was a determinant in both early and long-term vein graft patency. Schwartz and colleagues[25] noted that the SVG was a risk factor for graft occlusion in the Bypass Angioplasty Revascularization Investigation study, whereas the type of conduit was not associated with graft patency in our series. This discordance may be, in part, ascribed to routine heparin use.[12] Presumably, an increase in coagulability may account for the early graft occlusion. Therefore, we believe that high-risk patients may require aggressive anticoagulation in addition to antiplatelet therapy after OPCAB.

In 83 cases, proximal anastomotic devices were applied. We previously reported that the early patency rate of these SVGs was 100%.[12] As a result, these devices did not adversely influence the graft patency in this study.

Study Limitations

First, percent stenosis diameter was derived from qualitative assessment by one observer. Other investigators drew conclusions similar to ours in that small target vessel size adversely affected graft patency, although the size of the target vessel was derived from single-observer visual assessment at the time of patient enrollment and not quantitative angiography.[15] Second, all procedures were performed by a single surgeon, and the results of the angiography were derived from the OPCAB surgery on the basis of our grafting strategy, limiting the generalizability of these results. Third, catheter-based angiography was performed in only 89% of the consecutive patients, because MDCT took the place of catheter-based angiography after 2 patients experienced cerebral infarction. Because 16-detector row CT has some limitations (eg, lower spatial and temporal resolution), patients who underwent MDCT were omitted from the study cohort. In addition, the angiography results were read by several cardiologists. Fourth, we did not evaluate long-term patency rates. However, we agree with Goldman and colleagues[16] in that initial patency at 1 week after surgery is an important predictor of long-term graft patency. Fifth, we could not compare the angiographic results between OPCAB and on-pump coronary artery bypass grafting, because only 77 patients underwent on-pump coronary artery bypass grafting in Kokura Memorial Hospital (Kokura, Japan) during the study period. Sixth, we cannot reach any conclusions regarding the radial artery graft because of the small sample size. Finally, the quality of the recipient coronary arteries, the size of the conduits, and the flow data were not recorded in our database. Despite these limitations, the findings of this study were derived from the largest angiographic study to date of OPCAB surgery. In addition, the analyses were based on rigorous statistical methodology.

CONCLUSIONS

Severe percent stenosis diameter and small recipient coronary diameter were associated with graft patency in

OPCAB surgery. A better patency rate would be expected when anastomosing the LITA to a coronary artery with severe stenosis. Sequential grafting technique could be expected to improve the patency rates of off-pump bypass grafts, especially for the GEA. Patients with significant left main disease may be good candidates for OPCAB surgery.

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000 Early angiographic evaluation after off-pump coronary artery bypass grafting

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One of the potential drawbacks of OPCAB is reduced patency compared with conventional coronary artery bypass. This study examined the systematic angiographic evaluation after OPCAB. Smaller coronary diameter was found to be a predictor of graft failure, whereas percent stenosis diameter greater than 75%, sequential graft, and left main disease were protective factors.

Comparison of Frequency of Postoperative Stroke in Off-Pump Coronary Artery Bypass Grafting Versus On-Pump Coronary Artery Bypass Grafting Versus Percutaneous Coronary Intervention

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The stroke rate after coronary artery bypass grafting (CABG) compared to percutaneous coronary intervention (PCI) is generally considered high because cardiopulmonary bypass and aortic manipulations are often associated with cerebrovascular complications. However, an increasing number of CABGs performed without cardiopulmonary bypass (OPCAB) may improve those outcomes. Of 6,323 patients with multivessel and/or left main coronary artery disease, 3,877 patients underwent PCI, 1,381 conventional on-pump CABG, and 1,065 OPCAB. Median follow-up was 3.4 years. Stroke types were classified as early (onset of stroke within 24 hours after revascularization), delayed (within 30 days), and late (after 30 days). Propensity score analysis showed that the incidences of early, delayed, and late stroke did not differ between PCI and OPCAB (0.65, 95% confidence interval 0.08 to 5.45, p = 1.00; 0.36, 0.10 to 1.29, p = 0.23; 0.81, 0.52 to 1.27, p = 0.72, respectively). In contrast, incidence of early stroke after on-pump CABG was higher than after OPCAB (7.22, 1.67 to 31.3, p = 0.01), but incidences of delayed and late stroke were not different (1.66, 0.70 to 3.91, p = 0.50; 1.18, 0.83 to 1.69, p = 0.73). In conclusion, occurrence of stroke was not found to differ in patients after PCI versus OPCAB regardless of onset of stroke. Occurrence of early stroke after OPCAB was lower than that after on-pump CABG, yet occurrences of delayed and late strokes were similar for the 3 revascularization strategies. **(Am J Cardiol 2012;110:1773–1778)**

Off-pump coronary artery bypass grafting (CABG; OPCAB) was developed to decrease complications associated with cardiopulmonary bypass and aortic manipulations.[1] Although the long-term survival benefit of OPCAB compared to conventional on-pump CABG has been a source of controversy, several studies have reported the potential of OPCAB in decreasing stroke-related mortality and morbidity compared to on-pump CABG.[1–3] In addition, an increasing number of OPCAB procedures may improve the overall outcome of CABG. Therefore, an investigation of the impact of OPCAB for risk stratification and modification of strokes after coronary revascularization has important implications. The purpose of this study was to identify occurrences and preoperative risk factors of strokes after percutaneous coronary intervention (PCI), on-pump CABG, or OPCAB and to investigate the impact of OPCAB on stroke prevention.

Methods

The Coronary REvascularization Demonstrating Outcomes Study in Kyoto (CREDO-Kyoto) is a multicenter registry in Japan that enrolls consecutive patients undergoing first PCI or CABG and excludes those patients with acute myocardial infarction within 1 week before the index procedure.[4] This study was approved by the institutional review boards or ethics committees of all participating institutions. Because the subjects were enrolled retrospectively, written informed consent was not obtained in accord with guidelines for epidemiologic studies issued by the Ministry of Health, Labor and Welfare of Japan. However, 73 patients were excluded because of their refusal to participate in the study when contacted for follow-up.[4]

From January 2000 through December 2002, 9,877 patients were identified as having undergone PCI (6,878 patients) or CABG (2,999 patients) without previous coronary revascularization. Of these, patients with multivessel and/or left main coronary artery disease were included in the present study. Four hundred eighty-four patients undergoing

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Table 1
Baseline characteristics

Variables	PCI (n = 3,877)	On-Pump CABG (n = 1,381)	OPCAB (n = 1,065)	p Value*
Age (years)	68.3 ± 10.0	66.3 ± 9.3	68.6 ± 9.3	<0.01
Age >75 years	1,081 (27.9%)	260 (18.8%)	306 (28.7%)	<0.01
Male gender	2,704 (69.7%)	1,007 (72.9%)	751 (70.5%)	0.08
Body mass index (kg/m²)	23.7 ± 3.3	23.5 ± 3.2	23.7 ± 3.2	0.03
Number of narrowed coronary arteries	2.35 ± 0.53	2.58 ± 0.73	2.55 ± 0.74	<0.01
3	1,461 (37.7%)	958 (69.4%)	705 (66.2%)	<0.01
Left main coronary artery	165 (4.3%)	410 (29.7%)	330 (31.0%)	<0.01
Chronic total occlusion	1,301 (33.6%)	672 (48.7%)	455 (42.7%)	<0.01
Proximal left anterior descending coronary artery disease	2,831 (73.0%)	1,179 (85.4%)	909 (85.4%)	<0.01
Old myocardial infarction	1,006 (25.9%)	489 (35.4%)	338 (31.7%)	<0.01
Heart failure	569 (14.7%)	316 (22.9%)	302 (28.4%)	<0.01
Ejection fraction (%)	62.1 ± 13.6	58.6 ± 15.0	61.3 ± 13.7	<0.01
Ejection fraction <40%	279 (7.2%)	174 (12.6%)	86 (8.1%)	<0.01
Peripheral artery disease	367 (9.5%)	239 (17.3%)	248 (23.3%)	<0.01
Carotid artery disease	105 (2.7%)	114 (8.3%)	158 (14.8%)	<0.01
Stroke	607 (15.7%)	237 (17.2%)	286 (26.9%)	<0.01
Atrial fibrillation	254 (6.6%)	80 (5.8%)	60 (5.6%)	0.41
Chronic pulmonary disease	83 (2.1%)	30 (2.2%)	22 (2.1%)	0.98
Malignancy	321 (8.3%)	80 (5.8%)	79 (7.4%)	0.01
Hypertension	2,810 (72.5%)	918 (66.5%)	801 (75.2%)	<0.01
Diabetes mellitus	1,651 (42.6%)	642 (46.5%)	498 (46.8%)	<0.01
Hyperlipidemia	1,955 (50.4%)	710 (51.4%)	608 (57.1%)	<0.01
Chronic kidney disease	1,411 (36.4%)	532 (38.5%)	424 (39.8%)	0.08
Dialysis	167 (4.3%)	69 (5.0%)	53 (5.0%)	0.45
Hemoglobin (mg/dl)	13.1 ± 2.0	12.7 ± 2.0	12.6 ± 2.0	<0.01
Hemoglobin <12 mg/dl	972 (25.1%)	452 (32.7%)	350 (32.9%)	<0.01
Emergency	191 (4.9%)	77 (5.6%)	75 (7.0%)	0.03
Critical preoperative state†	40 (1.0%)	25 (1.8%)	24 (2.3%)	<0.01

* Comparison among percutaneous coronary intervention, on-pump off-pump coronary artery bypass grafting, and off-pump coronary artery bypass grafting by analysis of variance and chi-square test.

† Ventricular tachycardia/ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anesthesia, preoperative inotropes or intra-aortic balloon pumping, preoperative acute renal failure.

concomitant valvular, left ventricular, or major vascular surgery were excluded from the present analysis. Patients with 1-vessel disease without left main coronary artery disease (3,001 patients with PCI and 65 patients with CABG) were also excluded. Therefore, the study group consisted of 6,323 patients undergoing first coronary revascularization (3,877 patients with PCI, 2,446 patients with CABG). Demographic, angiographic, and procedural data were collected from hospital charts or databases in each center by independent clinical research coordinators according to prespecified definitions. 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 hospital charts. Left ventricular ejection fraction was measured by contrast left ventriculography or echocardiography. Chronic kidney disease was regarded as present when creatinine clearance estimated by the Cockcroft–Gould formula was <60 ml/min. Anemia was defined as a blood hemoglobin level <12 g/dl as previously described.[4]

Stroke was defined as any new permanent global or focal neurologic deficit that could not be attributed to other neurologic or medical processes. In most patients, strokes were diagnosed by neurologists and confirmed by computed tomographic or magnetic resonance imaging head scans. Documentation of previous stroke required verification by each patient's primary care physician, review of medical records, and review of results of computed tomography and magnetic resonance imaging if available. Follow-up data were obtained from hospital charts or by contacting patients or referring physicians and were closed at December 2006 with a survey for all patients. An independent clinical events committee adjudicated all events. If sufficient follow-up data were unavailable, investigators contacted patients by telephone or letter. If a patient was deceased at time of contact, the investigators tried, to the furthest extent possible, to obtain data from the family regarding the patient's death including nonfatal events such as stroke that may have occurred before time of death.

The primary end point determined type of stroke. A stroke that occurred within 24 hours after coronary revascularization was regarded as an "early" stroke, that after 24 hours and within 30 days as a "delayed" stroke, and that after 30 days as a "late" stroke. An independent clinical events committee adjudicated events. Baseline characteristics of patients in the 3 groups are presented in Table 1. The on-pump CABG and OPCAB groups generally included more high-risk patients such as those with a history of stroke, left ventricular dysfunction, heart failure, previous

Table 2
Incidence of stroke after coronary revascularization

Variables	Patients	Early (≤24 hours)	Delayed (>24 hours to ≤30 days)	Late (>30 days)	Total
Percutaneous coronary intervention	3,877	3 (0.08%)	6 (0.15%)	182 (4.69%)	191 (4.93%)
On-pump coronary artery bypass grafting	1,381	18 (1.30%)	17 (1.23%)	72 (5.21%)	107 (7.75%)
Off-pump coronary artery bypass grafting	1,065	2 (0.19%)	8 (0.75%)	54 (5.07%)	64 (6.01%)
Total	6,323	23 (0.36%)	31 (0.49%)	308 (4.87%)	362 (5.73%)

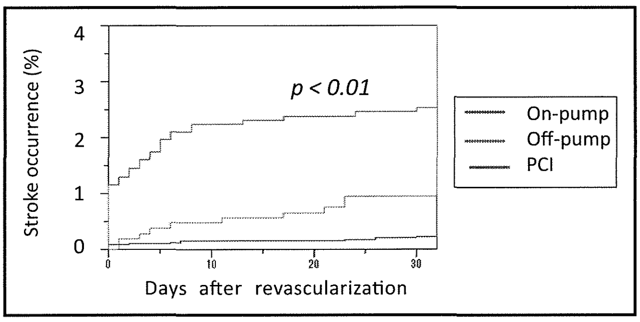

Figure 1. Kaplan–Meier curves for stroke within 30 days comparing percutaneous coronary intervention *(bottom curve)*, on-pump coronary artery bypass grafting *(top curve)*, and off-pump coronary artery bypass grafting *(middle curve)*.

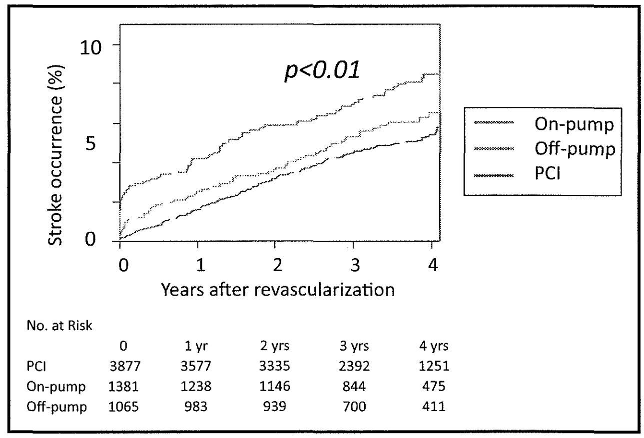

Figure 2. Kaplan–Meier curves for overall stroke comparing percutaneous coronary intervention *(bottom curve)*, on-pump coronary artery bypass grafting *(top curve)*, and off-pump coronary artery bypass grafting *(middle curve)*.

myocardial infarction, chronic kidney disease, and anemia. Patient with diabetes were more commonly found in the on-pump CABG and OPCAB groups. Regarding the complexity of coronary artery anatomy, the on-pump CABG and OPCAB groups included more complex patients such as those with 3-vessel disease, left main coronary artery disease, involvement of the proximal left anterior descending coronary artery, and total occlusion. All continuous variables were expressed as mean ± SD. Differences in baseline characteristics across the 3 groups were examined by analysis of variance of chi-square test. Logistic regression and Cox proportional hazard models were used to identify risk factors for early, delayed, and late stroke. Proportional hazard assumption was checked using a log-log plot. Odds or hazard ratios, 95% confidence intervals [CIs], and p values were reported. Propensity scores, which identified the probability that a patient would undergo PCI or on-pump CABG, were calculated for each patient. Propensity scores were estimated separately with a multivariable polytomous logistic regression model. Confounding factors in the logistic regression included age, gender, body mass index, emergency procedure, critical preoperative state (ventricular tachycardia/ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anesthesia room, preoperative inotropes or intra-aortic balloon pumping, preoperative acute renal failure), previous myocardial infarction, congestive heart failure, stroke, peripheral arterial disease, carotid artery disease, atrial fibrillation, chronic obstructive pulmonary disease, malignancy, hypertension, diabetes, hemodialysis, chronic kidney disease, anemia, current smoker status, left ventricular ejection fraction, total occlusion, proximal left anterior descending coronary artery disease, 3-vessel disease, and left main coronary artery disease. The c-statistics of the propensity score for PCI was 0.941 (95% CI 0.936 to 0.946) and that for on-pump CABG was 0.896 (95% CI 0.888 to 0.903).

Outcomes after PCI, on-pump CABG, or OPCAB were compared by logistic regression or Cox proportional hazard models stratified by quartiles of propensity scores. This analysis was performed according to the intent-to-treat principle. There were few patients with the opposite treatment in the first quartile of the propensity score for PCI and the fourth quartile of the propensity score for on-pump CABG, suggesting a systematic treatment selection; thus, we excluded these subsets. Propensity score–adjusted odds or hazard ratios, 95% CIs, and p values were reported. The p values for multiple comparisons, namely PCI versus OPCAB and on-pump CABG versus OPCAB, were adjusted by Bonferroni correction. Further, we conducted propensity score–adjusted logistic regression and Cox regression analyses with random effects for center-to-center differences as sensitivity analyses.

All reported p values were 2-sided. All analyses were conducted by a statistician using SAS 9.2 (SAS Institute, Cary, North Carolina) and S-Plus 7.0 (Insightful Corp., Seattle, Washington). The authors had full access to the data and take responsibility for their integrity. All authors have read and agreed to the report as written.

Results

Clinical follow-ups were completed for 98% of patients at 1 year and for 95% of patients at 2 years. Median follow-up period was 1,287 days. Thirty-day mortalities were 0.85%, 2.2%, and 0.83% in the PCI, on-pump CABG,

Table 3
Risk ratios for death after revascularization adjusted by propensity score stratification

Variables	Propensity Score–Adjusted Risk Ratio (95% CI)	p Value
Early stroke		
Percutaneous coronary intervention vs off-pump coronary artery bypass grafting	0.65 (0.08–5.45)	1.00
On-pump vs off-pump coronary artery bypass grafting	7.22 (1.67–31.3)	0.01
Delayed stroke		
Percutaneous coronary intervention vs off-pump coronary artery bypass grafting	0.36 (0.1–1.29)	0.23
On-pump vs off-pump coronary artery bypass grafting	1.66 (0.7–3.91)	0.50
Late stroke		
Percutaneous coronary intervention vs off-pump coronary artery bypass grafting	0.81 (0.52–1.27)	0.72
On-pump vs off-pump coronary artery bypass grafting	1.18 (0.83–1.69)	0.73

There were 4,608 patients because patients in the first quartile of the propensity score for percutaneous coronary intervention and the fourth quartile of the propensity score for on-pump off-pump coronary artery bypass grafting were excluded owing to systematic treatment selection.

and OPCAB groups and overall mortalities were 11.7%, 11.2%, and 11.7%, respectively.

Occurrences of stroke after each revascularization procedure for each period are presented in Table 2. Kaplan–Meier curves for stroke within 30 days are shown in Figure 1. Unadjusted occurrences of stroke varied among the 3 groups ($p < 0.01$). Kaplan–Meier curves for overall stroke are shown in Figure 2. Occurrences of stroke at 30 days, 1 year, and four years were 0.23%, 1.6%, and 5.4% for PCI, 2.5%, 4.2%, and 8.5% for on-pump CABG, and 0.94%, 2.5%, and 6.5% for OPCAB, respectively. Unadjusted occurrences of stroke varied among the 3 groups ($p < 0.01$).

Risk ratios for stroke after PCI versus OPCAB or on-pump CABG versus OPCAB are listed in Table 3. Propensity score analysis showed that the incidence of early stroke after PCI was similar to that after OPCAB. In contrast, the incidence of early stroke after on-pump CABG was much higher than that after OPCAB. However, the incidence of delayed stroke was not different between PCI and OPCAB or between on-pump CABG and OPCAB. Similarly, the incidence of late stroke was not different between PCI and OPCAB or between on-pump CABG and OPCAB. Predominant preoperative risk factors for early, delayed, and late stroke are presented in Table 4.

Discussion

In the present study, we investigated preoperative risk factors for stroke for each period and evaluated the impact of OPCAB on the prevention of stroke compared to PCI in Japanese patients with coronary artery disease. It is noteworthy that propensity score–adjusted occurrences of stroke were not found to differ between the PCI and OPCAB groups regardless of the onset of stroke (early, delayed, or late). Because the early stroke rate after OPCAB was lower than that after on-pump CABG, OPCAB may decrease the probability of perioperative stroke to a value comparable to that of PCI. Further improvements in postoperative management after OPCAB may decrease the occurrence of early stroke similar to that after PCI. The late (>30 days) stroke rates did not differ among the 3 revascularization procedures.

Table 4
Preoperative risk factors for early, delayed, and late stroke

	Odds/Hazard Ratio* (95% CI)	p Value
Early stroke		
Stroke	3.95 (1.73–9.00)	<0.01
Atrial fibrillation	3.16 (1.13–8.87)	0.03
Chronic kidney disease	2.79 (1.18–6.59)	0.02
3-vessel disease	2.15 (0.8–5.8)	0.13
Peripheral artery disease	1.41 (0.58–3.47)	0.45
Delayed stroke		
Atrial fibrillation	3.90 (1.72–8.85)	<0.01
Malignancy	3.39 (1.45–7.92)	<0.01
Stroke	2.97 (1.47–5.99)	<0.01
Diabetes mellitus	1.97 (0.99–3.92)	0.05
Peripheral artery disease	1.67 (0.62–4.51)	0.31
Left main coronary artery disease	1.51 (0.65–3.50)	0.34
3-vessel disease	1.45 (0.67–3.15)	0.34
Carotid artery disease	1.08 (0.31–3.72)	0.91
Late stroke		
Hemodialysis	2.99 (1.93–4.63)	<0.01
Stroke	2.23 (1.8–2.77)	<0.01
Atrial fibrillation	2.19 (1.66–2.89)	<0.01
Age (years)	1.03 (1.01–1.04)	<0.01
Peripheral artery disease	1.33 (1.03–1.73)	0.03
Chronic kidney disease	1.25 (0.99–1.59)	0.06

These variables were selected from the following potential variables (univariate $p < 0.01$): age, gender, body mass index, emergency procedure, critical preoperative state, previous myocardial infarction, heart failure, stroke, peripheral arterial disease, carotid artery disease, atrial fibrillation, chronic obstructive pulmonary disease, malignancy, hypertension, diabetes mellitus, hemodialysis, chronic kidney disease, hemoglobin, current smoker status, left ventricular ejection fraction, total occlusion, proximal left anterior descending coronary artery disease, 3-vessel disease, and left main coronary artery disease.

* Odds ratio for early and delayed strokes and hazard ratio for late stroke.

Predominant preoperative significant risk factors for early stroke were stroke history, atrial fibrillation, and chronic kidney disease. Predominant adjusted risk factors for delayed stroke were atrial fibrillation, malignancy, and stroke history. Postoperative coagulopathy during this period and hypercoagulability in such patients with malignancy may be associated with delayed stroke. Predominant adjusted risk factors for late stroke were hemodialysis, stroke history, atrial fibrillation, and advanced age. These factors are generally regarded as risk factors for stroke after coronary revascularization.

Although the overall rate of stroke after left heart catheterization or PCI is low (range 0.2% to 0.4%), it is the most debilitating complication from a patient's perspective and is associated with a high rate of morbidity and mortality.[5–7]

The National Cardiovascular Data Registry in the United States reported that periprocedural stroke developed in 0.22% of 706,782 patients.[6] A report from the New York State Angioplasty Registry showed that the periprocedural stroke rate was 0.18% for 76,903 patients.[8] Multivariate analysis has shown that the occurrence of stroke is more frequently associated with diabetes mellitus, hypertension, previous stroke, or renal failure and that it is independently associated with in-hospital death. In the present study, stroke rate within 30 days after PCI was 0.23%, which was similar to previously published data. Previous stroke, renal dysfunction, or diabetes was also a risk factor for stroke in the present study. Thirty-day mortality after PCI was 0.85%; thus, occurrence of stroke after PCI may not necessarily be associated with death. Patients who developed a stroke who previously underwent longer cardiac catheterization procedures and those who had a greater use of contrast were more likely to have had the procedure for urgent reasons and to have had intra-aortic balloon counterpulsation, a procedure known to increase the risk of stroke.[9]

The Society of Thoracic Surgeons National Adult Cardiac Surgery Database demonstrated that the overall occurrence of cerebrovascular accident is 2.3%. Anyanwu et al[10] reported that the mortality rate in patients with stroke was increased >10-fold compared to patients without this complication. This rate varies depending on preoperative comorbidities.[11] Approximately 1/2 of perioperative strokes are identified within the first day after surgery[12–14]; these events result from manipulation of the heart and aorta or from the release of particulate matter from the cardiopulmonary bypass.[11,14] The remaining 1/2 occur after uneventful recovery from anesthesia[13,14]; these strokes are often attributed to postoperative atrial fibrillation, myocardial infarction, and coagulopathy.[11] In the present study, stroke rate within 30 days after CABG was 1.8%. Interestingly, the temporal pattern of stroke after on-pump CABG was similar to that of previous reports. However, the temporal pattern was different in OPCAB in the present study. Most strokes occurred 24 hours after surgery. Some studies that used transcranial Doppler ultrasonography demonstrated the production of aortic emboli from cannulation and application of aortic clamps[15] and the production of large quantities of aortic emboli during cardiopulmonary bypass without manipulation of the aorta.[16] Thus, occurrence of early strokes could be decreased by avoiding cardiopulmonary bypass or by minimizing manipulation of the aorta.

Several randomized controlled trials (RCTs) have been conducted in the previous decade to compare outcomes of OPCAB and on-pump CABG procedures. Equivalent short- and long-term angiographic graft patencies have also been demonstrated. However, the benefit of OPCAB in regard to mortality and morbidity remains controversial.[1–3,17,18] Most RCT data failed to demonstrate the superiority of OPCAB in stroke prevention compared to on-pump CABG. Recently, even a large RCT by Shroyer et al[19] was unable to demonstrate the superiority of OPCAB. Møller et al[17] reported there were no significant differences in mortality, myocardial infarction, stroke, and renewed revascularization in a meta-analysis of 66 RCTs.

In contrast, several large registry data analyses, including the present study, have provided compelling evidence in favor of OPCAB.[1–3,18] The New York State Angioplasty Registry reported that OPCAB had significantly lower risk-adjusted 30-day mortality and postoperative stroke and respiratory failure rates.[18] A meta-analysis of systematically reviewed trials found a 50% relative risk decrease of stroke when coronary surgery was performed off pump.[3] A selection bias of patients in RCTs may be a major reason for differences between RCT and registry outcomes. Limitations of RCTs are due in part to limitations involved in patient selection for enrollment. OPCAB has been reported to be associated with better outcomes, particularly in high-risk populations who are often excluded in RCTs. Thus, registry data, which include higher-risk patients than RCTs, can better demonstrate the advantages of OPCAB compared to on-pump CABG.

A 5-year follow-up of the Arterial Revascularization Therapies Study (ARTS) demonstrated that occurrences of stroke were not significantly different between PCI and CABG at 3 years (1.01, 0.55 to 1.86, $p = 1.00$) or at 5 years (1.10, 0.62 to 1.97, $p = 0.76$).[20] A meta-analysis with 5-year patient-level data from the ARTS, Argentine Randomized Trial of Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple Vessel Disease (ERACI-II), Medicine Angioplasty or Surgery Study for Multi-Vessel Coronary Artery Disease (MASS-II), and the Stent or Surgery Trial (SoS) also demonstrated that the adjusted occurrence of stroke was similar between the PCI and CABG groups (1.16, 0.73 to 1.83).[21] These results indicate that the periprocedural occurrence of stroke was lower after PCI, but that the overall stroke rate was similar between the PCI and CABG groups. These evidences are also compatible with our present data.

There are several important limitations to this study. First, several biases may exist such as indications regarding revascularization strategies and level of expertise in the procedures for each institution and the physician involved in the registry. Propensity score analysis may not adequately adjust for these biases. Second, we had no precise information about the mechanism of stroke, adjunctive pharmacotherapy such as for arrhythmias, and significant carotid stenosis. Management of antiarrhythmic drugs and anticoagulants was left to the discretion of each institution, which may have influenced the stroke outcomes. Third, we do not have precise CABG information such as time of procedures or cross clamping, use of epiaortic scanning, and minimal or no-touch techniques for the diseased aorta. Fourth, because our study was nonrandomized, these potential confounders may influence our results.

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Original article

Impact of diabetes mellitus on outcomes in Japanese patients undergoing coronary artery bypass grafting☆

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Summary
Background and purpose: There have been no large-scale studies on the impact of diabetes mellitus (DM) on outcomes in Japanese patients undergoing coronary artery bypass grafting (CABG).
Methods and subjects: A multi-institutional retrospective cohort study was conducted in 14 Japanese centers. All adult patients who underwent isolated CABG from 2007 to 2008 were included ($n = 1522$, mean age: 68.5 years). The definitions of DM were all patients admitted with diagnosis of DM and preoperative glycated hemoglobin (Hb) A1c ≥ 6.5%. Univariate and multivariate analyses were performed to identify the risk of morbidity and mortality.
Results: There were 849 DM and 572 non-DM patients. Preoperative mean HbA1c were 7.1% in the DM group and 5.7% in the non-DM group ($p < 0.0001$). Preoperative, intraoperative, and 3-day average postoperative blood glucose (BG) were 146 mg/dl, 172 mg/dl, and 168 mg/dl in the DM group, and 103 mg/dl, 140 mg/dl, and 136 mg/dl in the non-DM group (all $p < 0.0001$). Although there were no significant differences in postoperative cardiovascular events, the incidence of infection was significantly higher in the DM group than in the non-DM group (9.2% vs 6.1%, $p = 0.036$) on the univariate analysis. The all-cause death was also relatively higher in the DM group than in the non-DM group (2.1% vs 1.1%, $p = 0.12$), and this was likely related to infection.
Conclusion: DM patients had worse perioperative BG control, higher incidence of infection, and higher mortality than non-DM patients. These results indicate that perioperative BG control guidelines should be standardized to obtain better surgical outcomes in Japanese DM patients.

Introduction

The prevalence of diabetes mellitus (DM) has increased dramatically in Western countries over the past several decades, leading in turn to increased mortality due to cardiovascular events [1]. This trend is also apparent in Asian countries, especially in Japan, where the number of DM patients has increased from 6.9 million to 8.9 million in the past decade (a 29% increase) [2]. The most important life-threatening complication in DM patients is obviously coronary artery disease [3]. There has been debate regarding the optimal treatment for DM patients; some physicians favor percutaneous catheter intervention (PCI), while others favor coronary artery bypass grafting (CABG). Some studies have shown that CABG yields better long-term outcomes in DM patients with multivessel disease [4,5]. However, it is well known that patients with DM who undergo CABG have worse early and late outcomes than CABG patients without DM [6,7]. Also, it has been shown that intraoperative and postoperative blood glucose (BG) control has a significant effect on complications such as infection and mortality [8—10]. However, there have been no large-scale studies on Japanese DM patients undergoing CABG. To better understand the impact of DM on coronary artery surgery and to establish the optimal BG control method during cardiac surgery, we organized a multicenter/multidisciplinary research group, which we called the JMAP study group (Japanese Study to Explore the Impact of Diabetes on Cardiac Surgery for Optimal Glycemic Control Protocol). Herein, we carried out a retrospective cohort study to identify the impact of DM and BG control on surgical outcomes in Japanese patients undergoing CABG.

Materials and methods

From 2007 to 2008, a total of 1522 patients underwent isolated CABG in 14 cardiac surgery centers including 10 university hospitals (Appendix I) in Japan. Patients who underwent redo CABG were included, but patients who underwent concomitant procedures such as valvular procedures, aneurysm repair, arrhythmia surgery, repair of ventricular septal perforation, and surgical ventricular restoration procedures were excluded from this study. The number of the cases enrolled in each hospital varied from 8 to 365, also the number of the operating surgeons ranged from one to three. All the patient characteristics and operative data were extracted from the prospective national database (the Japan Adult Cardiovascular Surgery Database: JACVSD), which is similar to the Society of Thoracic Surgeons (STS) national database in North America. Other study-specific data like preoperative glycated hemoglobin (Hb)A1c and perioperative BG control, as well as other blood laboratory data and postoperative complications including cardiovascular events and individual infections, which are not included in the JACVSD, were obtained from medical records at each study site. These two sets of data were merged, then blinded, and sent to a data center (the EBM Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan).

Demographic variables are listed in Appendix II. Of note, the Japanese Diabetes Society (JDS) value of HbA1c (%) is converted into the National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the following formula according to the JDS guidelines [11]:

$$\text{HbA1c (NGSP) (\%)} = \text{HbA1c (JDS) (\%)} + 0.4\,(\%)$$

Postoperative variables were acute myocardial infarction (MI), cerebrovascular events, acute renal failure, and other cardiovascular events (including cardiac tamponade, ventricular tachycardia or fibrillation, and complications after PCI). Postoperative infection was categorized into deep sternal wound infection (anterior mediastinitis), superficial sternal wound infection, graft harvesting site infection, blood stream infection, urinary tract infection, and pneumonia. Details of the definitions of the clinical events are summarized in Appendix III. Hospital death included all-cause death within 30 days of operation or during initial hospitalization. All the aforementioned clinical events were evaluated at the participating centers, and then assessed by the independent clinical events evaluation committee (Appendix IV) if necessary. The primary composite endpoint was defined as a composite of acute MI, cerebrovascular accidents, other cardiovascular events, all infections and their related deaths. Although cardio-cerebrovascular events were thought to be important for DM patients, this prespecified primary composite endpoint was not related to DM. Thus, we added a new composite endpoint (the additional composite endpoint), which consisted of all infections, acute renal failure, and all-cause deaths, and conducted a post hoc analysis.

DM patients were defined as those patients who were admitted to the participating hospitals with a diagnosis of DM. Patients without a previous diagnosis of DM who had preoperative HbA1c $\geq$ 6.5% (NGSP) were also included [12]. The intraoperative BG was an average of 3–4 BG measurements taken during surgery. In the intensive care unit, the frequency of BG measurement was similar among the participating hospitals: BG was measured every 2–4 h in patients with intravenous continuous insulin infusion, and at least 4 times in non-diabetic patients without insulin. The postoperative 3-day BG average was a composite average of the daily mean BG levels (BG was measured up to 12 times per day following surgery) from the day of the surgery to postoperative day 3.

Perioperative BG control methods varied from hospital to hospital, however, in all the participating institutions, it was standard practice to treat hyperglycemia with continuous insulin infusion whenever BG exceeded 200 mg/dl. Preoperative renal insufficiency was defined as an increased serum creatinine level equal to or more than 2.0 mg/dl. The internal thoracic arteries were harvested by means of skeletonized fashion using the Harmonic Scalpel (Ethicon, West Somerville, NJ, USA) in most of the participating centers. In terms of intraoperative steroid use, a large amount of steroid (methylprednisolone 500–1000 mg) was primed in a cardiopulmonary bypass circuit in some centers for on-pump CABG cases. Also, some surgeons and anesthesiologists preferred to give a moderate amount of intravenous steroid (methylprednisolone 125–500 mg) immediately after starting off-pump CABG cases to prevent systemic inflammatory responses.

Statistical analyses

Baseline characteristics of the DM and the non-DM groups are described as mean $\pm$ standard deviation for continuous variables and proportions for categorical variables. p-Values were calculated by the t-test and the chi-squared test. We compared the proportions of primary and additional composite endpoints and their components between the DM and the non-DM groups. Risk ratios and associated 95% confidence intervals were calculated.

Logistic regression analyses were conducted to estimate the magnitude of the effect of DM on the additional composite endpoint, all infections, and all-cause deaths adjusted by age (in 10-year increments), gender, body mass index, congestive heart failure, renal insufficiency, chronic obstructive pulmonary disease, peripheral artery disease, left ventricular ejection fraction < 50%, operative status (elective vs urgent or emergency), bilateral internal thoracic artery use, and intraoperative steroid use. Of note, these factors were prefixed before the statistical analyses. Odds ratios and their associated 95% confidence intervals were calculated. All analyses were performed with JMP 8.0 statistics software (SAS Institute Inc., Cary, NC, USA). The two-sided alpha level was set to 5%.

This study was approved by the Internal Review Board at all the participating hospitals and the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine. All the patients and their families gave written consent at the time of operation for participation in the JACVSD.

Results

A total of 1522 enrolled patients were classified into two groups: the DM group (n = 849) and the non-DM group (n = 572). Because there were no preoperative HbA1c data for 101 patients without a previous diagnosis of DM, these patients were excluded from this study. The preoperative management of BG in the DM group included subcutaneous insulin injection in 254 patients (29.9%), oral medications in 342 (40.3%), and diet regulation in 233 (27.4%). Patients' baseline characteristics are shown in Table 1. There were no differences in terms of age, gender, and body mass index (BMI). However, depressed left ventricular systolic function (ejection fraction < 50%), renal insufficiency, and peripheral artery disease were significantly higher in the DM group than in the non-DM group. On the other hand, chronic obstructive pulmonary disease was less common in the DM group. There was no difference in terms of usage of bilateral internal thoracic artery, however intraoperative administration of intravenous steroids was more common in the non-DM group. There were no differences in operative status. Off-pump technique was used frequently in both groups (about 70% of patients in each group).

Preoperative mean HbA1c were 7.1% in the DM group and 5.7% in the non-DM group ($p < 0.0001$). Also, preoperative fasting, intraoperative, and 3-day average postoperative BG were 146 mg/dl, 172 mg/dl, and 168 mg/dl in the DM group, and 103 mg/dl, 140 mg/dl, and 136 mg/dl in the non-DM group, respectively. At all measurement points, DM patients had significantly higher BG levels ($p < 0.0001$). In terms of postoperative BG control, 71% of the patients in the DM group were treated with continuous insulin infusion whereas only 22% of the patients in the non-DM group were treated with continuous insulin infusion. As shown in Table 2, the all-cause deaths were 2.1% (n = 18) in the DM group and 1.1% (n = 6) in non-DM group (p = 0.124). There was no significant difference in the primary composite endpoint, however, the additional composite endpoint was significantly higher in the DM group. In terms of complications, although there were no significant differences in the incidence of postoperative cardiovascular events and cerebrovascular accidents, the incidence of overall infection was significantly higher in the DM group than in the non-DM group (9.2% vs 6.1%,

Table 1 Patients' baseline characteristics.

Variables	DM group ($n = 849$)	Non-DM group ($n = 572$)	p-Value
Mean age (SD)	68.6 (8.4)	68.0 (10.1)	0.282
Age ≥ 75	208 (24.5%)	162 (28.3%)	0.107
Male gender	649 (76.4%)	451 (78.9%)	0.288
Preoperative HbA1c (SD)	7.1% (1.2)	5.7% (0.4)	<0.0001
Mean body mass index (SD)	23.7 (3.3)	23.4 (3.1)	0.094
Preoperative steroid use	18 (2.1%)	8 (1.4%)	0.320
Congestive heart failure	131 (15.5%)	98 (17.1%)	0.397
Renal insufficiency	117 (13.8%)	45 (7.9%)	0.001
Chronic obstructive pulmonary disease	57 (6.7%)	64 (11.2%)	0.003
Peripheral artery disease	193 (22.7%)	101 (17.7%)	0.021
Left ventricular ejection fraction < 50%	212 (26.6%)	115 (20.5%)	0.010
Operative status			
Elective	732 (86.2%)	484 (84.6%)	0.154
Urgent	76 (9.0%)	67 (11.7%)	
Emergency	41 (4.8%)	21 (3.7%)	
Bilateral internal thoracic artery use	400 (47.1%)	285 (49.8%)	0.316
Intraoperative steroid use	246 (29.0%)	200 (35.0%)	0.017
On-pump or off-pump			
On-pump	214 (25.2%)	154 (26.9%)	0.754
On-pump beating	43 (5.1%)	27 (4.7%)	
Off-pump	592 (69.7%)	391 (68.4%)	

DM, diabetes mellitus; HbA1c, glycated hemoglobin A1c.

$p = 0.036$). In particular, the incidence of deep sternal wound infection was higher in the DM group (2.0%) than in the non-DM group (1.1%) although this did not reach statistical significance ($p = 0.163$). The cause of death in the DM group was predominantly related to infection (10/18: 56%), while in the non-DM group there was only one patient who died of infection (1/6: 17%). On multivariate logistic regression analyses, the statistically significant risk factors for the

Table 2 Adverse events and outcomes.

	DM group ($n = 849$)	Non-DM group ($n = 572$)	Risk ratio (95% CI)	p-Value
Primary composite endpoint[a]	105 (12.4%)	60 (10.5%)	1.18 (0.87–1.59)	0.279
Additional composite endpoint[b]	92 (10.8%)	42 (7.3%)	1.48 (1.04–2.09)	0.027
All-cause deaths	18 (2.1%)	6 (1.1%)	2.02 (0.81–5.06)	0.124
Acute myocardial infarction	11 (1.3%)	12 (2.1%)		NA
Related death	2 (0.2%)	0		NA
Cerebrovascular accident	12 (1.4%)	6 (1.1%)		NA
Related death	1 (0.1%)	0		
Other cardiovascular event	11 (1.3%)	15 (2.6%)		NA
Related death	3 (0.4%)	1 (0.2%)		
All infections	78 (9.2%)	35 (6.1%)	1.50 (1.02–2.21)	0.036
Related death	10 (1.2%)	1 (0.2%)		
Infection site				
Deep sternal wound	17 (2.0%)	6 (1.1%)	1.91 (0.76–4.81)	0.163
Superficial sternal wound	22 (2.6%)	15 (2.6%)		
Graft harvest site	22 (2.6%)	9 (1.6%)		
Blood stream	5 (0.6%)	2 (0.4%)		
Urinary tract	5 (0.6%)	1 (0.2%)		
Pneumonia	9 (1.1%)	8 (1.1%)		
Acute renal failure	12 (1.4%)	5 (0.9%)	1.62 (0.57–4.57)	0.359
Related death	1 (0.1%)	0		
Other deaths	1 (0.1%)	4 (0.7%)		NA

CI, confidence interval; DM, diabetes mellitus; NA, not available due to too few events.
[a] Primary composite endpoint consisted of acute myocardial infarction, cerebrovascular accidents, other cardiovascular events, overall infection and their related deaths.
[b] Additional composite endpoint consisted of overall infection, acute renal failure, and all-cause deaths.

Table 3 Multivariate logistic regression analysis for the primary composite endpoint.[a]

Variables	Odds ratio	95% CI	*p*-Value
Diabetes mellitus	1.07	0.75–1.53	0.715
Age (in 10-year increments)	1.01	0.83–1.23	0.915
Male gender	0.58	0.40–0.86	0.006
Body mass index (in 1 kg/m^2 increments)	1.04	0.98–1.09	0.164
Congestive heart failure	1.01	0.58–1.70	0.985
Renal insufficiency	2.18	1.36–3.43	0.001
Chronic obstructive pulmonary disease	1.73	0.98–2.95	0.051
Peripheral artery disease	1.12	0.73–1.69	0.585
Left ventricular ejection fraction < 50%	1.25	0.83–1.86	0.268
Urgent	1.71	0.95–2.97	0.065
Emergency	0.79	0.22–2.24	0.689
Bilateral internal thoracic artery use	1.34	0.94–1.91	0.105
Intraoperative steroid use	0.72	0.49–1.06	0.100

CI, confidence interval.
[a] Primary composite endpoint consisted of acute myocardial infarction, cerebrovascular accidents, other cardiovascular events, overall infection and their related deaths.

Table 4 Multivariate logistic regression analysis for the additional composite endpoint.[a]

Variables	Odds ratio	95% CI	*p*-Value
Diabetes mellitus	1.28	0.85–1.92	0.235
Age (in 10-year increments)	1.01	0.81–1.26	0.935
Male gender	0.58	0.38–0.89	0.012
Body mass index (in 1 kg/m^2 increments)	1.07	1.02–1.14	0.012
Congestive heart failure	0.94	0.51–1.67	0.843
Renal insufficiency	3.23	2.00–5.14	0.000
Chronic obstructive pulmonary disease	1.91	1.02–3.41	0.034
Peripheral artery disease	0.94	0.57–1.49	0.787
Left ventricular ejection fraction < 50%	1.39	0.89–2.13	0.139
Urgent	1.60	0.82–2.95	0.149
Emergency	1.13	0.34–3.13	0.823
Bilateral internal thoracic artery use	1.31	0.89–1.94	0.177
Intraoperative steroid use	0.66	0.42–1.01	0.060

CI, confidence interval.
[a] Additional composite endpoint consisted of overall infection, acute renal failure, and all-cause death.

Table 5 Multivariate logistic regression analysis for all infections.

Variables	Odds ratio	95% CI	*p*-Value
Diabetes mellitus	1.29	0.84–2.01	0.253
Age (in 10-year increments)	0.96	0.76–1.22	0.751
Male gender	0.52	0.33–0.83	0.005
Body mass index (in 1 kg/m^2 increments)	1.08	1.02–1.14	0.014
Congestive heart failure	0.96	0.49–1.79	0.904
Renal insufficiency	3.13	1.86–5.16	0.000
Chronic obstructive pulmonary disease	1.85	0.93–3.46	0.064
Peripheral artery disease	0.85	0.49–1.40	0.533
Left ventricular ejection fraction < 50%	1.42	0.88–2.26	0.142
Urgent	1.37	0.65–2.69	0.386
Emergency	0.72	0.16–2.36	0.619
Bilateral internal thoracic artery use	1.37	0.90–2.09	0.144
Intraoperative steroid use	0.68	0.42–1.06	0.099

CI, confidence interval.

Table 6 Multivariate logistic regression analysis for all-cause death.

Variables	Odds ratio	95% CI	*p*-Value
Diabetes mellitus	1.89	0.72–5.61	0.219
Age (in 10-year increments)	1.10	0.67–1.88	0.715
Male gender	0.66	0.25–1.97	0.429
Body mass index (in 1 kg/m^2 increments)	0.90	0.78–1.04	0.169
Congestive heart failure	2.27	0.69–7.03	0.165
Renal insufficiency	3.04	1.12–7.80	0.023
Chronic obstructive pulmonary disease	4.22	1.24–12.60	0.013
Peripheral artery disease	1.56	0.55–4.07	0.374
Left ventricular ejection fraction < 50%	2.33	0.92–5.87	0.071
Urgent	3.15	0.89–10.32	0.065
Emergency	5.30	1.05–26.7	0.043
Bilateral internal thoracic artery use	1.85	0.71–4.81	0.204
Intraoperative steroid use	0.35	0.10–1.00	0.073

CI, confidence interval.

primary composite endpoint included female gender and renal insufficiency (Table 3). The statistically significant risk factors for the additional composite endpoint included female gender, BMI, renal insufficiency, and chronic obstructive pulmonary disease (Table 4). Also, the statistically significant risk factors for overall infection were female gender, BMI, and renal insufficiency (Table 5). Finally, the statistically significant preoperative or operative risk factors for all-cause death were renal insufficiency, congestive heart failure, and emergency surgery (Table 6). The presence of DM was not identified as a statistically significant independent risk factor on multivariate analyses for the composite endpoints and complications including overall infection and all-cause death which were linked to DM on the univariate analyses. On the other hand, it became apparent that preoperative renal insufficiency was a very strong common risk factor for both overall infection and all-cause death.

Discussion

In 2009, the Society of Thoracic Surgeons Blood Glucose Management Task Force published their guidelines regarding BG management during adult cardiac surgery [13]. According to these guidelines, it is highly desirable to maintain BG < 180 mg/dl during surgery and during the immediate postoperative period with intravenous insulin infusion in DM patients. Although it is unnecessary to use intravenous continuous insulin infusion in non-DM patients during surgery, both DM and non-DM patients benefit from maintaining BG < 180 mg/dl in order to prevent morbidity and mortality [13]. This begs the question of how low the target should be. Furnary et al. reported from their prospective observational study that there was a highly significant relationship between mortality and postoperative glucose levels rising above 175 mg/dl [10]. Our current BG levels in DM patients were barely below this cut-off value, given the intraoperative and postoperative 3-day average BG were 172 mg/dl and 168 mg/dl, respectively. Therefore, there seemed to be some room to lower the BG levels further, which potentially would reduce the morbidity and the mortality in the DM patients.

It has been reported that the presence of DM in patients undergoing CABG is a significant risk factor for hospital mortality and morbidity including stroke, deep sternal wound infection, and length of hospital stay from the STS database analyses [14]. In addition, DM patients have worse long-term survival than non-DM patients after surgery [6]. Our results from univariate analyses show that DM has a significant influence on the additional composite endpoint consisting of all-cause death, overall infection, and acute renal failure (10.8% vs 7.3%, $p = 0.027$). Looking at each complication, overall infection was the most significant factor contributing to this result (9.2% in DM group vs 6.1% in non-DM group, $p = 0.036$). Also, DM patients tended to have higher mortality than non-DM patients (2.1% vs 1.1%, $p = 0.124$). Moreover, DM patients tended to have a much higher incidence of deep sternal wound infection than non-DM patients (2.0% vs 1.1%, $p = 0.163$), although this difference did not reach statistical significance. However, the complication of infection definitely influenced mortality rates because the majority of deaths were related to infection in the DM group. There is no doubt that DM patients have unfavorable baseline characteristics such as diffuse coronary artery disease, peripheral artery disease, high BMI, and worse preoperative renal function, all of which would contribute to worse short- and long-term outcomes compared to non-DM patients.

Our multivariate logistic regression analyses failed to identify DM as an independent risk factor for any of the complications including overall infection and all-cause death. This is most likely because some other preoperative risk factors such as renal insufficiency (predominantly in the DM group) and chronic obstructive pulmonary disease (predominantly in the non-DM group) had too much influence to each endpoint, which attenuated the impact of the presence of DM. This is one of the well-known downsides of the logistic regression models. In fact, the prevalence of preoperative renal insufficiency in this study population is much higher (13.8% in the DM group) than that of other studies published in the literature [10]. It should also be noted that 85 patients (5.6% of all study patients) predominantly in the

DM group had been on chronic hemodialysis preoperatively, which must have given great impact to the multivariate analyses. We are now in the process of doing a sub-analysis in this regard to identify the relative impact of the presence of preoperative renal insufficiency.

The Portland Diabetic Project, which is an on-going prospective study of over 5000 DM patients, aims to show that tight glucose control from the end of surgery until the 2nd postoperative day with continuous insulin infusion may eliminate the diabetic disadvantage [15]. They showed that tight glucose control with a full 3 days of continuous insulin infusion (the Portland Protocol) significantly reduced mortality (by 65%), deep sternal wound infection (by 63%), and length of hospital stay (average 2-day reduction). Therefore, they concluded that DM is not the true risk factor for the seemingly unfair diabetic disadvantage in terms of increased mortality and morbidity. Since we showed that DM patients still have excess mortality and morbidity compared to non-DM patients in the current study, we might be able to reduce these excess complications by implementing tighter glucose control protocols.

It has been debated whether intensive BG control is better than conventional BG control. In a landmark paper, van den Berghe et al. conducted the first prospective randomized trial comparing tight BG control (target 80—110 mg/dl) with intensive insulin therapy to conventional BG control in critically ill surgical patients [16]. They demonstrated that tight BG control resulted in a significant reduction in mortality (10.6% with intensive treatment vs 20.2% with conventional treatment, $p = 0.005$), exclusively in those patients who required $\geq$5 days of intensive care unit (ICU) care with multiorgan failure and sepsis. Also, cardiac surgical mortality was reduced in those patients requiring $\geq$3 days of ICU care. D'Alessandro et al. reported a propensity analysis that showed that strict BG control significantly reduced the EuroSCORE expected mortality in DM patients undergoing CABG, especially in moderate- to high-risk patients [17]. Their BG target in the operating room and ICU were 150—200 mg/dl and $\leq$140 mg/dl, respectively. In terms of long-term outcomes, Lazar et al. showed that tight perioperative glucose control with glucose-insulin-potassium solution improved not only perioperative outcomes, but also long-term survival and freedom from recurrent angina [18]. These studies clearly demonstrate the superiority of tight BG control over conventional control, especially in critically ill patients. On the other hand, Gandhi et al. showed in a prospective randomized study on 400 patients undergoing CABG, including non-DM patients, that intraoperative intensive insulin therapy with a target range of 80—100 mg/dl did not reduce perioperative mortality and morbidity, but rather increased stroke rate and mortality [19]. Furthermore, a meta-analysis of 29 randomized studies focusing on the benefits and risks of tight glucose control in critically ill adult patients concluded that tight glucose control was not associated with significantly reduced hospital mortality but was associated with an increased risk of hypoglycemia [20]. To support these results, a recent prospective randomized multicenter trial (the NICE-SUGAR study) demonstrated that intensive BG control with a target of 81—108 mg/dl increased mortality among adults in the ICU compared with conventional BG control with a target of 180 mg/dl or less [21]. In this study, however, the mortalities in the intensive control group and conventional control group were 27.5% and 24.9% at 90 days after randomization, respectively. In both groups, potentially life-sustaining treatments were withheld or withdrawn in more than 90% of the patients who died. Also, it seems that severe hypoglycemia commonly occurred in the intensive BG control group of the study, which may raise the question of the safety and feasibility of the tight glucose control protocol itself. Because these patients in the study were so sick at the time of enrollment, it is difficult to compare the results of these studies with studies on regular cardiac surgery patients, given the current acceptable mortality after CABG of around 1—2%. It may be necessary to conduct a prospective randomized study to compare tight glucose control and conventional glucose control using more sophisticated protocols with a minimum risk of hypoglycemia in exclusively cardiac surgery patients to reach a definitive conclusion, which we are currently planning to initiate as a next step to our ultimate goal.

Perhaps, one of the other interesting features of this multi-center study is the fact that about 70% of all isolated CABG procedures were performed using the off-pump technique in both the DM and non-DM groups. This trend is far above the typical rates in North America, given the fact that the adoption of off-pump CABG was only 21.8% in 2009 according to the STS database [22]. A systematic review and meta-analysis of propensity score analyses in more than 123,000 patients comparing off-pump and on-pump CABG demonstrated that off-pump provides favorable outcomes in mortality, stroke, renal failure, wound infection, blood transfusion, intraaortic balloon pump support, and prolonged ventilation [23]. It will be interesting to see the impact of off-pump techniques in DM patients in terms of not only preoperative, intraoperative, and postoperative glucose control, but also in terms of postoperative complications and related mortality [24]. We are also planning to perform a post hoc subgroup analysis focusing on this in the near future.

There are several limitations to this study. This was a retrospective, observational study, and hence unknown patient selection processes may cause a bias. Importantly, there was no standard BG control protocol across the participating hospitals. Our sample size was relatively large, however, it was not large enough to stratify the level of perioperative BG control as an indicator of risk events. In fact, we were unable to show any difference in terms of the morbidity and mortality according to the level of intraoperative and postoperative BG control due to too few complications.

Conclusions

DM patients had poor perioperative BG control and higher incidence of infection with a higher mortality rate than non-DM patients. These results highlight the need to initiate prospective studies to standardize perioperative BG control protocols to obtain strict BG control, which may yield better surgical outcomes in Japanese DM patients undergoing cardiac surgery.

Acknowledgments

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Appendix I. The list of the participating surgical centers

Iwate Medical University Hospital, Sakakibara Heart Institute, Jichi Medical University Hospital, Nagoya University Hospital, Handa City Hospital, University Hospital of Kyoto Prefectural University of Medicine, Kyoto University Hospital, Tominaga Hospital, Wakayama Medical University Hospital, Kobe University Hospital, Kobe City Medical Center General Hospital, Kawasaki Medical School Hospital, Kurume University Hospital, Kagoshima University Hospital.

Appendix II.

Preoperative variables include age, gender, height, and weight. Preoperative co-morbidities included systemic hypertension, dyslipidemia, insulin-controlled diabetes mellitus (DM), oral medication-controlled DM, diet-controlled-DM, congestive heart failure, renal insufficiency, chronic obstructive pulmonary disease, peripheral artery disease, cigarette smoking, cerebrovascular accidents, and advanced New York Heart Association functional class. Cardiovascular variables included left main coronary disease, number of diseased coronary arteries, left ventricular ejection fraction, unstable angina, acute myocardial infarction (MI), previous MI, history of atrial fibrillation and ventricular tachycardia or fibrillation, cardiogenic shock, percutaneous coronary intervention, and intra-aortic balloon pump insertion. Preoperative blood laboratory variables included random and fasting serum glucose, glycated hemoglobin A1c, albumin, serum creatinine, blood urea nitrogen, total cholesterol, high-density and low-density lipoproteins, triglycerides, and C-reactive protein. Preoperative medications included digitalis, beta-blockers, nitrates, inotropic agents, oral hypoglycemics, insulin, diuretics, steroids, and immunosuppressants. Intraoperative variables were operative status (elective, urgent, or emergency), reoperative procedure, single or bilateral internal thoracic artery or other arterial conduit usage, saphenous vein grafts and their targets, use of cardiopulmonary bypass, application of aortic cross-clamping, aortic cross-clamp time, cardiopulmonary bypass time, administration of intravenous insulin and steroids, and blood transfusion.

Appendix III. Definitions of clinical events

Acute myocardial infarction: the presence of at least two of the following symptoms or findings:

(1) Creatine kinase (CK)-MB $\geq$ 5% of total CK and total CK $\geq$ 3$\times$ normal control, or CK-MB $\geq$ 100 mg/dl.
(2) Typical symptoms.
(3) Typical electrocardiographic (ECG) change (new onset of ST-T change in more than 2 consecutive leads on 12-lead ECG or abnormal Q wave).
(4) New onset abnormal wall motion abnormality lasting $\geq$24 h on echocardiography.

Of note, a pathological diagnosis of acute MI on autopsy does not require any of the above findings.

Cerebral infarction: including all the following symptoms and findings:

(1) Apparent focal neurological deficits and symptoms or signs compatible with no other identified causes.
(2) Neurological symptoms and signs lasting $\geq$24 h (excluded if patient died).
(3) Radiological diagnosis on computed tomography or magnetic resonance image.

Acute renal failure: increased creatinine of more than twice the preoperative baseline and equal to or more than 2.0 mg/dl, or newly requiring hemodialysis.

Infection: infection occurs within 30 days after surgery

1. *Deep sternal wound infection*: infection involving deep sternum and/or anterior mediastinum (fascia, sternum, mediastinum) and either:
   (1) Purulent drainage from the deep incision or the chest tube which is placed in the area communicating to the anterior mediastinum.
   (2) Organisms isolated from an aseptically obtained culture of fluid or tissue from the deep sternal wound or anterior mediastinum.
   (3) A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38 °C), localized pain, or tenderness, unless site is culture-negative.
   (4) An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
   (5) Diagnosis of a deep incisional surgical site infection by a surgeon or attending physician.
2. *Superficial sternal wound infection*: infection involving only the skin or subcutaneous tissue of the incision and either:
   (1) Purulent drainage, with or without laboratory confirmation, from the superficial incision.
   (2) Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
   (3) At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is

deliberately opened by surgeon, unless the incision is culture-negative.
(4) Diagnosis of superficial incisional surgical site infection by the surgeon or attending physician.

3. *Graft harvest site infection*: surgical site(s) infection including saphenous vein and radial artery harvesting:
   (1) At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat.
   (2) Superficial incision is deliberately opened by the surgeon, or required resection of tissue or drainage, unless the incision is culture-negative.
   (3) Diagnosis of superficial incisional surgical site infection by the surgeon or attending physician.
4. *Blood stream infection*: the presence of a positive non-contaminated blood culture.

   Contamination is diagnosed if one or more of the following organisms is identified in only one of a series of blood cultures: coagulase-negative staphylococci; *Propionibacterium acnes*; *Micrococcus* species; "viridans"-group streptococci; *Corynebacterium* species; or *Bacillus* species.
5. *Urinary tract infection*: defined as the presence of symptoms or signs compatible with no other identified source of infection along with either:
   (1) $>10^5/mm^3$ colony forming units/ml of at least one bacterial species in a single urine specimen.
   (2) purulent urine (>10 white blood cells/field in a microscopic urinalysis).
6. *Pneumonia*: The clinical suspicion of pneumonia is based on clinical criteria; new or progressive radiological pulmonary infiltrate plus more than two of the following characteristics: temperature (38 °C < or < 35.5 °C), leukocyte count ($>12,000\,cells/mm^3$ or $<4000\,cells/mm^3$) or purulent respiratory secretions. Ventilator-associated pneumonia is diagnosed in patients with microbiologic evaluation including the collection of at least one lower respiratory airway sample by sputum, tracheobronchial aspirate, bronchoscopy or by blind bronchoalveolar lavage. Blood cultures and cultures of pleural fluid specimens, if puncture was indicated, were also undertaken. Microbiologic confirmation of pneumonia was defined by the presence of ≥ 1 potentially pathogenic microorganism in the respiratory samples above the predefine thresholds (for bronchoalveolar lavage specimens, $>10^4$ colony forming units/ml; for sputum or tracheobronchial aspirate specimens, $>10^5$ colony forming units/ml); in pleural fluid specimens; or in blood cultures, if an alternative cause of bacteremia was ruled out.

Appendix IV.

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