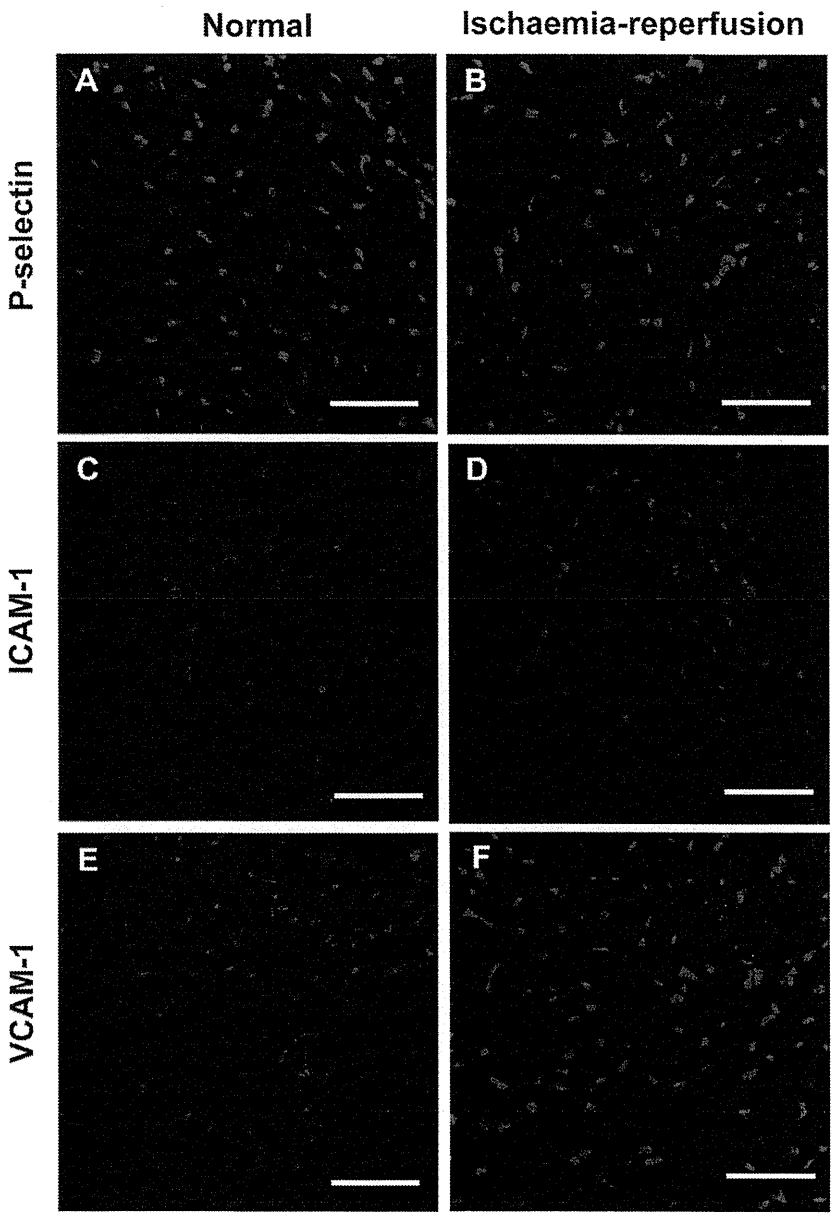

Figure 1 Expression of adhesion molecules in the myocardium. Representative confocal micrographs [red for P-selectin in (A) and (B); ICAM-1 in (C) and (D); VCAM-1 in (E) and (F); purple for nuclei] show upregulated P-selectin after 30-minute global ischemia and 30-minute reperfusion (B) compared with that in the normal heart (A). ICAM-1 was expressed in the normal heart at a low level (C), and not upregulated after I/R (D). VCAM-1 was rarely expressed in normal hearts (E) or hearts with ischemia–reperfusion (F). Scale bar = 50 μm.

ful for dissecting the effect and mechanism of the central determiner of retention—cell–cell interactions between injected BMMNC and the coronary endothelium, using antibody inhibition and excluding any unexpected artifact caused by blood. Thus, this simplified, focused model proved suitable to achieve the aims of this study.

In the common clinical setting of intracoronary BMMNC injection, donor cells are injected in a non-blood, serum-free solution into the coronary artery while blocking the proximal portion.[2,4–6] Hence, most blood components are flushed out from the intravascular space with crystalloid solution and thus donor cell retention takes place in almost blood-free circumstances, assuring the clinical relevancy of our model using crystalloid perfusion. In addition, although the condition of the coronary endothelium may affect retention, this is not dissimilar between our model and clinical settings. Crystalloid perfusion in our protocol (without I/R) did not influence the expression of major adhesion molecules, including P-selectin, ICAM-1 and VCAM-1, in the coronary endothelium (Figure 1). In addition, in our I/R model, BMMNC were injected at an early stage of reperfusion (30 minutes after the onset of reperfusion), at which time-point the likelihood of blood components (neutrophils and/or cytokines) causing myocardial/endothelial damage is negligible compared with that of free radicals generated within the heart tissue.[18] These factors collectively corroborate that the results and conclusions obtained in our model are clinically relevant.

Using this model, we demonstrated that only 13.3 ± 1.2% of BMMNC injected via the coronary arteries were

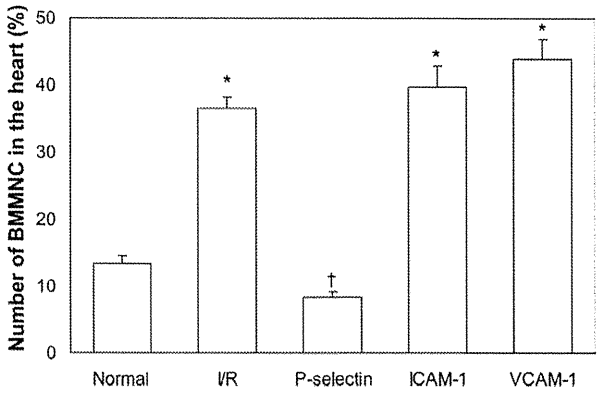

Figure 2 Retention efficiency of BMMNC into the heart. Under isolated-heart perfusion, the number of retained BMMNC into the heart after intracoronary injection was quantified by counting the GFP-positive cell number in the coronary effluent. The I/R (30-minute global ischemia and 30-minute reperfusion) group showed a significantly higher retention efficiency than the Normal group. The P-selectin group (I/R plus administration of anti–P-selectin antibody) showed significantly reduced retention compared with the I/R group. Retention efficiency in the ICAM-1 (I/R plus administration of anti–ICAM-1 antibody) and VCAM-1 (I/R plus administration of anti–VCAM-1 antibody) groups was similar to that in the I/R group; $n = 8$ in the Normal and I/R groups; $n = 6$ in the P-selectin, ICAM-1 and VCAM-1 groups. $^{*}p < 0.05$ vs the Normal group; $^{\dagger}p < 0.05$ vs the I/R group.

retained into the normal heart, suggesting the important clinical implication that, when intracoronary injection of BMMNC is applied to patients in whom the coronary endothelium is relatively normal (such as idiopathic dilated cardiomyopathy), the retention efficiency may be similarly poor. In addition, we observed that prior I/R induction increased the retention frequency up to 36.5 ± 1.6%. Herein we demonstrated that inhibition of P-selectin totally diminished the enhanced retention after I/R without altering coronary flow, proposing a role of P-selectin in enhancing BMMNC retention. This information may imply a new clinical strategy to increase donor cell retention after intracoronary BMMNC injection. Interestingly, we found that the majority of retained BMMNC did not express PSGL-1, whereas 49.3% were positive for PSGL-1 before injection. This phenomenon is unlikely to be a result of preferential retention of PSGL-1–negative BMMNC, and we speculate that PSGL-1 expression on injected BMMNC is quickly downregulated and/or removed after endothelial adhesion in order to facilitate subsequent transendothelial migration, as reported previously.[19]

We showed that antibody inhibition of either ICAM-1 or VCAM-1 did not affect the retention efficiency of BMMNC in hearts undergone ischemia–reperfusion. The antibody dose was carefully chosen based on previous reports that achieved significant inhibition of these molecules in the mouse heart in vivo by systemic intravenous administration.[20,21] Given that the ratio of coronary flow to the systemic blood flow is 5% to 10% and that a considerable amount of intravenously injected antibodies will be lost before reaching the heart by adherence to other organs or degradation in the circulation, the antibody dose used in our ex vivo isolated perfused heart model is considered to be more than sufficient. Furthermore, expression levels of these molecules after I/R were very low as demonstrated by immunolabeling, consistent with established findings that endothelial expression of ICAM-1 and VCAM-1 starts several hours after I/R injury.[21,22] Such a marginal expression level of these molecules further justifies that the antibody dose used here was sufficient to block ICAM-1 and VCAM-1. We therefore consider that injected BMMNC, once adhered to the endothelium mediated by P-selectin, might be able to cross the endothelial barrier regardless of interactions related to ICAM-1 or VCAM-1. This appears to contradict recent reports indicating that expression of CD18[9] or VCAM-1[10] plays an important role in the retention into the heart. However, it should be noted that these previous studies used substantially different experimental protocols, including donor cell types, and differing methods of inhibiting molecules (antibody inhibition of the myocardium or the donor cells), nature of myocardium (with or without reperfusion) and timing of cell injection.

Our results also suggest that, in addition to the P-selectin/PSGL-1–mediated cell–cell interactions, there may be another mechanism for BMMNC retention. At least 13.3% of injected BMMNC were retained into the normal heart where any adhesion molecules are unlikely to be significantly expressed on the endothelium. In addition, 8.3% of BMMNC were retained into I/R hearts even after P-selectin inhibition. We consider that a specific population of BMMNC such as mesenchymal stem cells, which are large

Table 1 Coronary Flow

	Baseline (before I/R)	Baseline (after I/R)	1 min after cell injection	20 min after cell injection
Normal (ml/min)	1.77 ± 0.11	—	1.69 ± 0.08	1.76 ± 0.09
I/R (ml/min)	1.84 ± 0.13	1.39 ± 0.07[a]	1.30 ± 0.07[b]	1.41 ± 0.09[a]
P-selectin (ml/min)	1.77 ± 0.09	1.33 ± 0.08[a]	1.22 ± 0.08[b]	1.34 ± 0.09[a]
ICAM-1 (ml/min)	1.61 ± 0.13	1.22 ± 0.08[a]	1.20 ± 0.13[b]	1.19 ± 0.09[a]
VCAM-1 (ml/min)	1.75 ± 0.08	1.26 ± 0.13[a]	1.32 ± 0.07[b]	1.24 ± 0.12[a]

Normal and I/R groups: $n = 8$; P-selectin, ICAM-1 and VCAM-1 groups: $n = 6$.
[a] $p < 0.05$ vs baseline (before I/R) in each group.
[b] $p < 0.05$ vs Normal group at each time-point.

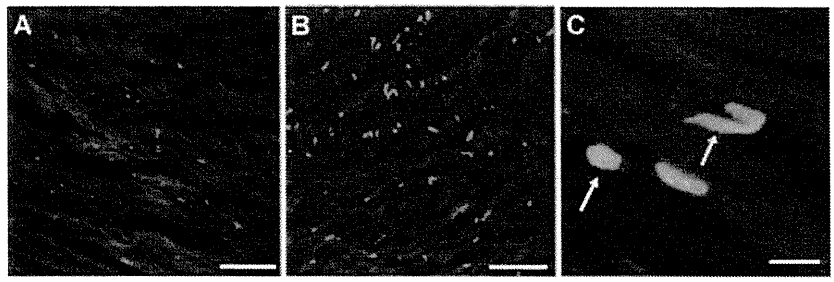

Figure 3 Distribution and morphology of BMMNC retained into the myocardium. The distribution and morphology of retained BMMNC were examined by confocal microscopy. Representative micrographs (green for GFP) show that larger numbers of GFP-positive cells were distributed in the myocardium in the I/R group after intracoronary injection into the heart (B), compared with the Normal group (A). PECAM-1 (red) and DAPI (purple) counterstaining demonstrated that a number of retained GFP-positive (green) cells were localized outside of the PECAM-1–positive vessels, showing a markedly elongated morphology (C) (yellow arrow), whereas in the other, a small number of GFP-positive cells appeared to adhere to the PECAM-1–positive endothelium retaining a round morphology (C) (white arrow). Scale bar =100 μm in (A) and (B); 10 μm in (C).

in cell size, may become physically trapped in the capillaries and subsequently cross the endothelial barrier regardless of adhesion molecules. We also showed that the proportion of Sca-1–positive cells was larger in the retained BMMNC (17.5%) than BMMNC before injection (6.4%), suggesting that Sca-1–positive BMMNC might have a greater ability to retain than Sca-1–negative cells, unless Sca-1 expression is altered during the course of retention. It has been reported that CD34-positive bone marrow–derived cells are preferentially retained in the myocardium.[23] However, as the CD34-positive population was small (0.6 ± 0.3%) in our murine model, it was difficult to clearly investigate retention of CD34-positive BMMNC. The c-kit–positive population was also too small (<0.5%) to investigate.

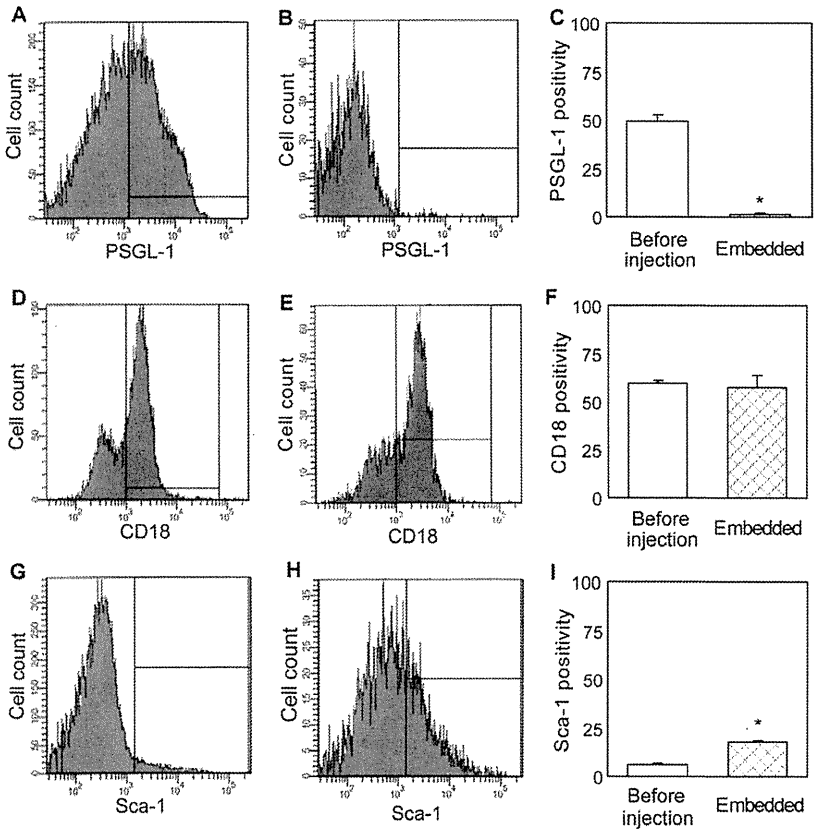

Figure 4 Change in expression of PSGL-1, CD18 and Sca-1 during retention. Flow cytometry demonstrated that approximately a half of the BMMNC were positive for PSGL-1, the ligand of P-selectin, before injection (A). The degree of PSGL-1 expression varied widely. In contrast, PSGL-1 was almost negative in the retained BMMNC, which were collected from enzymatically digested hearts after intracoronary cell injection (B, C). The pattern and proportion of CD18 expression was similar between the BMMNC before injection and BMMNC after retention into the heart (D–F). The proportion of Sca-1–positive cells was significantly higher in retained BMMNC compared with BMMNC before injection (G–I) (n = 6). *p < 0.05 vs BMMNC before injection.

In conclusion, retention frequency of BMMNC injected into the coronary arteries was poor in hearts with normal endothelium, but increased by prior induction of I/R via PSGL-1/P-selectin–mediated BMMNC–endothelial interaction. These data may suggest important implications in determining future protocols of clinical cell transplantation for heart disease.

Disclosure statement

This work was supported by the National Institute of Health Research Biomedical Research Unit (UK), Barts and the London Charity (UK), Magdi Yacoub Institute (UK), Medical Research Council (UK) and the British Heart Foundation (UK). Ken Suzuki was a Senior Clinical Fellow of the Medical Research Council (UK). Niall Campbell is a British Heart Foundation Clinical Research Training Fellow.

The authors have no conflicts of interest to disclose.

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European Journal of Cardio-Thoracic Surgery 41 (2012) 94–101
doi:10.1016/j.ejcts.2011.04.004

ORIGINAL ARTICLE

Significance of off-pump coronary artery bypass grafting compared with percutaneous coronary intervention: a propensity score analysis

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Received 28 December 2010; received in revised form 23 March 2011; accepted 1 April 2011

Abstract

OBJECTIVE: Although there have been several studies that compared the efficacy of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), the impact of off-pump CABG (OPCAB) has not been well elucidated. The objective of the present study was to compare the outcomes after PCI, on-pump CABG (ONCAB), and OPCAB in patients with multivessel and/or left main disease.

METHODS: Among the 9877 patients undergoing first PCI using bare-metal stents or CABG who were enrolled in the CREDO-Kyoto Registry, 6327 patients with multivessel and/or left main disease were enrolled into the present study (67.9 ± 9.8 years old). Among them, 3877 patients received PCI, 1388 ONCAB, and 1069 OPCAB. Median follow-up was 3.5 years.

RESULTS: Comparing PCI with all CABG (ONCAB and OPCAB), propensity-score-adjusted all-cause mortality after PCI was higher than that CABG (hazard ratio (95% confidence interval): 1.37 (1.15–1.63), $p < 0.01$). The incidence of stroke was lower after PCI than that after CABG (0.75 (0.59–0.96), $p = 0.02$). CABG was associated with better survival outcomes than PCI in the elderly (interaction $p = 0.04$). Comparing OPCAB with PCI or ONCAB, propensity-score-adjusted all-cause mortality after PCI was higher than that after OPCAB (1.50 (1.20–1.86), $p < 0.01$). Adjusted mortality was similar between ONCAB and OPCAB (1.18 (0.93–1.51), $p = 0.33$). The incidence of stroke after OPCAB was similar to that after PCI (0.98 (0.71–1.34), $p > 0.99$), but incidence of stroke after ONCAB was higher than that after OPCAB (1.59 (1.16–2.18), $p < 0.01$).

CONCLUSIONS: In patients with multivessel and/or left main disease, CABG, particularly OPCAB, is associated with better survival outcomes than PCI using bare-metal stents. Survival outcomes are similar between ONCAB and OPCAB.

Keywords: Coronary artery bypass grafting • Percutaneous coronary intervention • Off-pump

INTRODUCTION

Several randomized controlled trials (RCTs) and meta-analyses comparing percutaneous coronary interventions (PCIs) with coronary artery bypass grafting (CABG) demonstrated similar long-term survival outcomes for PCI and CABG [1–4]. However, these studies may not accurately reflect current clinical practice of coronary revascularization for following reasons. First, these studies had limitations that mitigated against the prognostic and symptomatic benefits of CABG in many patients with left main disease and/or more complex disease in 'real-world' clinical practice [5,6]. Second, technical development of CABG has not been well reflected in those studies. CABG was primarily performed with the use of cardiopulmonary bypass (on-pump CABG (ONCAB)). In the mid-1990s, CABG without cardiopulmonary bypass (off-pump CABG (OPCAB)) has been introduced to reduce postoperative complications such as stroke which are associated with the use of cardiopulmonary bypass [7,8]. Thus, it is important to investigate the impact of OPCAB in patients with more complex coronary lesions.

The Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) is a multicenter registry in Japan enrolling consecutive 9877 patients undergoing first PCI or CABG and excluding those patients with acute myocardial infarction within a week before index procedure [9]. We reported that adjusted survival outcomes tended to be better after CABG than those after PCI in patients with multivessel disease without left main disease (hazard ratio (HR), 95% confidence interval (CI): 1.23 (0.99–1.53), $p = 0.06$ for PCI vs CABG). However, we did not evaluate the impact of OPCAB on outcomes. Thus, the purpose of the present study was to compare the outcomes of PCI, ONCAB, or OPCAB using the data from the CREDO-Kyoto Registry by propensity score model. To reflect the real world of coronary revascularization in the analysis, we included patients with multivessel and/or left main disease.

PATIENTS AND METHODS

Study population

The CREDO-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. This study was approved by the institutional review boards or ethics committees of all participating institutions. As the study subjects were retrospectively enrolled, written informed consent was not obtained, in concordance with the 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 the follow-up [9].

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. Among them, patients with multivessel and/or left main coronary artery disease were included in the present study. Four hundred eighty-four patients undergoing concomitant valvular, left ventricular, or major vascular operation were excluded from the current analysis. Patients with single-vessel disease without left main disease (PCI: 3001 patients and CABG: 65 patients) were also excluded. Therefore, the study group comprised 6327 patients with multivessel and/or left main coronary artery disease undergoing first coronary revascularization (PCI: 3877 patients and CABG: 2450 patients).

Data collection and definitions

Demographic, angiographic, and procedural data were collected from hospital charts or databases in each center by independent clinical research coordinators according to prespecified definitions. Follow-up data were obtained from hospital charts or by contacting patients or referring physicians. If sufficient follow-up data are unavailable, the investigators contact patients by telephone or letter. If the patient died at the time of contact, the investigators try to obtain data from the family regarding death including non-fatal events before the time of death as great an extent as possible.

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. Left ventricular ejection fraction (LVEF) was measured either by contrast left ventriculography or by echocardiography. Chronic kidney disease was regarded as present when creatinine clearance estimated by Cockcroft-Gault formula was less than 60 ml min^{-1}. Anemia was defined as blood hemoglobin level <12 g dl^{-1} as previously described [9].

Endpoints

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 was defined as any new permanent global or focal neurologic deficit that could not be attributed to other neurologic or medical processes. In the majority of patients, strokes were diagnosed by neurologists and confirmed by computed tomography or magnetic resonance imaging head scans. Stroke at follow-up was defined as symptomatic stroke.

Primary endpoint was death from any cause. Secondary endpoints were cardiovascular death, stroke, myocardial infarction, composite cardiovascular event (cardiovascular death, stoke, or myocardial infarction), and need for any revascularization procedures (PCI or CABG) during the follow-up period.

Statistical analyses

All continuous variables are expressed as the mean ± standard deviation. Differences in baseline characteristics across the three groups were examined by analysis of variance of χ^2-test.

Propensity scores, which were the probabilities that a patient would undergo PCI or probability that a patient would undergo OPCAB, were calculated for each patient. The propensity scores were estimated with multivariable logistic regression analyses separately. Confounding factors in the logistic regression included 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, hemodialysis, chronic kidney disease, anemia, current smoker status, LVEF, total occlusion, proximal left anterior descending artery (LAD) disease, triple-vessel disease, and left main disease.

Outcomes after PCI, ONCAB, or OPCAB are compared by the Cox proportional hazard models stratified by the quartiles of propensity scores. Propensity-score-adjusted HRs, 95% CIs, and p values are reported. The p values for multiple comparisons, namely PCI versus OPCAB and ONCAB versus OPCAB, were adjusted by the Bonferroni correction, that is, we multiplied the original p values by 2. All reported p values were two sided. Subgroup analysis was also conducted with regard to five prespecified risk factors, including triple-vessel disease, diabetes, left ventricular dysfunction, proximal LAD disease, and the elderly [9], and p values for the interaction term were reported additionally.

All reported p values were two sided. All analyses were conducted by a statistician with the use of SAS software version 9.2 (SAS Institute Inc. North Carolina, USA) and S-Plus version 7.0 (Insightful Corp. Seattle, USA). The authors had full access to the data and take responsibility for their integrity. All authors have read and agreed to the manuscript as written.

RESULTS

Baseline characteristics

Among the 6327 patients with multivessel and/or left main disease, 3877 patients (61%) received PCI, 1381 ONCAB (22%), and 1069 OPCAB (17%). Baseline characteristics of the patients in the three groups are shown in Table 1. ONCAB and OPCAB groups generally included more high-risk patients, such as those

Table 1: Baseline characteristics

	PCI (n = 3877)		ONCAB (n = 1381)		OPCAB (n = 1069)		p value*
Age	68.3 ± 10.0		66.3 ± 9.3		68.6 ± 9.4		<0.01
Male gender	2704	70%	1000	72%	757	71%	0.17
Body mass index	23.7 ± 3.3		23.5 ± 3.2		23.6 ± 3.2		0.02
No. of diseased vessels	2.36 ± 0.53		2.58 ± 0.73		2.55 ± 0.74		<0.01
Two-vessel disease	2351	61%	305	22%	271	25%	<0.01
Triple-vessel disease	1461	38%	958	69%	707	66%	<0.01
Left main disease	165	4%	410	30%	332	31%	<0.01
Proximal LAD disease	1545	40%	791	57%	639	60%	<0.01
Total occlusion	1301	34%	672	49%	457	43%	<0.01
Emergency procedure	191	5%	77	6%	75	7%	0.03
Ejection fraction (%)	62.1 ± 13.6		58.6 ± 15.0		61.2 ± 13.7		<0.01
Prior myocardial infarction	1006	26%	489	35%	342	32%	<0.01
Heart failure	569	15%	316	23%	303	28%	<0.01
Atrial fibrillation	254	7%	80	6%	60	6%	0.40
History of stroke	607	16%	237	17%	289	27%	<0.01
Peripheral artery disease	367	9%	239	17%	243	23%	<0.01
Chronic pulmonary disease	83	2%	30	2%	22	2%	0.98
Current smoker	1056	27%	355	26%	250	23%	0.04
Malignancy	321	8%	80	6%	79	7%	0.01
Diabetes	1651	43%	642	46%	499	47%	0.01
Hypertension	2810	72%	918	66%	805	75%	<0.01
Hyperlipidemia	1955	50%	710	51%	609	57%	0.00
Chronic kidney disease	1411	36%	532	39%	426	40%	0.08
Hemodialysis	167	4%	69	5%	54	5%	0.42
Hemoglobin (g dr^{1})	13.1 ± 2.0		12.7 ± 2.0		12.6 ± 2.0		<0.01
Medications at discharge							
Statins	1287	33%	207	15%	289	27%	<0.01
Aspirin	3441	89%	1080	78%	957	90%	<0.01
Thienopyridines	2964	76%	87	6%	197	18%	<0.01
ACE inhibitor	1025	26%	135	10%	136	13%	<0.01
ARB	599	15%	102	7%	153	14%	<0.01
β antagonist	847	22%	123	9%	117	11%	<0.01
Calcium antagonist	2320	60%	801	58%	682	64%	0.02
Nitrates	2805	72%	677	49%	457	43%	<0.01

Mean ± standard deviation, or number of patients and percentage. LAD: left anterior descending artery; ACE: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers.
p value is for comparison among PCI, ON- and OPCAB by analysis of variance or x^2 test.

with left ventricular dysfunction, heart failure, prior myocardial infarction, chronic kidney disease, history of stroke, and anemia. Patient with diabetes was more common in ONCAB and OPCAB. Regarding the complexity of coronary artery anatomy, ONCAB and OPCAB groups included more complex patients, such as those with triple-vessel disease, left main disease, involvement of proximal LAD, and total occlusion. In the PCI group, bare-metal stents were used in 85% of patients. None of the patients received drug-eluting stents. Medications such as statins, 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. Types of bypass grafts are shown in Table 2. OPCAB was performed using more arterial grafts than ONCAB.

Table 2: CABG data

	ONCAB (n = 1381)		OPCAB (n = 1069)		p value
No. of anastomotic sites	3.3 ± 1.0		3.2 ± 1.2		<0.01
Type of bypass grafts					
Left internal thoracic artery	1263	91%	1000	94%	0.05
Right internal thoracic artery	185	13%	577	54%	<0.01
Right gastroepiploic artery	279	20%	371	35%	<0.01
Radial artery	550	40%	253	24%	<0.01
Saphenous vein	1035	75%	462	43%	<0.01
Total arterial revascularization	346	25%	607	57%	<0.01

Mean ± standard deviation, or number of patients and percentage.

PCI versus CABG

Clinical follow-up were completed in 98% at 1 year and 95% at 2 years. The median follow-up period was 1314 days in the PCI group (interquartile range, 979–1649) and 1267 days in the CABG group (interquartile range, 950–1584).

Propensity score analysis showed that all-cause mortality adjusted for confounders was higher after PCI than that after CABG (HR (95% CI): 1.37 (1.15–1.63), p < 0.01, Table 3). This finding was similar when patients were stratified to propensity score and institutes (1.30 (1.06–1.61), p = 0.01). The incidences

Table 3: Hazard ratios for outcomes after PCI compared with that after CABG adjusted by propensity score stratification

	Number of events		HR	95% CI	*p* value
	PCI (n = 3877)	CABG (n = 2450)			
All-cause death	454	279	1.37	1.15–1.63	<0.01
Cardiovascular death	282	186	1.39	1.12–1.73	<0.01
Stroke	192	171	0.75	0.59–0.96	0.02
Myocardial infarction	188	83	1.82	1.34–2.47	<0.01
Composite event[a]	564	369	1.19	1.02–1.39	0.03
Any revascularization	1873	277	6.72	5.84–7.73	<0.01

[a] Composite event: cardiovascular death, stroke, or myocardial infarction e.g. all-cause mortality after PCI was 1.37 times higher than that after CABG (p <.0.01), whereas stroke rate after PCI was 0.75 times lower than CABG (p = 0.02).

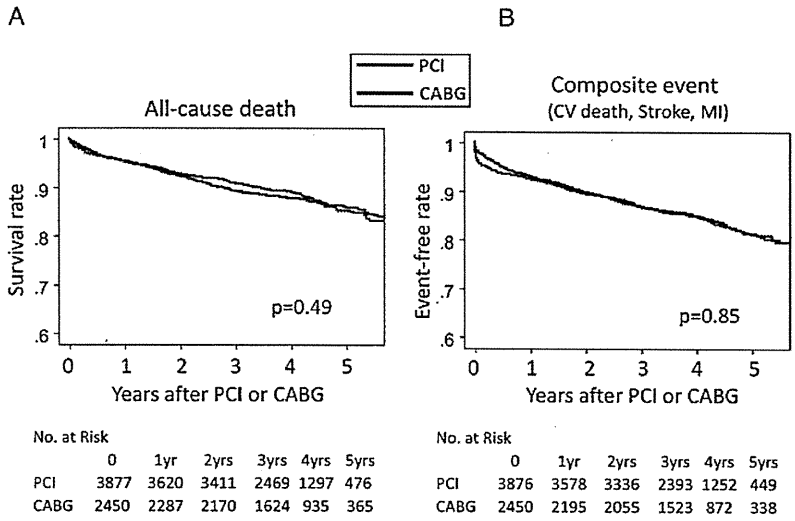

Figure 1: Kaplan–Meier curves for each endpoint comparing PCI with CABG. CV: cardiovascular; MI: myocardial infarction.

after PCI were higher than those after CABG in the adjusted analysis regarding cardiovascular death (1.39 (1.12–1.73), p < 0.01) and myocardial infarction (1.82 (1.34–2.47), p < 0.01). However, the incidence of stroke was lower after PCI (0.75 (0.59–0.96), p = 0.02). The incidence of composite cardiovascular event was higher after PCI (1.19 (1.02–1.39), p = 0.03). The incidence of repeated revascularization was far higher after PCI (6.72 (5.84–7.73), p < 0.01). Kaplan–Meier survival curve and event-free curve for composite cardiovascular event are presented in Fig. 1A and B.

A forest plot in Fig. 2 presents subset analysis for all-cause death after adjusted for propensity score. Interaction p value indicated that CABG was associated with better survival outcomes than PCI particularly in patients with the age of ≥75 (interaction p = 0.04) and possibly in patients with LVEF of <40% (p = 0.09).

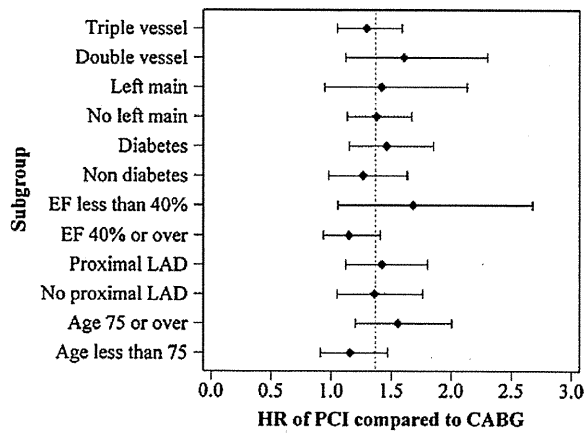

Figure 2: Forest plot of propensity-score-adjusted hazard ratios for death after PCI as compared with that after CABG in subgroups. Dashed line indicates hazard ratio in all patients of 1.37. Interaction tests, which are design to detect whether the specific factor modifies the effect of PCI relative to CABG, were significant for age (p = 0.04) and borderline for ejection fraction (p = 0.09). These indicate that CABG is associated with better survival outcomes than PCI particularly in patients with the age of ≥75 and possibly in patients with LVEF of <40%.The other interaction tests were not significant.

OPCAB versus PCI or ONCAB

Propensity score analysis showed that all-cause mortality after PCI was higher than that after OPCAB (1.50 (1.20–1.86), p < 0.01; Table 4), but similar between ONCAB and OPCAB

Table 4: Hazard ratios for outcomes after PCI or ONCAB compared with that after OPCAB adjusted by propensity score stratification

	Number of events			Versus OPCAB	HR	95% CI	*p* value*
	PCI (*n* = 3877)	ONCAB (*n* = 1381)	OPCAB (*n* = 1069)				
All-cause death	454	154	125	PCI	1.50	1.20–1.86	<0.01
				ONCAB	1.18	0.93–1.51	0.33
Cardiovascular death	282	113	73	PCI	1.74	1.32–2.31	<0.01
				ONCAB	1.49	1.11–2.02	0.02
Stroke	192	107	64	PCI	0.98	0.71–1.34	1.00
				ONCAB	1.59	1.16–2.18	<0.01
Myocardial infarction	188	54	29	PCI	2.41	1.57–3.71	<0.01
				ONCAB	1.61	1.01–2.55	0.09
Composite event[a]	564	230	139	PCI	1.52	1.24–1.86	<0.01
				ONCAB	1.53	1.24–1.90	<0.01
Any revascularization	1873	152	125	PCI	6.61	5.46–8.01	<0.01
				ONCAB	0.97	0.77–1.24	1.00

[a] Composite event : cardiovascular death, stroke, or myocardial infarction.
*Adjusted for multiple comparison by the Bonferroni correction, i.e. we multiplied the original *p* values by 2 e.g. all-cause mortality after PCI was 1.50 times higher than that after OPCAB ($p < 0.01$), whereas that after ONCAB was similar to OPCAB (hazard ratio = 1.18, $p = 0.33$).

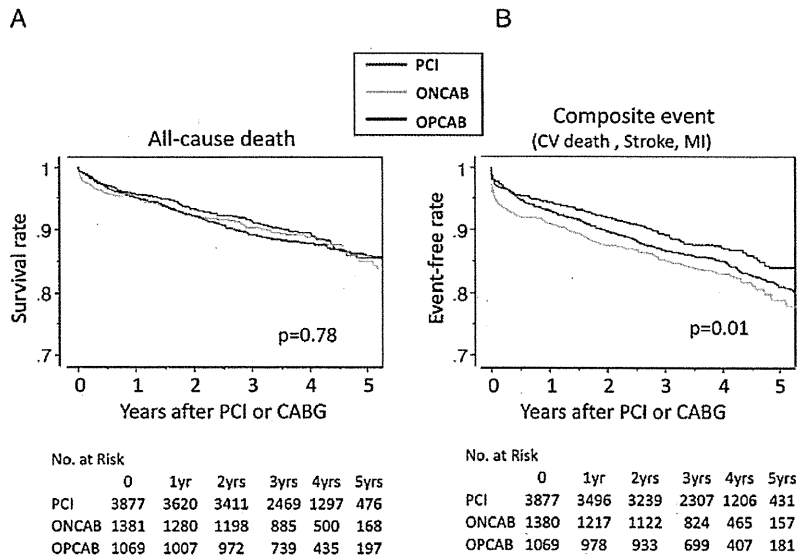

Figure 3: Kaplan–Meier curves for each endpoint comparing PCI, ONCAB, and OPCAB. CV: cardiovascular; MI: myocardial infarction.

(1.18 (0.93–1.51), $p = 0.33$). Cardiovascular mortality after PCI and ONCAB was higher than that after OPCAB (1.74 (1.32–2.31), $p < 0.01$ and 1.49 (1.11–2.02), $p = 0.02$, respectively). The incidence of stroke after OPCAB was similar to that after PCI (0.98 (0.71–1.34), $p > 0.99$), but incidence of stroke after ONCAB was higher than that after OPCAB (1.59 (1.16–2.18), $p < 0.01$). The incidence of myocardial infarction after PCI was higher than that after OPCAB (2.41 (1.57–3.71), $p < 0.01$). The incidence of composite cardiovascular event after OPCAB was lower than that after PCI (1.52 (1.24–1.86), $p < 0.01$) or ONCAB (1.53 (1.24–1.90), $p < 0.01$). These findings were similar when patients were stratified to propensity score and institutes. Kaplan–Meier survival curve and event-free curve for composite cardiovascular event are presented in Fig. 3A and B.

Forest plots in Fig. 4 show subset analysis for comparison of all-cause mortalities after OPCAB, ONCAB, and PCI. There were no significant interactions between PCI compared to OPCAB or ONCAB compared to OPCAB, and subgroups, indicating that there was no evidence against consistency of the adjusted HRs across subgroups.

DISCUSSION

Main findings

In the present study, we investigated the impact of CABG, particularly OPCAB, on long-term outcomes after PCI or CABG in Japanese patients with multivessel and/or left main disease. In this

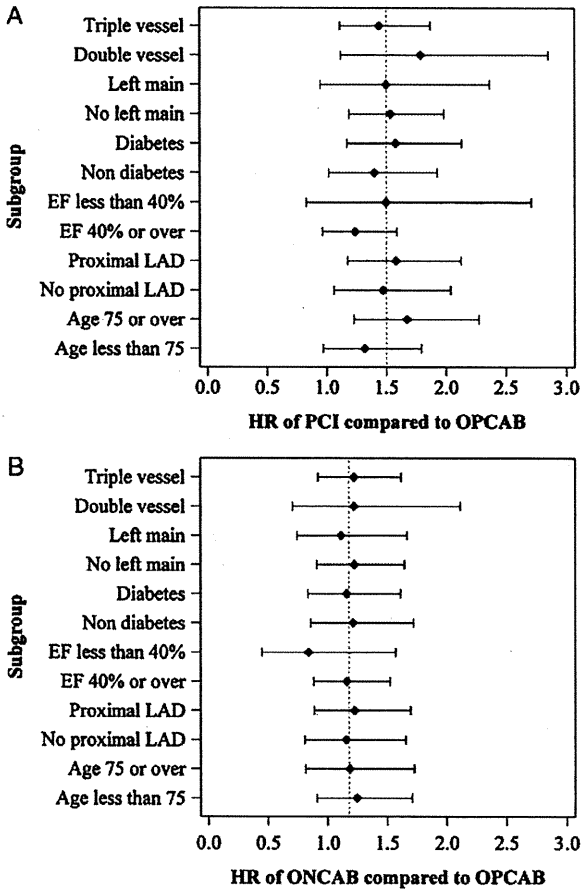

Figure 4: Forest plot of propensity-score-adjusted hazard ratios for death after PCI (A) or ONCAB (B) as compared with that after OPCAB in subgroups. Dashed line indicates hazard ratio in all patients of 1.50 (A) or 1.18 (B). Interaction tests, which are design to detect whether the specific factor modifies the effect of PCI or ONCAB relative to OPCAB, were not significant for all subgroups.

population, we showed that CABG reduced the incidences of propensity adjusted all-cause and cardiovascular mortality compared with PCI and reduced the incidences of myocardial infarction and repeated revascularization. In addition, CABG was associated with better adjusted survival outcomes than PCI in high-risk subgroups such as with triple-vessel disease, diabetes, left ventricular dysfunction, proximal LAD disease, and the elderly. However, CABG was associated with higher stroke rate than PCI.

When comparing OPCAB with PCI or ONCAB, OPCAB was associated with better survival outcomes than PCI. Importantly, OPCAB significantly reduced the incidence of stroke compared with ONCAB, which was similar to PCI. OPCAB reduced the incidence of composite cardiovascular event in comparison to PCI or ONCAB. Need for any revascularization of OPCAB was far lower than that of PCI, which was similar to ONCAB. OPCAB was associated with better adjusted survival outcomes than PCI in high-risk subgroups such as with triple-vessel disease, diabetes, proximal LAD disease, and the elderly. There were no differences in survival outcomes between ONCAB and OPCAB in those prespecified high-risk subgroups. These outcomes strongly support the novel guidelines on myocardial revascularization of European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) [10], which strongly recommends CABG in complex coronary lesions such as triple-vessel and/or left main disease.

PCI versus CABG in multivessel without left main disease

A number of RCTs and meta-analyses have compared revascularization by PCI or CABG in the management of coronary artery disease with multivessel without left main disease [1–4]. A meta-analysis of four RCTs comparing PCI that involves bare-metal stents with CABG (Arterial Revascularization Therapies Study (ARTS), 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) showed similar 5-year survival outcomes but higher revascularization rates among patients with bare-metal stents [1,2]. Similarly, a meta-analysis of 23 RCTs by Bravata et al. has reported that survival outcomes up to 10 years were similar between PCI and CABG, although CABG was superior to PCI in that it relieved angina and led to fewer repeated revascularization [3]. Recently, pooled analysis of 10 RCTs by Hlatky et al. reported that long-term mortality is similar after PCI and CABG, although CABG might be a better option for patients with diabetes and those aged 65 years or older in terms of lower mortality [4]. However, all these trials used selected study population which tended to exclude high-risk patients such as with left main disease, the elderly, or left ventricular dysfunction. Thus, their results may not be generalized to current clinical practice [5,6].

On the other hand, several registry data that included more complex patients than RCTs have shown superiority of CABG in comparison to PCI [11–14]. Hannan et al. reported that CABG is associated with better 3-year adjusted survival outcomes than PCI in patients with two or more diseased coronary arteries using the data from the New York Registry, which included approximately 60 000 patients [11]. Similarly, Malenka et al. reported that adjusted survival is better after CABG than that after PCI in patients with triple-vessel disease [12]. Hannan et al. also compared outcomes between PCI using drug-eluting stent and CABG and showed that CABG constitutes to be associated with lower mortality than does treatment with drug-eluting stents, and is associated with lower mortality or myocardial infarction and repeat revascularization [13]. Meta-analysis of observational cohorts by Benedetto et al. also demonstrated that overall major adverse cardiac and cerebrovascular event rate continues to be higher after PCI by drug-eluting stents due to an excess of redo revascularization compared with CABG [14]. These results indicate that survival outcomes are similar between PCI and CABG in low- or moderate-risk patients; however, CABG is associated with better survival outcomes than PCI in high-risk patients [5,6].

PCI versus CABG in multivessel with left main disease

There are few registry data that investigated patients including left main disease. Brener et al. studied 6033 patients with high

risks in which half of the patients had significant LV dysfunction or diabetes [15]. In addition, the study population included approximately 20% patients with left main disease. They showed that PCI was associated with an increased risk of death (propensity-adjusted HR = 2.3, $p < 0.0001$). Left main disease was one of significant independent predictors for mortality ($p < 0.01$). Biryukova et al. reported that CABG is associated with improved major adverse cardiovascular and cerebrovascular events in patients with three-vessel and/or left main stem disease compared with PCI at 6 and 12 months [16]. Recently, a larger RCT of drug-eluting stents versus CABG for left main disease (the Synergy between PCI and Taxus and Cardiac Surgery (SYNTAX) trial) demonstrated that CABG was associated with better outcomes at 1 year proportionally with the increase in SYNTAX score [17]. In patients undergoing CABG, the binary 12-month rates of major adverse cardiac or cerebrovascular events were similar among patients with low (0–22, 14.7%) and those with high scores (>33, 10.9%). By contrast, in patients with PCI, the rate of those events was significantly increased among patients with high SYNTAX scores (23.4%) as compared with those with low scores (13.6%) ($p = 0.002$ for high vs low scores). This result also indicates that CABG is associated with better outcomes than PCI in high-risk patients with more complex coronary lesions, including left main disease. Registry arm of SYNTAX trial also reported that CABG still remains the dominant revascularization strategy in patients with multivessel or left main disease [18].

In our previous report, we could not demonstrate the superiority of CABG in comparison to PCI regarding adjusted survival outcomes ($p = 0.06$) in patients with multivessel disease without left main disease in the CREDO-Kyoto Registry [9]. In the present study, however, we have shown that CABG, particularly OPCAB, is associated with better adjusted survival and event-free outcomes than PCI. Furthermore, OPCAB was associated with better survival outcomes in high-risk subgroups such as those with LV dysfunction and the elderly. The present analysis additionally included patients with left main disease into analysis data set, and the differences in outcomes between the two studies appear to be attributable to inclusion of patients with left main disease. It should be noted that PCI for left main disease was adopted more selectively in the era of bare-mental stent (BMS) as compared with contemporary clinical practice and, therefore, patients with left main disease are more prone to be subjected to selection bias.

Impact of OPCAB on coronary revascularization

Several RCTs and meta-analyses have been conducted over the last decade comparing outcomes of OPCAB and ONCAB. Equivalent short- and long-tem angiographic graft patency has also been demonstrated [19,20]. However, the benefit of OPCAB regarding mortality and morbidity (stroke and myocardial infarction) has been controversial [7,8,20–22]. This may be because these studies have been underpowered to determine significant differences in these endpoints [23]. Recently, a large RCT by Shroyer et al. (The ROOBY trial) reported that patients undergoing OPCAB had worse 1-year composite outcomes (death, myocardial infarction, or repeated revascularization) and poorer graft patency than those undergoing ONCAB [22]. However, the study excluded high-risk patients with small target vessels or diffuse coronary disease. More importantly, most of the operations were performed by relatively inexperienced surgeons. Thus, a study involving surgeons with more experience and high-risk patients will more accurately reflect real-world CABG outcomes.

On the other hand, several large registry data have provided compelling evidence in favor of OPCAB. The New York State Registry reported that OPCAB had significantly lower risk-adjusted 30-day mortality, as well as postoperative stroke and respiratory failure [24]. Survival outcome was similar between ONCAB and OPCAB, although patients undergoing OPCAB needed more repeated revascularization. An intension-to-treat analysis of 42 477 patients from the Society of Thoracic Surgeons National Adult Cardiac database showed a reduction in risk-adjusted mortality, stroke, and preoperative myocardial infarction in patients undergoing OPCAB [25]. In the present study of the CREDO-Kyoto Registry, there were no differences in survival and event-free (myocardial infarction and repeated revascularization) between ONCAB and OPCAB. However, the incidences of stroke and composite cardiovascular event were lower after OPCAB [9].

Study limitations

There are several important limitations of this study. First, this study deals with patients with PCI using bare-metal stents. Further study comparing CABG with PCI using drug-eluting stents will be favorable. Second, important medications, statins in particular, to prevent cardiovascular events are obviously underused. Although inclusion or exclusion of medications did not influence the survival outcomes in the present study, more optimal use of medications might have changed the long-term outcome of both PCI and CABG.

CONCLUSIONS

CABG, particularly OPCAB, is associated with better survival and event-free outcomes than PCI in patients with multivessel and/or left main disease in bare-metal stent era. The incidence of stroke after OPCAB was lower than that after ONCAB and is similar to PCI. OPCAB may be a favorable coronary revascularization strategy, especially in high-risk populations. Further study comparing CABG with drug-eluting stents with longer follow-up is favorable.

Funding

This work was supported in part by a Grant for Clinical Research for Evidence Based Medicine from the Ministry of Health, Labor and Welfare in Japan to T. Kimura and an educational grant from the Research Institute for Production Development (Kyoto, Japan).

Conflict of interest: none declared.

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Coronary Revascularization in Patients With Liver Cirrhosis

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Background. Liver cirrhosis is a major risk factor for cardiac surgery using cardiopulmonary bypass. However, percutaneous coronary intervention (PCI) or off-pump coronary artery bypass graft surgery (OPCABG) may be a less invasive alternative strategy.

Methods. Among the 9,877 patients undergoing first PCI or CABG enrolled in the CREDO-Kyoto Registry (a registry of first-time PCI and CABG patients in Japan), 332 patients diagnosed with liver cirrhosis were entered into the study (age 67.1 ± 9.4 years; 246 male). Liver cirrhosis was diagnosed by liver biopsy or signs of portal hypertension with characteristic morphologic liver and spleen changes.

Results. A total of 233 patients received PCI, 58 conventional on-pump CABG (CCABG), and 41 OPCABG. Median follow-up was 3.3 years. The PCI group included less complex coronary lesions such as triple vessel and left main disease ($p < 0.01$ each). Propensity score adjusted in-hospital mortality after CCABG or OPCABG was higher than that after PCI; however, the differences were not significant (odds ratio [95% confidence interval]: 6.84 [0.52 to 90.8], $p = 0.14$ for CCABG versus PCI; and 1.86 [0.08 to 45.8], $p = 0.71$ for OPCABG versus PCI). Adjusted overall mortality after CCABG or CABG was lower than that after PCI, but the differences were not significant (0.66 [0.31 to 1.40], $p = 0.28$; and 0.64 [0.28 to 1.49], $p = 0.31$, respectively). Approximately two thirds of patients died of noncardiovascular morbidities (malignancies, including hepatocarcinoma, or hepatic decompression).

Conclusions. Because overall noncardiovascular mortality is high among patients with liver cirrhosis, complete revascularization may not be associated with better survival outcomes. Further study is warranted to determine the impact of a coronary revascularization strategy for liver cirrhosis patients.

(Ann Thorac Surg 2011;91:1393–9)

Liver cirrhosis (LC) is one of the major causes of morbidity and mortality and is regarded as an increased risk factor for hepatic decompression after surgery [1]. It has also been shown to be a major risk factor for cardiac surgery particularly when using cardiopulmonary bypass [2, 3]. However, to date, only a few studies based on a small number of patients with mixed surgical procedures have been performed [2-9]. In addition, most of these reports included only in-hospital or short follow-up periods. The prognosis of patients with LC is generally poor owing to noncardiovascular disorders such as hepatic decompression. Thus, to determine an effective revascularization strategy for patients with LC, it is important to investigate not only cardiovascular but also noncardiovascular outcomes with a longer follow-up period.

Accepted for publication Jan 12, 2011.

Presented at the Poster Session of the Forty-sixth Annual Meeting of The Society of Thoracic Surgeons, Fort Lauderdale, FL, Jan 25–27, 2010.

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0003-4975/$36.00
doi:10.1016/j.athoracsur.2011.01.022

Off-pump coronary artery bypass graft surgery (OPCABG) has been developed to reduce the risk of cardiopulmonary bypass [10]. Furthermore, percutaneous coronary intervention (PCI) may be a less invasive alternative strategy for patients with LC, particularly for those with less complex coronary lesions. The Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) is a multicenter registry from 30 institutions in Japan enrolling consecutive patients undergoing their first PCI or CABG [11]. In the present study, we show the current state of coronary revascularization strategies for LC patients in Japan, and analyze the outcomes of each revascularization strategy using the data from the registry.

Patients and Methods

Study Population

This study was approved by the Institutional Review Board or Ethics Committee of all participating institutions. Because the study subjects were retrospectively

enrolled, written informed consent was not obtained, in concordance with the 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 [11].

Between January 2000 and December 2002, 9,877 patients were identified as having undergone either CABG or PCI without prior history of coronary revascularization. Among these, 332 patients who were diagnosed with LC were the subjects of the present study.

Data Collection and Definitions

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

A diagnosis of LC was made either by liver biopsy or signs of portal hypertension with characteristic morphologic changes in the liver and spleen confirmed by ultrasonography, computed tomography, and magnetic resonance imaging [5]. Other diagnostic criteria, such as varices, thrombocytopenia, ascites, encephalopathy, and biological abnormalities, were also employed. Left ventricular ejection fraction (LVEF) was measured either by contrast left ventriculography or by echocardiography. Chronic kidney disease was regarded as present when creatinine clearance estimated by the Cockcroft-Gould formula was less than 60 mL/min. Anemia was defined as a blood hemoglobin level less than 12 g/dL, as previously described [11].

Endpoints

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 [12]. Within 1 week of the index procedure, only Q-wave myocardial infarctions were adjudicated as myocardial infarctions. Stroke at follow-up was defined as symptomatic stroke. The primary endpoint was death from any cause. Secondary endpoints were cardiovascular death, myocardial infarction, stroke, and the need for any revascularization procedures (PCI or CABG) during the follow-up period.

Table 1. Baseline Characteristics

	PCI n = 233	%	CCABG n = 58	%	OPCABG n = 41	%	*p* Value[a]
Age, years	67.0 ± 9.9		66.4 ± 8.4		68.4 ± 7.2		0.58
Male	171	73	46	79	29	71	0.57
Body mass index	23.5 ± 3.3		22.8 ± 2.9		22.6 ± 3.2		0.10
Emergency procedure	21	9	2	3	1	2	0.15
Ejection fraction	63.6 ± 11.6		58.8 ± 17.2		61.0 ± 14.8		0.05
Prior myocardial infarction	57	24	21	36	13	32	0.14
Heart failure	28	12	22	38	16	39	< 0.01
Atrial fibrillation	25	11	8	14	2	5	0.36
Stroke history	38	16	14	24	15	37	< 0.01
Peripheral vascular disease	17	7	10	17	13	32	< 0.01
Chronic pulmonary disease	3	1	1	2	3	7	0.045
Hypertension	166	71	35	60	31	76	0.19
Diabetes mellitus	99	42	32	55	25	61	0.04
Hyperlipidemia	80	34	24	41	19	46	0.27
Chronic kidney disease	73	31	22	38	15	37	0.56
Hemodialysis	21	9	6	10	4	10	0.95
Malignancy	35	15	6	10	5	12	0.62
Anemia	63	27	21	36	15	37	0.25
Current smoker	77	33	21	36	12	29	0.74
Coronary characteristics							
Number of diseased vessels	1.8 ± 0.8		2.3 ± 0.9		2.5 ± 0.8		< 0.01
Triple vessel disease	52	22	32	55	28	68	< 0.01
Left main disease	10	4	17	29	10	24	< 0.01
Proximal LAD disease	155	67	50	86	36	88	< 0.01
Total occlusion	66	28	20	34	19	46	0.06

[a] The *p* value is for comparison among percutaneous coronary intervention (PCI), conventional on-pump coronary artery bypass graft surgery (CCABG), and off-pump coronary artery bypass graft surgery (OPCABG).

LAD = left anterior descending artery.

Statistical Analyses

All continuous variables are expressed as the mean ± SD. Differences in baseline characteristics across the three groups were examined by analysis of variance of a χ^2 test. We used Kaplan-Meier estimates to plot survival curves in each group. The log rank test was used to identify significant differences in unadjusted survival curves.

Propensity scores, which represented the probabilities that a patient would undergo PCI, conventional on-pump CABG (CCABG), or OPCABG, were calculated for each patient. The propensity scores were estimated separately using multivariable logistic regression analyses. Confounding factors in the logistic regression included age, sex, body mass index, emergency procedure, prior myocardial infarction, congestive heart failure, stroke, peripheral arterial disease, atrial fibrillation, chronic obstructive pulmonary disease, malignancy, hypertension, diabetes mellitus, hemodialysis, chronic kidney disease, anemia, current smoker status, LVEF, total occlusion, proximal left anterior descending artery (LAD) disease, triple vessel disease, and left main disease. Outcomes after PCI, CCABG, or OPCABG were compared using the Cox proportional hazard models stratified by the quartiles of propensity scores. Propensity score adjusted hazard ratios, 95% confidence intervals, and p values are reported. The p values for multiple comparisons among the three groups were adjusted by the Bonferroni correction. All reported p values were two-sided.

To determine the baseline predictive factors for mortality, other than revascularization modality, we used the same potential variables above. Those variables for which p values were less than 0.05 in univariate analysis were included in the multivariate Cox proportional hazard model.

All analyses were conducted by a statistician using SAS software version 9.2 (SAS Institute, Cary, NC) and S-Plus version 7.0 (Insightful Corp, Seattle, WA), and all reported p values were two-sided. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the contents of the manuscript as written.

Results

Baseline Characteristics

Among the 332 patients diagnosed with LC, 233 patients (70.1%) were treated with PCI, 58 (14.51%) with CCABG, and 41 (12.4%) with OPCABG. Baseline characteristics of the patients in the three groups are shown in Table 1. Age, ratio of emergency procedure, and ejection fraction did not differ among the groups. Comorbidities such as malignancy and hemodialysis also did not differ among the groups. The PCI group generally included less high risk patients, such as those with diabetes and left ventricular dysfunction. The numbers of diseased vessels were lower in the PCI group. The PCI group included less complex patients, such as those with left main and proximal LAD disease. In the PCI group, bare-metal stents were used in 79% of patients. None of the patients received drug-eluting stents.

Operative outcomes are shown in Table 2. The number of diseased vessels and anastomotic sites did not differ between CCABG and OPCABG patients. More left and bilateral internal thoracic artery grafts were used in the OPCABG group. Concomitant operations were more common in the CCABG group.

In-Hospital and Follow-Up Outcomes

Clinical follow-up was 100% during the entire study period. The median follow-up period was 1,214 days for

Table 2. Operative Outcomes

	CCABG n = 58	%	OPCABG n = 41	%	p Value
Number of diseased vessels	2.3 ± 0.9		2.5 ± 0.8		0.20
Number of anastomotic sites	3.0 ± 1.1		3.3 ± 1.6		0.21
Preoperative IABP use	1	1.7	1	2.4	0.91
Emergency	2	3.4	1	2.4	0.77
Type of bypass graft					
Left internal thoracic artery	51	87.9	40	97.6	0.08
Bilateral internal thoracic artery	8	13.8	18	43.9	< 0.01
Right gastroepiploic artery	8	13.8	6	14.6	0.91
Radial artery	19	32.8	12	29.3	0.71
Saphenous vein	40	69.0	22	53.7	0.12
Concomitant surgery					
Aortic valve	5	8.6	0	0.0	
Mitral valve	5	8.6	0	0.0	
Thoracic aortic	2	3.4	0	0.0	
Abdominal/peripheral vascular	0	0.0	4	9.8	
Others	4	6.9	0	0.0	
Concomitant surgery total	16	27.6	4	9.8	0.03

CCABG = conventional on-pump coronary artery bypass graft surgery; IABP = intraaortic balloon pump; OPCABG = off-pump coronary artery bypass graft surgery.

the PCI group and 1,168 days for the CABG group. Regarding in-hospital outcomes, 1 patient in the PCI group, 4 in the CCABG group, and 1 in the OPCABG group died in the hospital (Table 3). Bleeding complications, such as postprocedure tamponade were more common in the CCABG group. During follow-up, 21 patients died of cardiovascular events, and 40 patients died of noncardiovascular events. Approximately two thirds of patients died of noncardiovascular events. Of the 40 patients who died of noncardiovascular events, 26 patients (65%) died of malignancy, including hepatocarcinoma or hepatic failure, during the follow-up period.

Survival Analyses

KAPLAN-MEIER ANALYSIS. Unadjusted freedom from all-cause death values of all patients at 30 days, 1 year, and 3 years were 98.5%, 93.9%, and 81.1%, respectively (Fig 1A). Freedom from all-cause death values did not differ between PCI and CABG groups ($p = 0.34$, Table 1). Freedom from all-cause and cardiovascular death values did not differ among PCI, CCABG, and OPCABG groups ($p = 0.61$ in Fig 1C, and $p = 0.48$ in Fig 1D).

PROPENSITY SCORE ANALYSIS. Propensity score adjusted in-hospital mortality did not differ between PCI and CABG groups (Table 4). There were also no significant differences in adjusted in-hospital mortality among PCI, CCABG, and OPCABG groups. Similarly, adjusted overall mortality did not differ between PCI and CABG groups (Table 4). There were no significant differences in adjusted overall mortality among the three groups.

RISK FACTORS FOR MORTALITY. The strongest predictive variable for overall all-cause death was comorbid malignancy (Table 5). Significant predictive variables for cardiovascular death were hemodialysis, heart failure, stroke history, anemia, triple vessel disease, and left main disease (Table 5).

Comment

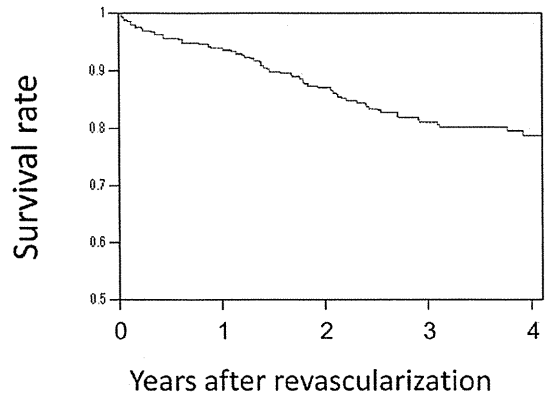
Main Findings

In the present study, we show the current state of coronary revascularization strategies for LC patients in Japan, and analyze the outcomes of each revascularization strategy. We obtained the following findings: (1)

Table 3. In-Hospital and Follow-Up Outcomes

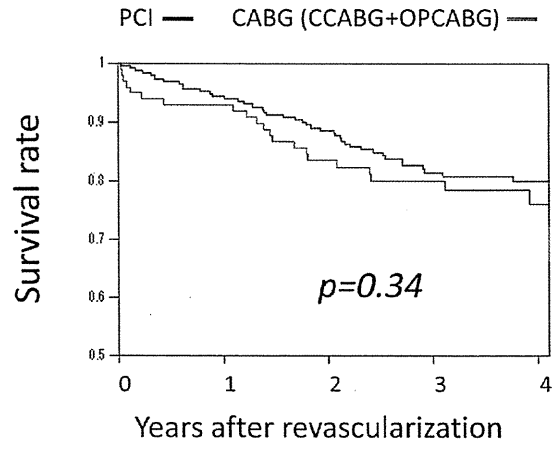
	PCI		CCABG		OPCABG		Total	
In-hospital outcomes	(n =233)		(n = 58)		(n = 41)		(n = 332)	
Death								
Myocardial infarction	1	0.4%	1	1.7%	0	0.0%	2	0.6%
Renal failure	0	0.0%	1	1.7%	0	0.0%	1	0.3%
Sepsis	0	0.0%	1	1.7%	1	2.4%	2	0.6%
Bleeding	0	0.0%	1	1.7%	0	0.0%	1	0.3%
Death total	1	0.4%	4	6.9%	1	2.4%	6	1.8%
Events								
Stroke	0	0.0%	1	1.7%	2	4.9%	3	0.9%
Myocardial infarction	9	3.9%	0	0.0%	2	4.9%	11	3.3%
Bleeding	1	0.4%	5	8.6%	2	4.9%	8	2.4%
Follow-up outcomes	(n = 232)		(n = 54)		(n = 40)		(n = 326)	
Death								
Cardiovascular	16	6.9%	3	5.6%	2	5.0%	21	6.4%
Noncardiovascular								
Hepatic failure	0	0.0%	1	1.9%	1	2.5%	2	0.6%
Hepatocarcinoma	7	3.0%	2	3.7%	2	5.0%	11	3.4%
Other carcinomas	11	4.7%	0	0.0%	2	5.0%	13	4.0%
Renal failure	2	0.9%	1	1.9%	0	0.0%	3	0.9%
Pneumonia	0	0.0%	1	1.9%	1	2.5%	2	0.6%
Sepsis	3	1.3%	0	0.0%	0	0.0%	3	0.9%
Gastrointestinal	2	0.9%	1	1.9%	0	0.0%	3	0.9%
Unknown	2	0.9%	0	0.0%	1	2.5%	3	0.9%
Noncardiovascular total	27	11.6%	6	11.1%	7	17.5%	40	12.3%
Death total	43	18.5%	9	16.7%	9	22.5%	61	18.7%
Events								
Stroke	9	3.9%	4	7.4%	1	2.5%	14	4.3%
Myocardial infarction	10	4.3%	2	3.7%	0	0.0%	12	3.7%
Revascularization	95	40.9%	7	13.0%	5	12.5%	107	32.8%

CCABG = conventional on-pump coronary artery bypass graft surgery; OPCABG = off-pump coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.



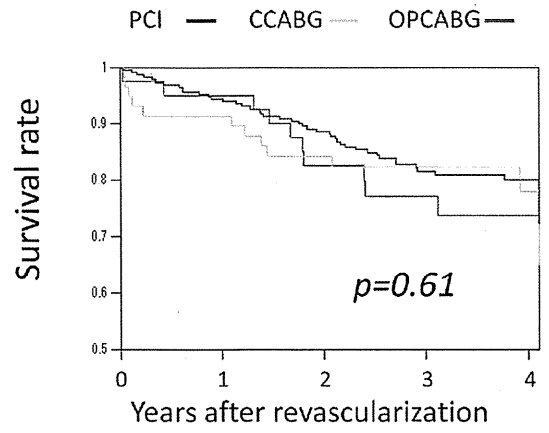
No. at risk	0	1m	1yr	2yrs	3yrs	4yrs	5yrs
All patients	332	324	306	275	193	95	36

A



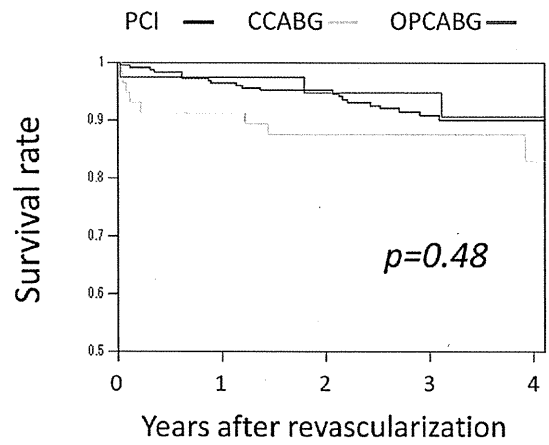
No. at risk	0	1m	1yr	2yrs	3yrs	4yrs	5yrs
PCI	233	230	216	197	134	67	24
CABG	99	94	90	78	59	28	12

B



No. at risk	0	1m	1yr	2yrs	3yrs	4yrs	5yrs
PCI	233	230	216	197	134	67	24
CCABG	58	54	52	45	35	17	9
OPCABG	41	40	38	33	24	11	3

C



No. at risk	0	1m	1yr	2yrs	3yrs	4yrs	5yrs
PCI	233	230	216	197	134	67	24
CCABG	58	54	52	54	35	17	9
OPCABG	41	40	38	33	24	11	3

D

Fig 1. (A) Freedom from all-cause death (all patients). (B) Freedom from all-cause death, percutaneous coronary intervention (PCI [red line]) versus coronary artery bypass graft surgery (CABG [blue line]). (C) Freedom from all-cause death, PCI (red line) versus conventional on-pump CABG (CCAB [green line]) versus off-pump CABG (OPCAB [blue line]). (D) Freedom from cardiovascular death, PCI (red line) versus CCAB (green line) versus OPCAB (blue line).

Compared with PCI, CABG was applied to patients with more complex coronary lesions and more comorbidities, such as heart failure and diabetes. (2) Propensity score adjusted in-hospital morality after PCI tended to be low compared with that of CCABG or OPCABG. (3) Adjusted in-hospital mortality after OPCABG tended to be low compared with that of CCABG. (4) Adjusted overall all-cause mortality after CABG tended to be low compared with that of PCI. (5) Adjusted overall mortality was similar for CCABG and OPCABG. (6) Overall mortality was high regardless of revascularization strategy because of the high incidence of noncardiovascular death caused primarily by malignancy or hepatic decompression.

These results indicate that it is not possible to determine the optimal revascularization strategy for patients with LC from our registry because there were significant differences in the patient population for the three revascularization strategies, and noncardiovascular mortality was high. A randomized controlled trial may clarify the problem, but it is difficult to obtain matched patient populations because such patients are less common owing to varying degrees of severity of LC.

Table 4. Odds and Hazard Ratios for Death Comparing Each Revascularization Strategy By Propensity Score Stratification

	Propensity Score Adjusted		
	Odds Ratio	95% CI	*p* Value
In-hospital death			
CABG versus PCI	4.37	0.30 to 62.5	0.28
CCABG versus PCI	6.86	0.52 to 90.8	0.14
OPCABG versus PCI	1.86	0.08 to 45.8	0.71
CCABG versus OPCABG	3.70	0.33 to 40.7	0.29
Overall death			
CABG versus PCI	0.66	0.34 to 1.27	0.21
CCABG versus PCI	0.66	0.31 to 1.40	0.28
OPCABG versus PCI	0.64	0.28 to 1.49	0.31
CCABG versus OPCABG	1.03	0.43 to 2.44	0.95

CABG = coronary artery bypass graft surgery; CCABG = conventional on-pump coronary artery bypass graft surgery; CI = confidence interval; OPCABG = off-pump coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

Liver Cirrhosis and Cardiac Surgery

There have been several observational studies that investigated the outcomes of cardiac surgery in patients with LC [2–9]. Although these studies included a limited population with mixed surgical procedures, all these studies demonstrated that LC is a serious risk factor of cardiac surgery. The studies employed the Child-Turcotte-Pugh classification to evaluate the severity of LC [13, 14]. The operative mortality rate of class A patients was relatively low (0% to 10%) [2-9]. On the contrary, early studies reported higher mortality rates in class B patients, which ranged from 50% to 80% [2, 3]. Recent studies, with the exception of the report from Lin and colleagues [5], also reported relatively high mortality rates of 18% to 67% for group B patients as compared with class A patients [6–9]. However, all these studies involved in-hospital or short-term follow-up periods. The Model for End-Stage Liver Disease scoring system [15] has been validated for predicting survival in patients with end-stage liver disease. This score may be useful in predicting the prognosis of patients undergoing cardiac surgery [8, 9].

Benefit of Complete Revascularization for LC

Long-term survival outcomes in patients with LC were poor as compared with those of the whole population of the CREDO-Kyoto registry. Freedom from all-cause death values of the whole population at 30 days, 1 year, and 3 years were 99.4%, 96.6%, and 91.6% in the PCI group and 98.0%, 94.3%, and 89.3% in the CABG group, respectively; whereas, in the present study of patients with LC, freedom from all-cause death values at 30 days, 1 year, and 3 years were 99.6%, 99.4%, and 81.6% in the PCI group and 96.0%, 92.9%, and 80.1% in the CABG group, respectively. It is noteworthy that approximately two thirds of patients died of noncardiovascular morbidities such as malignancy, including hepatocarcinoma or hepatic failure, during follow-up. These results indicate that late mortality rather than early mortality was higher in patients with LC because noncardiovascular causes such as malignancy lower the chance of survival. This finding might mean that complete revascularization may not contribute to improving long-term outcome.

Coronary Revascularization and LC

Regardless of recent decreases in overall perioperative mortality, postoperative morbidities remain a major issue in this population. It is well known that cardiopulmonary bypass triggers production and release of numerous vasoactive substances and cytotoxic mediators that affect coagulopathy, the immune system, vascular resistance, vascular permeability, fluid balance, and major organ functions [7]. Therefore, OPCABG may be advantageous in avoiding such perioperative complications. Hayashida and associates [6] reported that no patient with the Child-Turcotte-Pugh classification class B undergoing OPCABG died in the hospital. Filsoufi and coworkers [8] also reported that no mortality occurred among patients who underwent OPCABG.

Based on these findings, we suggest the following

Table 5. Predictive Variables[a] for All-Cause Death and Cardiovascular Death

	Multivariate Hazard Ratio	95% CI	*p* Value
All-cause death			
Malignancy	3.26	1.86 to 5.75	< 0.01
Left main disease	2.11	1.09 to 4.08	0.03
Hemodialysis	2.03	0.99 to 4.18	0.05
Diabetes mellitus	1.88	1.11 to 3.19	0.02
Triple vessel disease	1.60	0.96 to 2.68	0.07
Age, per years old	1.03	0.99 to 1.06	0.12
Anemia	1.49	0.83 to 2.69	0.18
Stroke history	1.38	0.78 to 2.43	0.27
Chronic total occlusion	1.36	0.81 to 2.29	0.25
Heart failure	1.12	0.61 to 2.07	0.71
Cardiovascular death			
Hemodialysis	4.65	3.12 to 6.94	< 0.01
Heart failure	1.56	1.14 to 2.12	< 0.01
Stroke history	1.55	1.12 to 2.15	< 0.01
Anemia	1.55	1.12 to 2.15	< 0.01
Triple vessel disease	1.49	1.05 to 2.13	0.03
Left main disease	1.47	1.05 to 2.06	0.02
Peripheral artery disease	1.27	0.91 to 1.78	0.17
Diabetes mellitus	1.02	0.76 to 1.37	0.90

[a] These variables were selected from the following potential variables (univariate $p < 0.05$): age, sex, body mass index, emergency procedure, prior myocardial infarction, congestive heart failure, stroke, peripheral arterial disease, atrial fibrillation, chronic obstructive pulmonary disease, malignancy, hypertension, diabetes mellitus, hemodialysis, chronic kidney disease, anemia, current smoker status, left ventricular ejection fraction, total occlusion, proximal left anterior descending artery disease, triple vessel disease, and left main disease.

CI = confidence interval.

revascularization strategy: because long-term outcomes are largely influenced by noncardiovascular events in LC patients, PCI, rather than complete revascularization (by CCABG or OPCABG), should be recommended for patients with complex coronary lesions accompanied by malignancies or severe hepatic decompression as well as for patients with less complex coronary lesions. If CABG is indicated, CCABG or OPCABG should be selected based on the balance between the patient's general condition and the need for complete revascularization, because complete revascularization may not be associated with better survival outcomes. However, further study is warranted to determine the impact of a coronary revascularization strategy for LC patients.

Study Limitations

There are several important limitations to the present study, the most important being that the CREDO-Kyoto registry lacks the preoperative data of hepatic function, such as bilirubin and aspartate aminotransferase. The severity of liver disease could not be determined by the Child-Turcotte-Pugh classification or the Model for End-Stage Liver Disease score. These data may influence the outcomes of multivariate analyses. Second, several biases may exist, such as indications regarding the revascularization strategies and level of expertise in the procedures for each institution and physician involved in the registry. Finally, since our study is nonrandomized, these potential confounders may influence our results.

In conclusion, because overall noncardiovascular mortality (eg, malignancy or hepatic decompression) is high among patients with LC, complete revascularization may not necessarily be associated with better survival outcomes. The revascularization modality should be selected after consideration of the balance between the patient's general condition and the severity of coronary lesions. Further study is warranted to determine the impact of the different coronary revascularization strategies on long-term outcomes for patients with LC.

This work was supported in part by a grant for clinical research for evidence-based medicine from the Ministry of Health, Labor, and Welfare in Japan, awarded to Dr Kimura, and an educational grant from the Research Institute for Production Development, Kyoto, Japan.

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Oral pretreatment with a green tea polyphenol for cardioprotection against ischemia–reperfusion injury in an isolated rat heart model

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Objective: Ischemia–reperfusion injury is among the most serious problems in cardiac surgery. Epigallocatechin-3-gallate, a major polyphenolic component of green tea, is thought to be cardioprotective through its antioxidant activities. We investigated cardioprotective effects of oral epigallocatechin-3-gallate pretreatment against ischemia–reperfusion injury in isolated rat hearts and considered possible underlying mechanisms.

Methods: Rats were given epigallocatechin-3-gallate solution orally at 0.1, 1, or 10 mmol/L (n = 12 per group) for 2 weeks; controls (n = 12) received tap water alone for 2 weeks. Subsequently, Langendorff-perfused hearts were subjected to global ischemia for 30 minutes, followed by 60 minutes of reperfusion.

Results: Recoveries at 60 minutes after reperfusion of left ventricular developed pressure and maximum positive and minimum negative first derivatives of left ventricular pressure were significantly higher in 1-mmol/L group than in 0.1-mmol/L ($P < .0001$), 10-mmol/L ($P < .05$), and control ($P < .0001$) groups. Oxidative stress after reperfusion, as reflected by 8-hydroxy-2′-deoxyguanosine index, was lower in 1-mmol/L group than in control ($P < .01$) and 0.1-mmol/L ($P < .05$) groups. Western blot analysis after reperfusion showed p38 activation and active caspase-3 expression to be lower in 1-mmol/L group than in control group ($P < .05$).

Conclusions: Oral pretreatment with epigallocatechin-3-gallate preserved cardiac function after ischemia–reperfusion, an effect that may involve its antioxidative, antiapoptotic properties, although a high dose did not lead to dramatic improvement in cardiac function. Oral epigallocatechin-3-gallate pretreatment may be a novel and simple cardioprotective method for preventing perioperative cardiac dysfunction in cardiac surgery. (J Thorac Cardiovasc Surg 2011;141:511-7)

Ischemia–reperfusion injury (IRI) remains among the most serious problems in cardiac surgery. Several mechanisms and mediators of IRI have been described.[1] Reactive oxygen species reportedly play an important role in the pathogenesis of myocardial IRI.[2,3] Administrations of various free radical scavengers and exogenous antioxidants have been demonstrated to reduce myocardial IRI and improve cardiac function in animal models.[4,5]

Epigallocatechin-3-gallate (EGCG) is well known to be the most abundant polyphenolic catechin in green tea. Green tea is safe, popular, and known for its antioxidant properties, mainly through scavenging of reactive oxygen species (eg, superoxide anion, hydrogen peroxide, and hydroxyl radical).[6] Several studies have shown green tea consumption to have potential protective effects against cardiovascular disease,[7,8] thought to be attributable to its antioxidant activities.[9] Little is known, however, about the cardioprotective effects of preoperative oral intake of green tea polyphenols against ischemia followed by reperfusion of the heart.

We previously demonstrated, with a Langendorff-perfused rat heart model, that several exogenous antioxidants may enhance recovery after myocardial IRI by diminishing oxidative stress.[10,11] In this study, we evaluated the significance of the cardioprotective effects against myocardial IRI of oral pretreatment with a green tea polyphenol and examined its dose effects, as well as the possible underlying mechanisms, in an isolated rat heart model.

MATERIALS AND METHODS

Green Tea Polyphenol Solutions

Green tea extract in pure form of EGCG was purchased from DSM Nutritional Products Ltd (Basel, Switzerland). EGCG solutions at concentrations of 1 mmol/L, 0.1 mmol/L, and 10 mmol/L were made with drinking water.

Animals

Male 11-week-old Sprague–Dawley rats (350–450 g body weight) were used for this study. All animals in this study received humane care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health, (www.nap.edu/catalog/5140.html).

Study Groups

The rats were randomly divided into 4 groups of 12 animals each. In the 0.1-mmol/L, 1-mmol/L, and 10-mmol/L EGCG groups, rats were allowed

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Disclosures: Authors have nothing to disclose with regard to commercial support.
Received for publication Jan 17, 2010; revisions received March 27, 2010; accepted for publication April 16, 2010; available ahead of print May 24, 2010.

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0022-5223/$36.00

doi:10.1016/j.jtcvs.2010.04.016