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ORIGINAL ARTICLE

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

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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

ADULT CARDIAC

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 ($p = 0.02$).

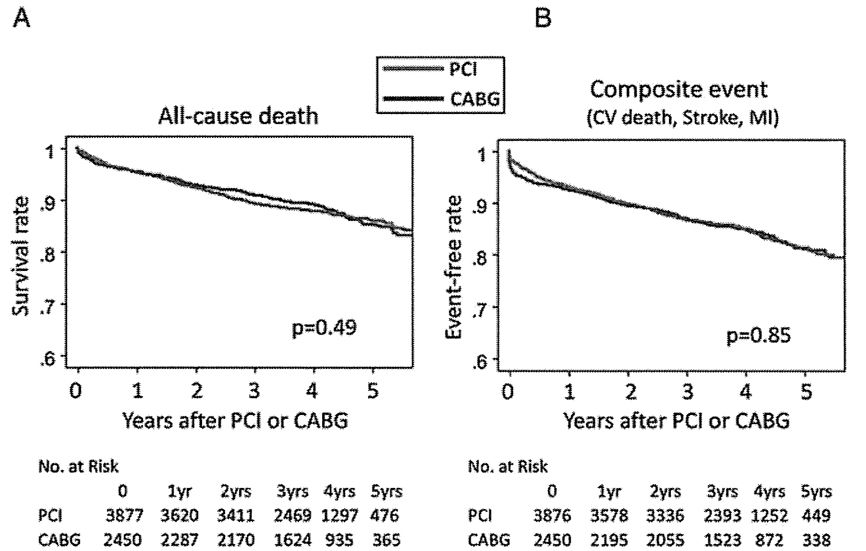

Figure 1: Kaplan–Meier curves for each endpoint comparing PCI with CABG. CV: cardiovascular; MI: myocardial infarction.

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% ($p = 0.09$).

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

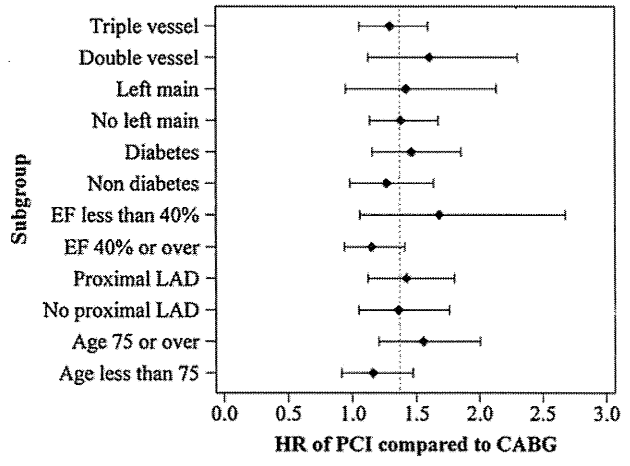

Figure 2: Forest plot of propensity-score-adjusted hazard ratios for death after PCI as compared with that after CABG in subgroups. Dashed line indicates hazard ratio in all patients of 1.37. Interaction tests, which are design to detect whether the specific factor modifies the effect of PCI relative 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.

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, $p = 0.33$).

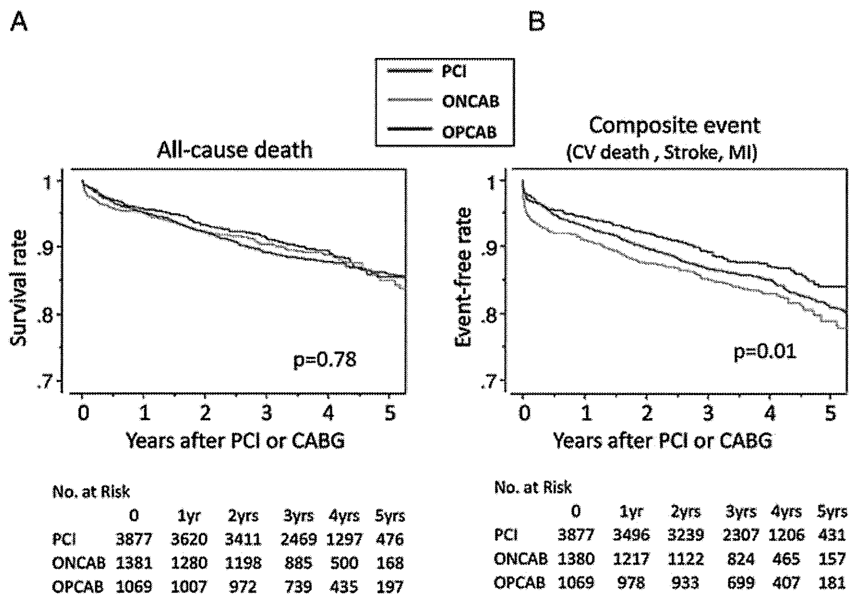

Figure 3: Kaplan-Meier curves for each endpoint comparing PCI, ONCAB, and OPCAB. CV: cardiovascular; MI: myocardial infarction.

(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

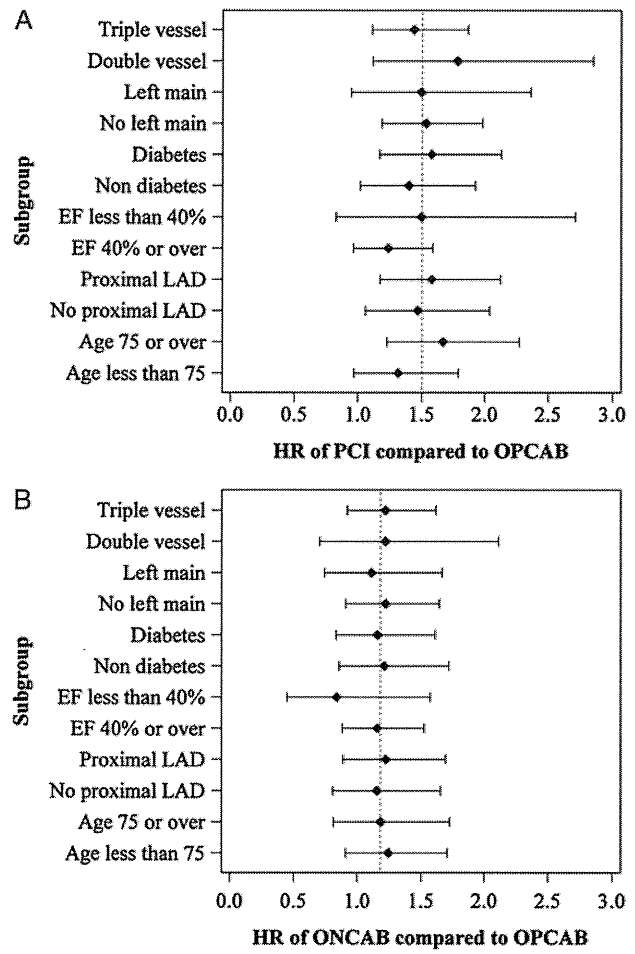

Figure 4: Forest plot of propensity-score-adjusted hazard ratios for death after PCI (A) or ONCAB (B) as compared with that after OPCAB in subgroups. Dashed line indicates hazard ratio in all patients of 1.50 (A) or 1.18 (B). Interaction tests, which are design to detect whether the specific factor modifies 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.

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Ventricular Approach for Functional Mitral Regurgitation in Cardiomyopathy

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ABSTRACT

Background: The key mechanism of functional mitral regurgitation (FMR) in cardiomyopathy is leaflet tethering caused by displacement of the papillary muscles (PM) due to left ventricular dilatation. The attendant remodeling process is characterized by intraventricular widening between both PM. Recently, surgical ventricular restoration (SVR) has been proposed as a technique to reduce leaflet tethering by improving ventricular geometry. However, it is unknown how SVR improve FMR. **Methods and Results:** From 2003 to 2010, we surgically treated FMR in 100 patients with idiopathic dilated cardiomyopahy (DCM) or ischemic cardiomyopathy (ICM). Of those, we performed posterior wall exclusion procedures by either resection (the Batista procedure, n = 13) or plication (n = 19) to approximate papillary muscle distance in a total of 32 patients (DCM in 17, ICM in 15), and these patients formed the cohort of this study. There were two 30-day mortalities (6.3%). There was no significant change in left ventricular ejection fraction, however, the size of the left ventricle, degree of MR, tethering height and distance of PM significantly decreased after operation and well maintained at the mean follow up of 3.3 ± 2.1 years. **Conclusions:** Posterior wall resection or plication with PM approximation provides excellent reduction of leaflet tethering and MR. Thus, reduction of PM distance may be helpful to treat FMR due to leaflet tethering.

Keywords: Cardiomyopathy; Heart Failure Operations; Mitral Regurgitation; Myocardial Remodeling

1. Introduction

It is increasingly evident that functional mitral regurgitation (FMR) is more likely to recur or persist after mitral annuloplasty if there is severe mitral leaflet tethering in patients with idiopathic dilated cardiomyopathy (DCM) or ischemic dilated cardiomyopathy (ICM) [1]. Several techniques have been proposed to treat FMR, in addition to the common technique of mitral annuloplasty (MAP) using downsized annuloplasty rings. Most of these techniques aim to reduce leaflet tethering, and are thus referred to as "subvalvular procedures." To date, proposed subvalvular techniques used to treat leaflet tethering include: 1) papillary muscle relocation or approximation [2,3]; 2) chordal cutting [4]; and 3) surgical ventricular restoration (SVR) [5]. Each of these techniques can play an important role in reducing leaflet tethering via different mechanisms. As such, it seems practical to use a combination of these techniques [6,7]. We have aggressively treated patients with FMR using different techniques at our institutions [8,9], and herein we report on the early and mid-term outcomes of our series of patients, focusing mainly on posterior wall exclusion procedures.

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2. Materials and Methods

2.1. Patient Selection

From June 2003 to May 2010, a total of 100 patients who had FMR associated with either ICM (n = 78) or DCM (n = 22) underwent MAP with various types of SVR procedures at our institutions. The indications for SVR procedures included dilated left ventricle (left ventricular end-diastolic dimension ≥65 mm by echocardiography), presence of MR greater than moderate, and presence of congestive heart failure. According to the size and shape of the left ventricle and its myocardial condition, we performed SVR such as overlapping left ventriculoplasty [6] or septal-anterior wall ventricular exclusion (SAVE) with endocardial patch reconstruction [10] not only for patients with ICM due to a previous antero-septal infarcttion, but also for those with DCM. The main purpose of these techniques was to reduce the size and to restore the left ventricle to a more ellipsoidal shape. However, we realized that dilatation of the postero-lateral wall accompanied by an increased distance between both papillary muscles may be a more important cause of mitral leaflet tethering. Thus, we started to use a procedure to reduce inter-papillary muscle distance by excluding the posterior wall. During the study period, a total of 32 patients underwent posterior wall exclusion procedures with either resection (the Batista procedure) or plication accompanied with papillary muscle approximation (PMA). These patients formed the cohort of this study. The mean age was 61.7 ± 12.3 years (50% of patients were at the age ≥65), and male gender was predominant (75%). Preoperatively, all patients underwent coronary angiography, right-side heart catheterization, and myocardial nuclear study whenever feasible. Also, cardiac magnetic resonance study with or without gadolinium enhancement was performed if patients had no permanent pacemakers/defibrillators.

2.2. Echocardiographic Study

All patients underwent transthoracic echocardiography before and after operation. Standard two-dimensional and Doppler examination was performed. In addition to the baseline measurements of left ventricular end-diastole dimension (LVEDD) and end-systolic dimension (LVESD), left ventricular volumes (end-diastolic: LVEDV; end-systolic: LVESV) and ejection fraction (EF) were determined by the modified biplane Simpson's method. Degree of mitral regurgitation was assessed quantitatively using proximal isovelocity surface area and vena contracta method [11]. The effective regurgitant orifice (ERO) and regurgitant volume (RV) were calculated by the formula. Then, severity of MR was defined according to the current guideline as none (Grade 0), mild (Grade 1), moderate (Grade 2), moderately severe (Grade 3) and severe (Grade 4). The surgical indication of mitral valve procedures was a presence of MR greater than moderate (ERO ≥ 20 mm^2 and/or RV ≥ 30 ml). Tethering height was defined as the distance between the plane of the mitral annulus and the coaptation point. This was measured in the mid-systolic parasternal long axis view. The distance between the anterior and posterior papillary muscles was measured with the short-axis view at the level of the papillary muscle insertion to the endocardial surface in end-diastole. Intraoperative transesophageal echocardiography was performed in all the patients to evaluate anatomy, valvular competence and cardiac functions throughout the operation.

2.3. Operative Technique

All procedures were conducted on hearts arrested by antegrade tapid crystalloid cardioplegia, followed by tapid blood cardioplegia every 20-30 minutes. In addition, retrograde blood cardioplegia may be given in patients with severe coronary artery disease. We do not use terminal hot shot. First, complete coronary revascularization was performed when indicated, and additional antegradecardioplegia was given through saphenous vein grafts which are anastomosed to target coronary arteries in those patients. Then, the first incision was made in the anterior myocardial wall close to the apex parallel to the left anterior descending artery. This incision was extended distally beyond the apex and proximally as needed. The anterior and posterior papillary muscles were carefully identified and mitral leaflets were examined. Usually, the distal incision was further extended towards the posterior wall along to the midline of the anterior and posterior papillary muscles (**Figure 1(a)**).

As shown in **Figure 1(b)**, our PMA technique was as follows: two or three pledgeted 3-0 braided polyester sutures were passed through the body and base of the anterior and posterior papillary muscles, and then these sutures were tied so that both papillary muscles sat side by side. These sutures were usually passed through posterior wall of the left ventricle in between both papillary muscles to plicate the posterior wall as well. When the posterior wall was thin and severely dilated, the incision was extended towards the base of the left ventricle about 2cm distal to the coronary sinus, then a small section of the posterior wall was excised as needed (**Figure 1(c)**). Several deep and wide mattress sutures using 4-0 polypropylene sutures supported by felt strips were used to approximate the posterior wall to decrease the inter-papillary muscle distance (the Batista procedure; **Figure 1(d)**). PMA was occasionally performed to secure the alignment of both papillary muscles. The left ventriculotomy was then closed with two layers of sutures.

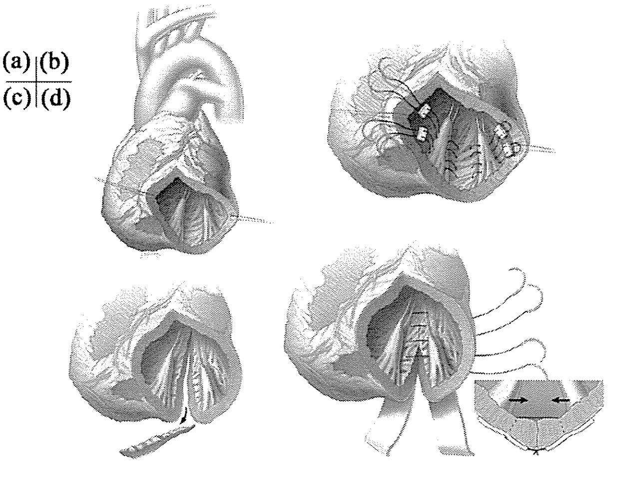

Figure 1. (a) Initial incision of the left ventriculotomy; (b) Papillary muscle approximation with posterior wall plication; (c) The incision is extended posteriorly towards the base of left ventricle; (d) Several deep and wide mattress sutures supported by felt strips are used to approximate the posterior wall to decrease the inter-papillary muscle distance (the Batista procedure).

MAP was performed in the usual fashion in all patients except one patient who had previously undergone MAP. This patient underwent only our Batista procedure. The rings used for MAP were Carpentier-Edwards Classic rings or Physio rings (Edwards Life Sciences, Irvine, CA, USA). The size used was 26 mm (n = 15) or 28 mm (n = 16).

The other additional subvalvular procedure used was chordal cutting. When preoperative echocardiography showed major secondary chordae contributing to the anterior leaflet tethering, an attempt was made to identify these chordae through the left ventriculotomy and then divide them. Care was taken not to cut any strut chordae, which may cause leaflet prolapse.

It has been reported that PMA through a left ventriculotomy per se reduces left ventricular volume to some degree [12]. However, the volume reduction effect of PMA alone may not be enough to achieve adequate ventricular volume reduction. In such cases, additional volume reduction techniques such as overlapping ventriculoplasty [6] or the SAVE procedure [10] were used in addition to PMA, particularly in patients with history of antero-septal myocardial infarction. The technical details of these procedures have been described elsewhere [6,10]. In brief, after a ventricular incision was extended proximally along the left anterior descending artery, the left marginal incision was directly sutured to the endocardium of the septal wall using continuous sutures (overlapping ventriculoplasty). Sometimes, an elliptical Dacron patch was sutured to the transitional zone to exclude the akinetic apical-septal area and restore the shape of the ventricle (SAVE procedure). The target left ventricular volume was estimated by the following formula:

$$\text{LVEDVI}\left(\text{ml/m}^2\right) = 1000 \times \text{Cardiac index/LVEF} \times \text{HR}$$
$$\left(\text{HR: heart rate}\right)$$

For example, given the average LVEF of approximately 30% with heart rate at 90 beats per minute (paced immediately postoperatively), the calculated LVEDVI would be approximately 90-110 ml/m^2under target cardiac index at 2.5-3.0 L/min/m^2. The sizing device was also sometimes used to estimate the cavity volume. In terms of the selection of additional techniques, the decision was made based on the preexisting myocardial status and the left ventricular size and shape.

2.4. Data Collection and Statistical Analysis

Demographic and other patient-related data were obtained from medical records. All patients were contacted during a subsequent outpatient clinic visit for follow-up examination. Echocardiographic studies were routinely performed every 6-12 months at our institutions or the outpatient clinics of referring physicians. Results are expressed as mean ± standard deviation. For comparison of each variable between before and after operation, the Wilcoxon test was used and a $p < 0.05$ was considered statistically significant. The probability of survival was estimated by the Kaplan-Meier method. All the statistical analyses were performed using the JMP 8.0 software package (SAS, Carey, North Carolina, USA). This study was approved by the Institutional Review Board, and patients and families gave informed consent.

3. Results

In this study, surgical techniques used were posterior wall resection (the Batista procedure; n = 13:8 (47%) in DCM patients and 5 (33%) in ICM patients) or posterior wall plication (n = 19:9 (53%) in DCM patients and 10 (67%) in ICM patients). PMA was performed in majority of patients (n = 24:12 (71%) in DCM patients and 12 (80%) in ICM patients) during the posterior wall exclusion. Additional volume reduction techniques used were SAVE procedure (n = 12) and overlapping left ventriculoplasty (n = 5). Also, chordal cutting was added in some cases (n = 19). Preoperatively, all the patients except one were in New York Heart Association functional class III (n = 16) or IV (n = 15), six patients were inotrope dependent, three patients were in cardiogenic shock, and five patients required IABP support. Other preoperative co-morbidities included chronic renal dysfunction (serum creatinine ≥ 1.5 mg/dl, n = 9, 28%; and 2 patients were on hemodialysis) and liver dysfunction (serum total bilirubin ≥ 1.5 mg/dl, n = 8, 25%). Concomitant procedures included coronary artery bypass grafting (CABG) in 16, tricuspid annuloplasy in 10, maze procedure in 9 and aortic valve replacement in 2.

The mean aortic cross-clamp time and cardiopulmonary bypass time were 132 ± 33 minutes and 194 ± 38 minutes, respectively. A total of 15 patients required IABP support at the time of weaning from cardiopulmonary bypass. All the patients could be weaned off without ventricular assist devices. Two patients died within 30 days of surgery (6.3%), one from sepsis and the other from low output syndrome associated with refractory supraventricular tachyarrhythmia. Another 2 patients died during hospitalization; one from pneumonia, and the other from multiorgan failure due to congestive heart failure. The overall hospital mortality was 12.5%. As shown in the **Table 1**, there was no significant improvement in EF, however LVEDD decreased from 65 ± 8 mm to 61 ± 7 mm ($p < 0.001$), and LVEDVI decreased from 134 ± 35 ml/m^2 to 99 ± 28 ml/m^2 ($p < 0.001$). There was a significant reduction in degree of MR (from 3.1 ± 1.0 to 0.3 ± 0.8, $p < 0.001$). Moreover, the tethering height and papillary muscle distance in diastole decreased from 9.4 ± 2.1 mm to 2.9 ± 2.4 mm ($p < 0.01$), and 35 ± 7 mm to 19 ± 6 mm ($p < 0.01$), respectively. The restricted motion of the anterior leaflet was im-

Table 1. Echocardiographic data.

Variables	Preoperative (n = 32)	Postoperative	
		Early (n = 30)	Mid-term (n = 26)
Left ventricular ejection fraction (%)	28 ± 8	31 ± 8	31 ± 8
Left ventricular end-diastolic dimension (mm)	65 ± 8	61 ± 7*	60 ± 7*
Left ventricular end-systolic dimension (mm)	57 ± 10	51 ± 9*	53 ± 9¶
Left ventricular end-diastolic volume index (ml/m^2)	134 ± 35	99 ± 28*	101 ± 20*
Left ventricular end-systolic volume index (ml/m^2)	101 ± 33	72 ± 28*	80 ± 27¶
Left atrial dimension (mm)	51 ± 11	48 ± 8*	53 ± 8
Mitral regurgitation grade	3.1 ± 1.0	0.3 ± 0.8*	0.6 ± 0.8*
Tricuspid regurgitation grade	2.1 ± 0.9	1.2 ± 0.8§	1.5 ± 0.6
Estimated right ventricular pressure (mmHg)	51 ± 17	42 ± 14¶	45 ± 14
Tethering height (mm)	9.4 ± 2.1	2.9 ± 2.4¶	2.0 ± 1.0¶
Papillary muscle distance in diastole (mm)	35 ± 7	19 ± 6¶	20 ± 8¶

*p < 0.001 comparing with preoperative value; ¶p < 0.01 comparing with preoperative value; §p < 0.05 comparing with preoperative value.

proved in almost all the patients. One patient required reoperation due to recurrent severe MR 4 weeks after the operation. The cause of MR was found to be recurrent leaflet tethering presumably due to re-dilatation of the posterior wall. Subsequently, this patient successfully underwent mitral valve replacement and was discharged later.

The mean length of follow-up was 3.3 ± 2.1 years. Follow-up echocardiography were performed in 26 patients out of 28 who were discharged home. These studies demonstrated that EF, LVEDD and LVEDVI remained in the same range as when assessed immediate following surgery. However, three patients had developed moderate MR. There were no significant changes in the tethering height and papillary muscle distance at the mid-term follow-up (**Table 1**). There were 7 late deaths. The cause of late deaths included congestive heart failure in 2, sudden death in 2, sepsis in 2 and cancer in one. Of note, there were no known patients who died of congestive heart failure accelerated by the presence of MR. The cause of congestive heart failure was essentially pump failure due to either systolic or diastolic dysfunction, or combination of these. The 1-, 2- and 3-year survival rates after operation were 78%, 68% and 57%, respectively (**Figure 2**).

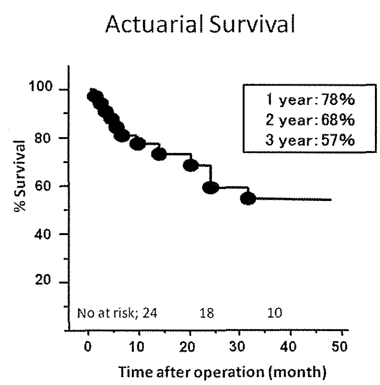

Figure 2. Probability of patient survival after operation.

4. Discussion

MR is one of the major complications following myocardial infarction, and the presence of MR is associated with excess mortality independent of baseline characteristics and degree of ventricular dysfunction [13]. The primary mechanism of FMR is mitral leaflet restriction with tethering due to left ventricular dilatation in addition to some degree of annular enlargement [1]. This is also true in patients with MR due to idiopathic DCM. Bolling *et al.* have demonstrated that MAP using undersized rings yields excellent early and mid-term outcomes in patients with severe FMR associated with DCM [14]. However, it has been reported that a significant number of patients developed recurrent MR in the early postoperative period [15]. If the leaflet tethering is too severe, the risk of recurrent MR becomes high [1]. In fact, it has been demonstrated that the risk factors for MAP failure include severely dilated left ventricle (LVEDD ≥ 65mm) [16] and severe leaflet tethering (tethering height ≥ 10 mm) [17]. In such cases, simple MAP is not sufficient to provide relief. In these circumstances, subvalvular procedures become necessary to reduce the tethering. To date, several techniques have been proposed to treat leaflet tethering. Liel-Cohen *et al.* reported that posterior wall plication in an animal model may reduce the leaflet tethering and MR caused by geometric changes after posterior wall myocardial infarction [18]. This technique can be translated to the clinical setting where posterior wall resection (the Batista procedure) may reduce leaflet tethering and FMR as shown in the current study. In fact, Menicanti *et al.* have demonstrated that intraventricular papillary muscle imbrication at the time of SVR can reduce FMR without ring annuloplasty [19]. Also, Buckberg *et al.* published a preliminary report showing how papillary muscle dimension can be restored during SVR by PMA [7]. Although the mechanisms of FMR are multifactorial, elongation of papillary muscle distance associated with postero-lateral wall dilatation seems to be one of the most significant determinants. In other words, reducing the inter-papillary muscle distance can be the key component in ameliorating leaflet tethering [19].

Batista's original technique involved a volume reduction achieved by a partial left ventriculectomy in which the posterior wall between anterior and posterior papillary muscles was excised [20]. The essence of this approach was to reduce the wall stress and energy consumption of the myocardium by reducing the radius of the ventricle. A few initial reports showed some favorable outcomes, but a relatively high incidence of early failure and late recurrence of ventricular dilatation precluded its wide clinical application [20]. At the time of these early reports, the issues of MR reduction and leaflet tethering were not discussed at all. Interestingly, McCarthy *et al.* reported the results of their initial series of the Batista procedure in which repositioning one or both papillary muscles so as to sit side by side, along with MAP, virtually eliminated MR [20].

As an alternative to a left ventricular intervention, Kron *et al.* reported that direct relocation of the posterior papillary muscle may be an option for patients with minimally dilated left ventricles as a treatment of FMR [2]. Hvass *et al.* also reported on a technique in which the base of the papillary muscles are drawn together and secured with an intraventricular sling inserted through the left atrium [3]. In addition, it has been reported that cutting the secondary chords contributing to leaflet tethering may improve coaptation and reduce FMR [4]. These techniques may be useful to reduce leaflet tethering, but may not be sufficient to completely eliminate the tethering, particularly in severely dilated hearts.

It is important to evaluate the left ventricular wall characteristics in patients with DCM. The extent of left ventricle (LV) fibrosis and dilatation in DCM is not always homogeneous. One drawback to SVR is that it may compromise viable muscle tissue to restore the LV. The decision of which technique to use must be based on the findings of preoperative myocardial evaluations such as cardiac MRI, nuclear study and echocardiography in addition to direct vision and palpitation. Care should be taken to minimize an excision of viable myocardium to preserve cardiac function. However, as the postero- lateral wall is always impaired without exception in severely dilated hearts with severe FMR in our experiences, the presence of severe FMR due to leaflet tethering per se may be a clinical indicator for the posterior wall resection in SVR.

The ideal surgical treatment for the patients with end-stage heart failure may be heart transplantation. Both the survivorship and the quality of life after heart transplantation have been reported to be excellent. However, it is obvious that heart transplantation is not always an option because of strict indications and limited donor availability. There are a number of factors such as medical condition, psychosocial circumstance and financial issues that restrict transplant candidacy. In the current study, half of the patients were age of 65 or older, and a significant number of patients had had preoperative kidney dysfunction (28%), liver dysfunction (25%), inotrope dependent (19%) and in cardiogenic shock (10%). Given the severity of preoperative condition and advanced age, the majority of the patients did not meet the candidate criteria for heart transplantation. On the other hand, these patients may benefit from other surgical options such as left ventricular assist devices (LVAD). LVAD implantation using current rotary pumps as a destination therapy may be a good option, especially in elderly patients. According to the latest report from the registry [21], 1- and 2-year survivals after primary LVAD implantation were 74% and 55%, respectively. The majority of the registry patients could have been sicker than those in the current study, however, the survival after our SVR with MAP procedure in the current study was not inferior to this result from the LVAD registry.

5. Limitations

There are several limitations which need to be addressed. First, this is a non-randomized and retrospective study without a control group. Also, this cohort is relatively small and includes heterogeneous subsets of patients. Often, one patient underwent more than two procedures so that it may be difficult to discriminate which procedure contributed more to the reduction in mitral leaflet tethering. Moreover, the mean follow-up period was only 3.3 years. Therefore, further study is needed to determine more clearly the indications for this procedure.

6. Conclusion

In patients with severe MR due to leaflet tethering, the posterior wall exclusion procedure by either resection or plication, paired with PMA as necessary, provides excellent reduction of leaflet tethering and MR. The reduction of tethering and MR was well maintained at the mid-term follow-up in this series. Thus, reduction of PM distance may be a key component in treating severe FMR.

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The impact of incomplete revascularization and angiographic patency on midterm results after off-pump coronary artery bypass grafting

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Objectives: Higher rates of incomplete revascularization (IR) and reduced patency are possible drawbacks of off-pump coronary artery bypass grafting (OPCAB); both may adversely affect outcome after surgery. This study was conducted to shed light on the relationships among IR, angiographic patency, and midterm results after OPCAB surgery.

Methods: A total of 1604 consecutive patients underwent OPCAB during a 6-year period; 1581 patients (95%) underwent systematic postoperative angiography. Complete follow-up was achieved in 99.5% (median, 3.2 years; up to 6.5 years). A total of 216 patients had IR (13%), and 225 had at least 1 graft failure (FitzGibbon B or O).

Results: All the event-free survival rates for all-cause mortality ($P < .001$), cardiac death ($P = .020$), and major adverse cardiac and cerebrovascular events ($P < .001$) were lower in the IR group. By using the Cox proportional hazards model, IR was an independent risk factor for all-cause mortality (hazard ratio [HR], 1.80; 95% confidence interval [CI], 1.15-2.81). Of those who underwent postoperative angiography, the patients with graft failure experienced reintervention more frequently than those with all grafts patent (HR, 5.49; 95% CI, 3.43-8.77). Even with excluding patients who had undergone reintervention immediately after angiography, graft failure was still an independent risk factor for reintervention afterwards (HR, 2.41; 95% CI, 1.30-4.47).

Conclusions: Incomplete revascularization was relevant to higher midterm mortality after OPCAB, whereas the risk of reintervention was higher for patients with occluded grafts. Complete revascularization, coupled with achievement of a higher patency rate, could be expected to improve follow-up outcomes after OPCAB surgery. (J Thorac Cardiovasc Surg 2013;■:1-8)

ACD

Since the introduction of off-pump coronary artery bypass (OPCAB), many studies have been published comparing OPCAB with conventional coronary artery bypass (CCAB). However, for major outcomes, such as mortality, OPCAB has not been demonstrated to be superior to CCAB.[1] In many randomized controlled trials,[2] the number of anastomoses was fewer and the rate of complete revascularization (CR) was lower in the OPCAB arm than in the CCAB arm, except for in a few studies[3]; similar observations were reported in retrospective studies.[4] CR has been well recognized as a main goal of CCAB.[5,6] Indeed, investigations have demonstrated that incomplete revascularization (IR) is one of the predictors of long-term mortality, even in OPCAB patients.[7,8]

Patency rate is another issue with OPCAB. A recently published, large-scale, randomized study[2] reported a lower patency rate in the OPCAB arm than in the on-pump arm on 12-month angiograms. This is partly because OPCAB is a more technically demanding procedure than CCAB. In fact, bypass grafting without extracorporeal circulation carries the risk of graft failure.

Lopes et al[9] have recently demonstrated that vein graft failure 1 year after coronary artery bypass surgery is associated with an increased risk of death, myocardial infarction (MI), or revascularization at 4 years after the angiogram. This association is driven mostly by revascularization. Retrospective studies have also reported that patients undergoing OPCAB experienced reintervention more frequently at follow-up than those undergoing CCAB,[10,11] and this may be owing to both IR and reduced patency in OPCAB. However, the relative contribution of the 2 possible causes has not yet been determined.[10,12,13] Therefore, this study was conducted to shed light on the associations among IR, systematic angiographic evaluation, and midterm results after OPCAB surgery.

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Abbreviations and Acronyms

BITA	= bilateral internal thoracic artery
BSA	= body surface area
CCAB	= conventional coronary artery bypass
COPD	= chronic obstructive pulmonary disease
CI	= confidence interval
CR	= complete revascularization
CRF	= chronic renal failure
CT	= computed tomography
EuroSCORE	= European System for Cardiac Operative Risk Evaluation
HR	= hazard ratio
IR	= incomplete revascularization
LAD	= left anterior descending
LCx	= left anterior circumflex
MACCE	= major adverse cardiac and cerebrovascular event
MDCT	= multidetector computed tomography
MI	= myocardial infarction
OPCAB	= off-pump coronary artery bypass
PCI	= percutaneous coronary intervention
RCA	= right coronary artery

METHODS

Study Design

This was a database study using Kokura Memorial Hospital (Fukuoka, Japan) patient medical records. The primary objective of this study was to compare the midterm results between the CR and the IR groups. The secondary objective was to investigate the effect of angiographic patency on midterm events. The study was approved by the Kokura Memorial Hospital Institutional Review Board.

Patients

From January 2000 to December 2005 inclusive, 1681 patients underwent isolated coronary artery bypass grafting by a single surgeon (H.O.) at Kokura Memorial Hospital. Seventy-seven patients who received CCAB were excluded, and the remaining 1604 (95%) consecutive OPCAB patients composed the study cohort. Almost half of the CCAB patients were in a hemodynamically unstable condition, even with an intra-aortic balloon pump; the remaining patients had previous cardiac surgery and required cardiopulmonary bypass for resternotomy and exposure. Six OPCAB procedures were converted to CCAB because of hemodynamic deterioration, and they were included in the cohort of this study. All data were collected prospectively and entered into the institutional database. The definitions of preoperative data in this study were based on those reported in the European System for Cardiac Operative Risk Evaluation (EuroSCORE).[14] Extracardiac arteriopathy includes any one or more of the following: claudication, carotid occlusion or greater than 50% stenosis, or previous or planned intervention on the abdominal aorta, limb arteries, or carotids.[14]

CR was defined according to the "traditional" classification described in the Coronary Artery Surgery Study[5]: revascularization is incomplete, with failure to graft into any system with significant stenosis (>50%) or lack of grafting into both the left anterior descending (LAD) and circumflex (LCx) systems for 50% or greater left main trunk disease.

Surgical Technique

All OPCAB procedures were performed under general anesthesia. The heart was approached via median sternotomy. Heparin (100 KIU/kg and an additional dose) was administered to achieve and maintain the activated clotting time at more than 250 seconds. The strategies of graft selection and distribution have been described elsewhere.[15,16] In specific cases, when distal vessels in the LCx or right coronary artery (RCA) systems were poorly visualized on preoperative angiography, and the territories of the vessels were deemed to have less myocardial viability based on the results of echocardiography and/or left ventriculography, we did not plan to place any grafts. These 98 cases were also included in the IR group throughout the study. Endarterectomy was performed if a coronary artery had a long, calcified plaque. Heparin was reversed with a half-reversal dose of protamine sulfate. Oral aspirin (100 mg) was administered from postoperative day 1 and through to and including the follow-up period.

Angiographic Evaluation

Bypass conduits and native coronary arteries were systematically evaluated in 95% of patients (1422 patients) by catheter-based angiography[16] or multidetector computed tomography (MDCT; SOMATOM Sensation 16; Siemens AG, Munich, Germany) before discharge with the patients' written informed consent. The postoperative angiography was performed as a routine evaluation, and is standard of care in Japan. Patients with cerebrovascular disease, renal dysfunction, or respiratory failure were excluded for clinical reasons. Although all the patients underwent angiography within the same hospitalization period as the index OPCAB, the dates of the angiography were not available from our database. The experienced interventional cardiologists or the radiologists reviewed the results of graftgraphy. On catheter-based angiography, the conduit was reviewed in at least 2 orthogonal views and scored on the worst appearance of the proximal anastomosis, body of the conduit, and distal anastomosis, according to the FitzGibbon classification.[17] On MDCT, volume-rendering images and curved multiplanar reconstruction of the anastomotic sites and conduits were constructed to evaluate and score the patency, according to the same classification. Based on the results of angiography, the cardiologists and/or radiologists judged the suitability and the need for postoperative reintervention.

Of 1521 patients who underwent angiographic evaluation, 225 (14.8%) were identified as having at least 1 suboptimal graft (FitzGibbon B or O) and were included in the occlusion group. The remaining 1296 patients were identified as having all patent grafts (FitzGibbon A) and were included in the patent group.

Follow-up

Complete follow-up was achieved in 99.5% of cases (median, 3.2 years; range, 1 month to 6.5 years). The patients were followed up in our outpatient clinic at 1, 6, and 12 months after discharge and at yearly intervals thereafter. The latest information was obtained by telephone call or by the attending surgeons consulting the referring cardiologists. Eight patients were lost to follow-up, and their data were censored at the time of the last contact, at which point they were alive and had not had any cardiac events. Prospectively gathered data on follow-up included death from any cause (including in-hospital mortality), MI, reintervention (surgical or percutaneous coronary intervention [PCI]), and stroke, which was defined as a neurological deficit diagnosed by a neurologist and confirmed by computed tomography (CT). Major adverse cardiac and cerebrovascular events (MACCEs) were defined as all-cause mortality, nonfatal MI, repeated revascularization (including in-hospital reintervention), or stroke. If more than one event arose in one patient, only the time to the first event was analyzed.

Statistical Analysis

Continuous data are expressed as means ± 1 SD or medians (interquartile range), and categorical variables are expressed as numbers (proportions). Categorical data were compared using the χ^2 test and the Fisher exact test. Continuous variables were compared by the Student *t*-test or the Mann-Whitney *U*-test, as appropriate. In the analysis of ranked data, the Kruskal-Wallis test was performed. Multivariable logistic regression analysis was performed to explore predictors of IR. Model variables used in the multivariable analyses were selected a priori on the presumption that they were clinically relevant. The model consisted of the following 22 variables: age, sex (female), body surface area (BSA), number of diseased vessels (3-vessel disease or not), left main disease, 1 or more total occluded lesion(s), congestive heart failure, previous MI, left ventricular ejection fraction (LVEF), atrial fibrillation, chronic renal failure (CRF; nonhemodialysis dependent or hemodialysis dependent), hypertension, hypercholesterolemia, diabetes mellitus (diet or oral drug use or insulin use), chronic obstructive pulmonary disease (COPD), extracardiac arteriopathy, cerebrovascular accident, previous PCI, previous cardiac surgery, and emergency operation. Odds ratios with 95% confidence intervals (CIs) were given for the logistic regression model. Survival curves were estimated using the Kaplan-Meier method, and differences were demonstrated by the log-rank test. Risk factors for midterm events were explored using the Cox model. In addition to the covariates used in the logistic regression model, the following 6 factors that were clinically relevant and reported by other investigators as predictors[10] were included in the analysis: conversion to CCAB, bilateral internal thoracic arteries (BITAs), right gastroepiploic artery, saphenous vein graft, number of anastomoses, and IR.

We also addressed potential confounding variables in the observed relationship between IR and survival through a propensity score analysis to account for the probability of a subject experiencing IR. We estimated propensity scores as predicted probabilities from a logistic regression model with IR as the outcome and the previously discussed covariates as predictors. We then created 10 equal-sized strata based on the quantiles of the propensity scores. The stratified Cox regression and the stratified log-rank test were conducted to evaluate the hazard ratio (HR) for survival, with IR versus CR.

Immediately after angiography, many revascularizations were performed in the occlusion group during the index hospitalization. To account for this, another HR for the periods after discharge was calculated for reintervention, in addition to the primary HR for all the reinterventions after surgery. Both occlusion (vs patent) and the interaction between IR and occlusion were tested with separate regression models.

HRs with 95% CIs were given for the Cox model. Statistical analyses were performed using SPSS statistics, version 19.0 (IBM, Armonk, NY). All *P* values quoted are 2 sided, and the significance levels were set to .05.

RESULTS

Early Results

There were 216 patients (13.5%) who underwent IR. Table 1 presents the baseline characteristics of the 2 groups. In the IR group, there was more 3-vessel disease (82% vs 67%; $P < .001$), previous MI (53% vs 42%; $P = .002$), and emergency operations (12% vs 7.4%; $P = .030$). Furthermore, the IR group appeared sicker, in that they had a higher prevalence of CRF (11% vs 6.8%; $P = .035$). There were no significant differences between the 2 groups with respect to mean age, sex, BSA, or COPD. The logistic EuroSCORE was higher in the IR group (4.0 vs 3.1; $P < .001$).

Operative and postoperative variables are also shown in Table 1. The CR group more frequently received BITA than the IR group (79% vs 70%; $P = .006$). The CR group had more anastomoses (3.8 ± 1.1 vs 2.9 ± 0.9; $P < .001$). Of 6 emergency conversions to CCAB, 5 were in the IR group (2.3% vs 0.1%; $P < .001$).

On postoperative angiography, overall graft patency (ie, FitzGibbon A or B) was 97.5% (97.5% in the CR group and 98.3% in the IR group; $P = .316$). The in-hospital mortality rate was slightly higher in the IR group ($P = .085$). The distribution and patency rates for each graft in OPCAB surgery have been described in our companion article.[16]

The maximum creatine kinase-myocardial band was higher in the occlusion group than in the patent group (median [interquartile range], 14.8 [9.5-31.8] vs 12.7 [8.4-22.1]; $P = .005$). Twenty patients (8.9%) in the occlusion group experienced perioperative MI (new Q-wave and creatine kinase-myocardial band, >50 IU/L), whereas 17 patients (1.3%) had perioperative MI in the patent group ($P < .0001$). The rates of low cardiac output and in-hospital mortality did not differ between the 2 groups ($P = .61$ and $P = 1.0$, respectively).

Ungrafted coronary systems in the IR group were as follows: LAD in 5 patients, LCx in 61 patients, RCA in 145 patients, and both LCx and RCA in 5 patients. The reasons for IR were the presence of a small-caliber coronary artery in 128 patients (59%), a diffuse lesion in 20 patients (9%), intramyocardial location in 1 patient (0.5%), and infarcted area in 51 patients (24%). In 16 cases, no reason was given in the operator's note. Multivariable logistic regression analysis was performed to identify predictors of IR; 1 or more total occluded lesion(s), BSA, 3-vessel disease, emergency operation, diabetes mellitus (diet or oral drug use), and female sex were identified as predictors of IR (Table 2).

Midterm Data

During the follow-up, 184 patients died: 61 from cardiac causes (23 sudden deaths) and 123 from noncardiac causes. Six patients experienced acute MI, and 29 developed stroke. Ninety-four patients received reintervention procedures: 24 received PCI during the same hospitalization as the index OPCAB, 66 underwent PCI after discharge, and 4 had reoperations (1 as an in-hospital redo surgery).

Figure 1, *A*, shows the Kaplan-Meier curves for all-cause mortality. The 5-year survival rates were 74.9% ± 3.7% for the IR group and 84.9% ± 1.4% for the CR group (log-rank test, $P < .001$). As presented in Figure 1, *B*, there were more deaths from cardiac causes in the IR group than in the CR group ($P = .020$). The disease-free survival rates for cardiac death after 5 years were 91.5% ± 2.4% in the IR group and 94.4% ± 0.9% in the CR group. The event-free survival rate for MACCE was significantly lower in the IR group (66.0% ± 4.1%) than in the CR group (75.7% ± 1.6%; $P < .001$) (Figure 1, *C*). There was no difference in the reintervention-free survival rate between the 2 groups ($P = .179$).

Results of the Cox model for all-cause mortality are presented in Table 3. The independent predictors of all-cause mortality were age, CRF (hemodialysis dependent and

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TABLE 1. Perioperative characteristics

Variables	CR (N = 1388)	IR (N = 216)	P value
Age, y*	68 ± 9	68 ± 9	.250
Female sex	389 (28)	52 (24)	.252
BSA, m^2*	1.61 ± 0.17	1.60 ± 0.16	.431
NYHA class ≥3	260 (19)	51 (24)	.096
Unstable angina	311 (22)	49 (23)	.930
Preoperative IABP	49 (3.5)	10 (4.6)	.435
Emergency operation	103 (7.4)	26 (12)	.030
Previous MI	579 (42)	114 (53)	.002
Recent MI (within 90 d)	133 (9.6)	25 (12)	.389
CHF	176 (13)	37 (17)	.084
LVEF, %*	62.0 ± 11.7	58.8 ± 14.2	<.001
AF	63 (4.5)	10 (4.6)	.862
Diseased vessels			
1- Or 2-vessel disease	459 (33)	39 (18)	<.001
3-Vessel disease	929 (67)	177 (82)	<.001
Left main disease	620 (45)	87 (40)	.239
≥1 Total occlusion	465 (34)	129 (60)	<.001
No. of significant lesions*	4.0 ± 1.7	4.3 ± 1.4	.049
Previous PCI	604 (44)	94 (44)	1.000
Previous cardiac surgery	29 (2.1)	5 (2.3)	.799
CRF (creatinine >200 μmol/L)			.046
Nonhemodialysis dependent	29 (2.1)	5 (2.3)	
Hemodialysis dependent	66 (4.8)	19 (8.8)	
Diabetes mellitus			.179
Diet or oral drug use	476 (34.3)	84 (38.9)	
Insulin use	163 (11.7)	30 (13.9)	
Hypertension	925 (67)	157 (73)	.086
Hypercholesterolemia	778 (56)	110 (51)	.163
COPD	36 (2.6)	7 (3.2)	.504
Extracardiac arteriopathy	297 (21)	55 (26)	.185
CVA	240 (17)	48 (22)	.086
Logistic EuroSCORE†	3.1 (1.7-5.7)	4.0 (2.1-8.2)	<.001
No. of anastomoses*	3.8 ± 1.1	2.9 ± 0.9	<.001
Conduits			
LITA	1337 (96)	205 (95)	.340
RITA	1121 (81)	158 (73)	.014
BITA	1096 (79)	152 (70)	.006
GEA	530 (38)	34 (16)	<.001
SVG	618 (45)	51 (24)	<.001
Radial artery	47 (3.4)	4 (1.9)	.299
Conversion to CCAB	1 (0.1)	5 (2.3)	<.001
Postoperative angiography (N = 3914 grafts)‡,§			.316
Fitzgibbon A	3291/3512 (94)	375/402 (93)	
Fitzgibbon B	132/3512 (3.8)	20/402 (5.0)	
Fitzgibbon O	89/3512 (2.5)	7/402 (1.7)	
In-hospital mortality	9 (0.6)	4 (1.9)	.085
Hospital length of stay, d†	14 (12-19)	15 (12-21)	.323

Values are given as number (percentage) unless otherwise indicated. *CR*, Complete revascularization; *IR*, incomplete revascularization; *BSA*, body surface area; *NYHA*, New York Heart Association; *IABP*, intra-aortic balloon pump; *MI*, myocardial infarction; *CHF*, congestive heart failure; *LVEF*, left ventricular ejection fraction; *AF*, atrial fibrillation; *PCI*, percutaneous coronary intervention; *CRF*, chronic renal failure; *COPD*, chronic obstructive pulmonary disease; *CVA*, cerebrovascular accident; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *LITA*, left internal thoracic artery; *RITA*, right internal thoracic artery; *BITA*, bilateral internal thoracic arteries; *GEA*, gastroepiploic artery; *SVG*, saphenous vein graft; *CCAB*, conventional coronary artery bypass. *Data are given as mean ± SD. †Data are given as median (interquartile range). ‡Overall, 1521 patients underwent postoperative angiography (3914 grafts). §Data are given as number/total (percentage).

TABLE 2. Multivariable analysis: predictors of incomplete revascularization

Variables	Odds Ratio	95% CI	P value
≥1 Total occluded lesion(s)	2.81	2.04-3.87	<.001
BSA, m^2	0.17	0.08-0.37	<.001
3-Vessel disease	1.70	1.18-2.44	.004
Emergency operation	1.73	1.05-2.41	.032
Diabetes mellitus (diet or oral drug use)	1.42	1.02-196	.035
Female sex	1.56	1.02-2.41	.042
LVEF, %	0.99	0.98-1.00	.110
Hypertension	1.29	0.92-1.81	.134
CVA	1.26	0.87-1.84	.224
CRF (hemodialysis dependent)	1.43	0.80-2.55	.231
CHF	0.77	0.49-1.20	.240
Age	0.99	0.98-1.01	.243
Diabetes mellitus (insulin use)	1.30	0.81-2.09	.274
Hypercholesterolemia	0.85	0.62-1.17	.320
AF	1.25	0.61-2.54	.548
Left main disease	1.08	0.79-1.49	.623
Previous cardiac surgery	1.17	0.43-3.19	.755
Extracardiac arteriopathy	1.06	0.74-1.52	.756
Previous MI	1.05	0.74-1.49	.790
Previous PCI	1.00	0.74-1.37	.979
CRF (non–hemodialysis dependent)	1.01	0.37-2.76	.989
COPD	1.00	0.42-2.40	.996

CI, Confidence interval; *BSA*, body surface area; *LVEF*, left ventricular ejection fraction; *CVA*, cerebrovascular accident; *CRF*, chronic renal failure; *CHF*, congestive heart failure; *AF*, atrial fibrillation; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *COPD*, chronic obstructive pulmonary disease.

non–hemodialysis dependent), extracardiac arteriopathy, diabetes mellitus (insulin use), saphenous vein graft, and IR (HR, 1.80; 95% CI, 1.15-2.81; $P = .010$), whereas the number of anastomoses and LVEFs was associated with a significantly better outcome.

In the propensity score analysis, the patients were stratified into 10 subgroups based on the estimated probabilities of IR occurring to interpret accurate differences observed in outcome. Applying the stratified Cox regression analysis, the all-cause mortality was also higher in the IR patients than in the CR patients (HR, 1.75; 95% CI, 1.10-2.79). Also, by the stratified log-rank test, a significant difference was obtained between the IR and CR patients ($P = .019$).

Figure 2 shows the Kaplan-Meier curves of the patent and occlusion groups. All-cause mortality did not differ between the groups ($P = .461$). On the other hand, the event-free survival rates for MACCE and reintervention were significantly lower in the occlusion group than in the patent group (both log-rank $P < .001$) (Figure 2, *A* and *B*). Immediately after angiography, many revascularizations

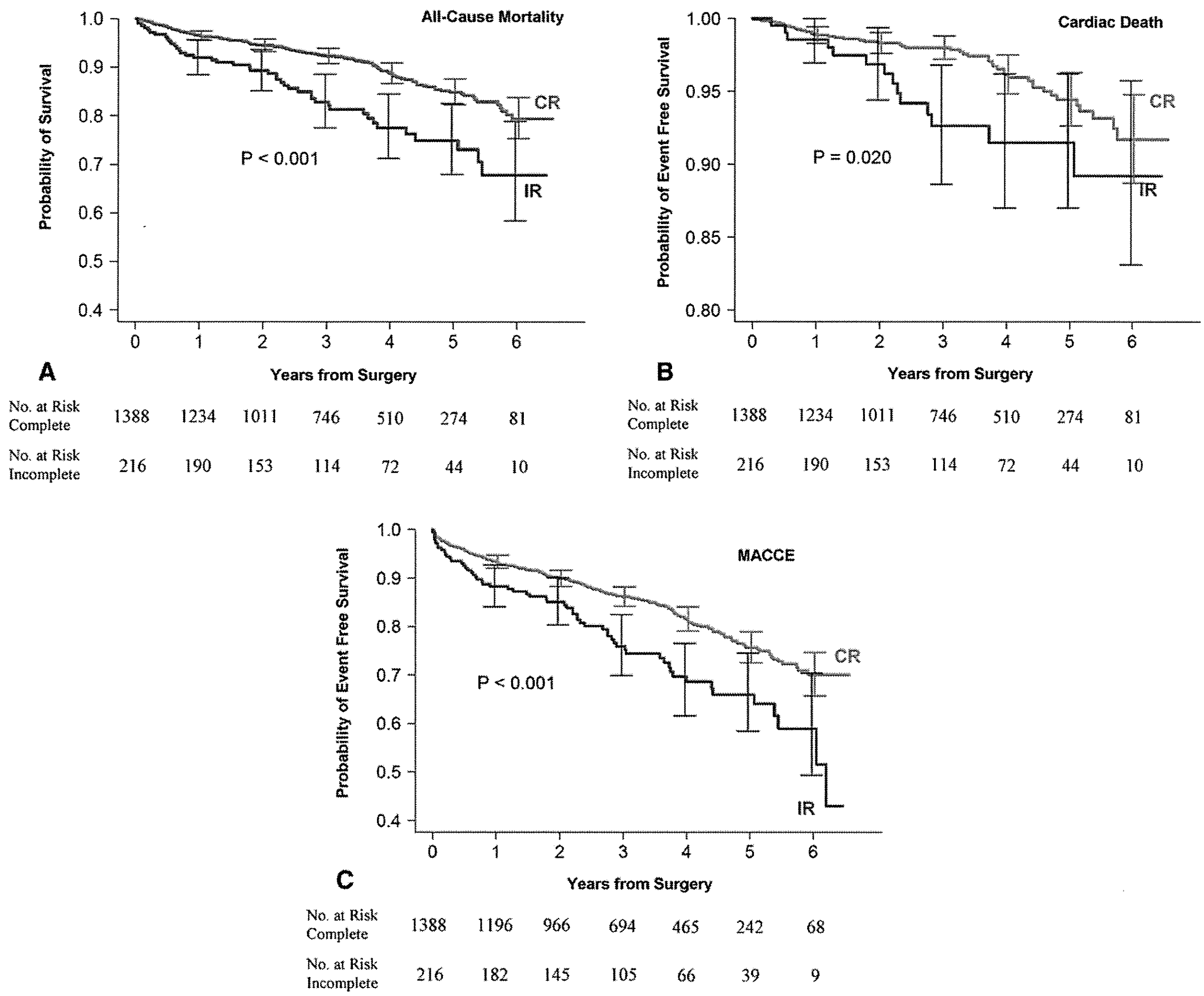

FIGURE 1. Kaplan-Meier estimates for the CR and IR groups. A, Survival curve for all-cause mortality. B, Event-free survival curve for cardiac death. C, Event-free survival curve for MACCE. *CR*, Complete revascularization; *IR*, incomplete revascularization; *MACCE*, major adverse cardiac and cerebrovascular events.

were performed during index hospitalization (24 PCIs and 1 reoperation). However, when the patients who underwent in-hospital reinterventions were excluded, the event-free survival rate for reintervention was still lower in the occlusion group than in the patent group ($P = .038$) (Figure 2, *C*). The Cox models revealed that graft occlusion was an independent risk factor for both all the reinterventions (HR, 5.49; 95% CI, 3.44-8.77; $P < .001$) and the reintervention after discharge (HR, 2.41; 95% CI, 1.30-4.47; $P = .005$). Interaction between IR and graft occlusion was not significant in the regression models for either all-cause mortality or reintervention ($P = .423$ and $P = .511$, respectively).

DISCUSSION

This study has clearly shown that IR was associated with decreased midterm survival after OPCAB surgery, whereas CR was not relevant to increased hazard of reintervention. In contrast, graft occlusion was not associated with overall survival, but was relevant to increased hazard of MACCE or reintervention. IR was also an independent risk factor for all-cause mortality using the Cox model, whereas graft occlusion was an independent risk factor for reintervention. Because the advantage of CR was not limited to groups of patients with low probabilities of IR occurring, there is no evidence of major selection bias, and the results previously stated are not altered by the propensity score analyses.

Completeness of Revascularization

CR has been recognized as a surgical mantra since the era of CCAB.[5,6] Alamanni et al[12] found that patients with IR experienced perioperative myocardial infarction more frequently than those without IR. Other investigators reported that IR was associated with long-term mortality after CCAB[18] and OPCAB.[7,8] The findings of this study are in

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