**Original
Article**

Acute Coronary Syndrome Does Not Have a Negative Impact on Outcomes after Coronary Artery Bypass Grafting in Patients with Left Main Disease

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Purpose: Early and long-term outcomes of coronary artery bypass grafting (CABG) in patients with left main disease (LMD) with acute coronary syndrome (ACS) have never been assessed.

Methods: Between September 2004 and April 2012, 459 patients with LMD underwent first-time isolated CABG. Of those, 191 patients had ACS and 268 did not. Early and late postoperative outcomes were compared between two groups.

Results: Patients in the LMD+ACS group were older and more likely to be female. Left ventricular ejection fraction was lower in the LMD+ACS group. In both groups, bilateral internal thoracic artery grafts were used in over 90% of patients and off-pump technique in over 95%. Operative death rate was not significantly different between the groups (LMD+ACS: 2.1% vs. LMD–ACS: 0.4%). Log-rank test revealed that the actuarial survival rate ($79.2 \pm 3.7\%$ vs. $81.5 \pm 3.5\%$) and freedom from major adverse cardiac and cerebrovascular events (MACCE) ($69.2 \pm 4.2\%$ vs. $67.0 \pm 4.1\%$) were similar between groups at 7 years. Multivariate analyses demonstrated that ACS was not identified as an independent predictor of operative death, late mortality, and late MACCE.

Conclusion: ACS did not have a negative impact on early and late outcomes of CABG in patients with LMD.

Keywords: coronary artery bypass grafting; acute coronary syndromes; left main disease

Introduction

Coronary artery bypass grafting (CABG) is considered the standard revascularization method for patients with left main disease (LMD). Current American and European guidelines consider LMD to be a class I indication for CABG.^{1,2)} However, patients with LMD may

have several cardiac conditions, including stable angina or acute coronary syndrome (ACS, non-ST-segment-elevation myocardial infarction [MI] or unstable angina). Historically, ACS has been considered to be a risk factor for morbidity and mortality in patients undergoing CABG.^{3,4)} Indeed, the Society of Thoracic Surgeons (STS) risk calculator includes ACS in preoperative cardiac status for the purpose of risk analysis.⁵⁾ Patients who have LMD with ACS often need emergency or urgent operation with or without an intra-aortic balloon pump (IABP). These situations may further increase the chance of operative mortality. However, there is no report demonstrating the difference between LMD patients with and without ACS.

The aim of this study was to compare early and long-term outcomes of CABG between LMD patients with and without ACS.

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Table 1 Preoperative characteristics of patients with left main disease with or without ACS

	LMD+ACS (n = 191)	LMD-ACS (n = 268)	P value
Age	71.4 ± 9.4	68.1 ± 9.5	<0.001
Sex, female	57 (29.8%)	46 (17.2%)	0.002
Body surface area (m ²)	1.6 ± 0.2	1.7 ± 0.2	0.064
Ejection fraction	56.2 ± 11.9	58.8 ± 9.4	0.012
Prior MI	59 (30.9%)	97 (36.2%)	0.279
Diseased vessel	2.7 ± 0.5	2.8 ± 0.4	0.249
Previous PCI	45 (23.6%)	78 (29.1%)	0.224
Congestive heart failure	20 (10.5%)	17 (6.3%)	0.153
Hypertension	129 (67.5%)	179 (66.8%)	0.946
Diabetes mellitus	73 (38.2%)	110 (41.0%)	0.608
Hyperlipidemia	117 (61.3%)	180 (67.2%)	0.228
Smoking	100 (52.4%)	159 (59.3%)	0.165
Peripheral vascular disease	10 (5.2%)	27 (10.1%)	0.089
Previous stroke	14 (7.3%)	27 (10.1%)	0.395
Creatinine > 1.5 mg/dL	14 (7.3%)	15 (5.6%)	0.584
Hemodialysis	4 (2.1%)	7 (2.6%)	>0.999
Chronic obstructive pulmonary disease	8 (4.2%)	5 (1.9%)	0.161
Atrial fibrillation	9 (4.7%)	12 (4.5%)	>0.999
Preoperative IABP use	52 (27.2%)	2 (0.7%)	<0.001

ACS: acute coronary syndrome; LMD: left main disease; IABP: intra-aortic balloon pumping; MI: myocardial infarction; PCI: percutaneous coronary intervention

Patients and Methods

Study Patients

Between September 2004 and April 2012, 1,382 patients underwent first-time isolated CABG at Sakakibara Heart Institute. Of these, 459 patients had LMD and were included in the study, and 191 of the 459 had ACS (unstable angina in 172 patients and non-ST-segment-elevation MI in 19 patients) and 268 did not. Preoperative characteristics of the study patients are presented in **Table 1**. The diagnosis of MI was made by electrocardiography and serum cardiac enzyme levels, and the location of the culprit lesion was confirmed by coronary angiography. Patients with ACS were initially treated with aspirin, beta blockers, and antithrombin therapy. All ACS patients received angiography soon after beginning medication.

Our facility's institutional review board approved this retrospective study and waived the requirement for written consent. We compared preoperative, intraoperative, and postoperative variables between patients with ACS and stable angina pectoris. Long-term outcomes were compared between the two groups. Multivariate analyses were performed to determine the significant predictors of operative death, late mortality and major adverse cardiac and cerebrovascular event (MACCE). All data were collected prospectively and reviewed retrospectively.

Operations

Our strategy for isolated CABG was directed at achieving complete myocardial revascularization with an off-pump technique whenever feasible. Complete revascularization was defined as *traditional* completeness in this study; i.e., that all diseased arterial systems (stenosis ≥50%) received at least one graft. Off-pump CABG technique has been described previously.⁶ We bypassed all substantially diseased coronary arteries (stenosis ≥50%) that were >1 mm in diameter. If necessary, concomitant extensive reconstruction (length ≥4.0 cm) with or without endarterectomy was performed in patients with a diffusely diseased left anterior descending artery.⁷ Deep pericardial stay sutures were not used, and a commercially available heart positioner and stabilizer were applied in all cases. Cardiopulmonary bypass with or without cardiac arrest was used in patients who were not suitable for off-pump technique, including patients with intramyocardial coronary arteries or severely impaired left ventricular function.

Bypass grafts were prepared after the patient was heparinized (300 IU/kg). Arterial grafts (internal thoracic artery [ITA], radial artery, and gastroepiploic artery) were skeletonized and harvested. Anastomoses between coronary arteries and grafts were performed using parachute technique with 8-0 polypropylene running sutures.

Low-dose aspirin was routinely begun in all patients postoperatively and continued indefinitely. In addition to low-dose aspirin, warfarin was titrated to a target international normalized ratio of 2.0 and continued for 3 months in patients with saphenous vein grafts.

Follow-up was achieved by outpatient office visits, direct communication with patients or their families, or reports by family physicians. The final follow-up was completed in all patients during a 1-month closing interval ending in August 2013.

Definitions

Unstable angina was defined as having chest pain at rest or of new onset or increasing in frequency and severity. Left main coronary artery disease was defined as the presence of 50% or greater stenosis in any angiographic view according to the STS database.

Operative death was defined as death within the same hospitalization or within 30 days of surgery. Low-output syndrome was defined as the need for adrenaline, $>5 \mu\text{g/kg/min}$ dopamine or dobutamine, or IABP. Perioperative MI was defined as new Q waves on electrocardiography or a peak creatine kinase-myocardial band level ≥ 5 times the upper limit of normal (25 IU/L). Respiratory failure was defined as a requirement for prolonged mechanical ventilation ($>48\text{h}$) or the occurrence of pneumonia. Postoperative stroke was defined as the occurrence of a new stroke confirmed by computed tomography. In patients with preoperative stroke, postoperative stroke was defined as a worsening of the neurological deficit with new radiological findings. MACCE was defined as death from any cause, stroke, MI, or repeat revascularization.

Statistical Analysis

All statistical analyses were performed using StatView 5.0 software or SAS for Windows release 9.2 (SAS Institute Inc., Cary, North Carolina, USA). Continuous variables are reported as mean $\pm$ standard deviation and were compared using Student's *t*-test. Discrete variables were compared by the χ^2 test or Fisher's exact test.

Univariate and multivariate logistic regression analyses were performed to determine the significant predictors of operative death. The variables used for univariate analysis were the clinical variables listed in **Table 1** in addition to ACS. Variables with $P < 0.1$ in univariate analyses were included in the multivariate model.

Actuarial event-free survival curves were estimated by the Kaplan-Meier method. The log-rank test was used to assess differences in survival between groups.

Univariate and multivariate Cox proportional hazard analyses were performed to investigate the significant predictors of late mortality and late MACCE. The variables used for univariate analysis were the clinical variables listed in Table 1 as well as ACS. Variables with $P < 0.1$ in univariate analyses were included in the multivariate model.

Results

Early Clinical Outcomes for All Patients

Preoperative characteristics of the LMD+ACS and LMD-ACS groups are listed in **Table 1**. Patients in the LMD+ACS group were older and more likely to be female. Left ventricular ejection fraction was lower and preoperative use of IABP more frequent, in the LMD+ACS group. Other characteristics were not significantly different.

Intraoperative and early postoperative outcomes of both groups are shown in **Table 2**. The number of anastomoses per patient was lower in the LMD+ACS group. There were no significant differences in the frequency of use of bilateral ITA grafts and off-pump procedure between groups. Intraoperative blood transfusion was performed more frequently in the LMD+ACS group.

Postoperatively, the rates of occurrence of low-output syndrome and requirement for hemodialysis were significantly higher in the LMD+ACS group. Causes of death in the LMD+ACS group were pneumonia in two patients, low-output syndrome in one, and ischemic colitis in one. In the LMD-ACS group, one patient died of pneumonia.

Univariate analyses identified age, smaller body surface area, ACS, lower ejection fraction, history of congestive heart failure, atrial fibrillation, and preoperative use of IABP to be associated with operative death. Multivariate analysis revealed that lower ejection fraction (Odds ratio 1.135; $P = 0.036$; 95% confidence interval [CI] 1.008–1.277) was the only independent predictor of operative death.

Long-Term Clinical Outcomes for All Patients

Follow-up was completed for all patients. During the follow-up period (44.1 ± 24.6 months), there were 30 deaths in the LMD+ACS group and 29 in the LMD-ACS group. The actuarial survival rate at 7 years was not different between groups ($79.2 \pm 3.7\%$ in the LMD+ACS group and $81.5 \pm 3.5\%$ in the LMD-ACS group; $P = 0.262$) (**Fig. 1A**). MACCE occurred in 44 patients in the LMD+ACS group and 58 patients in the LMD-ACS

Table 2 Operative and postoperative data of patients with left main disease with or without ACS

	LMD+ACS (n=191)	LMD-ACS (n = 268)	P value
Anastomoses	3.9 ± 1.2	4.2 ± 1.2	0.002
Bilateral internal thoracic artery use	168 (88.0%)	249 (92.9%)	0.099
Extensive reconstruction of LAD	19 (9.9%)	39 (14.6%)	0.186
Off-pump procedure	186 (97.4%)	260 (97.0%)	>0.999
Operation time (min)	249.6 ± 59.5	279.2 ± 63.9	<0.001
Non-elective	82 (42.9%)	11 (4.1%)	<0.001
Transfusion	96 (50.3%)	82 (30.6%)	<0.001
Intubation (h)	11.3 ± 12.0	8.2 ± 8.8	0.001
Intensive care unit stay (days)	3.3 ± 15.6	1.3 ± 1.1	0.031
Operative death	4 (2.1%)	1 (0.4%)	0.166
Re-exploration due to bleeding	1 (0.5%)	2 (0.7%)	>0.999
Low output syndrome	7 (3.7%)	2 (0.7%)	0.038
Perioperative myocardial infarction	2 (1.0%)	2 (0.7%)	>0.999
Severe ventricular arrhythmia	3 (1.6%)	0	0.071
Require of hemodialysis	7 (3.7%)	2 (0.7%)	0.038
Stroke	4 (2.1%)	1 (0.4%)	0.166
Mediastinitis	0	2 (0.7%)	0.513

ACS: acute coronary syndrome; LAD: left anterior descending artery

Fig. 1 (A) Freedom from all-cause death in all patients. (B) Freedom from major adverse cardiac and cerebrovascular events in all patients. LMD: left main disease; ACS: acute coronary syndrome; MACCE: major adverse cardiac and cerebrovascular events.

group. Freedom from MACCE at 7 years did not differ between groups ($69.2 \pm 4.2\%$ in the LMD+ACS group and $67.0 \pm 4.1\%$ in the LMD-ACS group; $P = 0.919$) (**Fig. 1B**).

Univariate analyses identified age, smaller body surface area, lower ejection fraction, number of diseased vessels, history of congestive heart failure, peripheral vascular disease, higher creatinine level, hemodialysis, chronic obstructive pulmonary disease, and atrial fibrillation to be associated with late mortality. Multivariate analysis (**Table 3**) revealed that age, history of congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, and atrial fibrillation were independent predictors of late mortality. ACS was not identified as an independent predictor of late mortality (hazard ratio [HR] 1.125; $P = 0.674$; 95% CI 0.649–1.949).

Univariate analyses identified age, smaller body surface area, lower ejection fraction, number of diseased vessels, history of congestive heart failure, hypertension, peripheral vascular disease, chronic obstructive pulmonary disease, and atrial fibrillation to be associated with late MACCE. Multivariate analysis (**Table 4**) revealed that history of congestive heart failure, hypertension, chronic obstructive pulmonary disease, and atrial fibrillation were independent predictors of late MACCE. ACS was not identified as an independent predictor of late MACCE (HR 0.810; $P = 0.328$; 95% CI 0.532–1.235).

Table 3 Multivariate Cox proportional hazard analysis for late mortality for all patients

Variable	Hazard ratio	P-value	95% CI
Age	1.042	0.037	1.002 – 1.084
Congestive heart failure	2.849	0.003	1.437 – 5.650
Peripheral vascular disease	2.597	0.009	1.274 – 5.291
Chronic obstructive pulmonary disease	3.135	0.016	1.242 – 7.937
Atrial fibrillation	3.322	0.003	1.490 – 7.407
Acute coronary syndrome	1.125	0.674	0.649 – 1.949

CI: confidence interval

Table 4 Multivariate Cox proportional hazard analysis for major adverse cardiac and cerebrovascular events for all patients

Variable	Hazard ratio	P-value	95% CI
Congestive heart failure	2.331	0.005	1.289 – 4.219
Hypertension	1.595	0.047	1.006 – 2.525
Chronic obstructive pulmonary disease	2.564	0.011	1.244 – 5.291
Atrial fibrillation	2.353	0.021	1.138 – 4.854
Acute coronary syndrome	0.810	0.328	0.532 – 1.235

CI: confidence interval

Discussion

Although percutaneous coronary intervention (PCI) procedures have been performed for LMD,⁸⁾ the current gold standard of care for LMD is still CABG because of superior long-term outcomes compared with PCI.⁹⁾ American and European guidelines recognize CABG as the only class IA recommendation for treatment of LMD.^{1,2)} Evolution of surgical techniques and perioperative management has improved surgical outcomes in patients with LMD. However, patients with LMD may have various preoperative conditions, including unstable angina, acute MI, and cardiogenic shock, which in the worst cases may require emergency or urgent operation. A subgroup study of the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial demonstrated that emergency revascularization priority was a significant multivariate predictor for increased MACCE in patients with LMD who underwent CABG.¹⁰⁾ Thus, ACS has generally been considered a critical condition in patients with LMD. In the present study, the operative death rate of the LMD+ACS group was slightly higher than that of the LMD–ACS group; however, ACS was not an independent predictor of early and long-term outcomes in patients with LMD by multivariate analysis.

Montalescot, et al. presented early results of PCI and CABG in patients with LMD and ACS.¹¹⁾ In that study, in-hospital mortality in patients who underwent CABG was significantly lower than in patients who did not

undergo revascularization (5.4% vs. 7.6%; $P = 0.001$). When compared with PCI, CABG is associated with favorable 6-month survival in patients with LMD and ACS. Caggegi, et al. compared 1-year outcomes between PCI and CABG in patients with LMD and ACS.¹²⁾ In their analyses, 1-year mortality was not different between the PCI and CABG groups (6.3% versus 3.6%; $P = 0.15$). However, the rate of MACCE was lower in the CABG group than in the PCI group (14.4% versus 5.3%; $P < 0.001$). The authors commented that this difference was driven mainly by a higher rate of target-lesion revascularization (8.1% vs. 1.7%; $P = 0.001$). CABG provides revascularization of most of the epicardial vessels, including the culprit lesion. Successful CABG may therefore reduce the likelihood of future ischemic events in patients with ACS. At our institution, the selection of PCI or CABG as a revascularization method in patients with LMD is made by the heart team.¹³⁾ In general, our heart team treats LMD with CABG; however, PCI is chosen for patients who are not candidates for CABG because of poor general condition, refusal to undergo CABG, a simple lesion in the left main trunk (isolated or single-vessel disease with an ostial or shaft lesion), a lesion of the distal bifurcation with a small left circumflex artery, or cardiogenic shock because of sudden occlusion of the left main trunk. In the present study, operative mortality (2.1%) in patients with LMD and ACS was lower than that reported previously. We believe our approach provides favorable long-term outcomes even in LMD patients with ACS.

The use of bilateral ITA grafts has been shown to provide survival benefit compared with the use of a single ITA graft.¹⁴⁾ Bonacchi, et al. demonstrated the safety and effectiveness of using bilateral ITA grafts in patients with ACS.¹⁵⁾ They also showed the superiority of bilateral ITA grafts compared with single ITA grafts in mid-term and event-free survival in patients with ACS.¹⁵⁾ In the present study, we used bilateral ITA grafts in the majority of patients. Bonacchi, et al. stated that during emergency/urgent myocardial revascularization with careful patient management, the important early and long-term advantages of this second ITA conduit, such as early improved flow/reperfusion and freedom from late atherosclerotic disease in patients with unstable angina pectoris, compensate for the few more minutes spent skeletonizing and harvesting both vessels.¹⁶⁾ We believe that bilateral ITA grafts should be used even in patients with ACS because of the long-term survival advantage as long as they are harvested expeditiously.¹⁷⁾

In this study, we used IABP in a higher proportion of patients with than without ACS. All IABPs were placed preoperatively. The effects of IABP support, such as reduction of ventricular afterload, improvement of diastolic coronary perfusion, and enhancement of subendocardial perfusion, are very beneficial to patients with ACS. However, these benefits may have influenced the favorable results in patients with ACS in this study.

Limitations

Our study has the following limitations. This is a retrospective observational study. One of reasons of no-significant difference in operative death rate may be because the number of patients was small. Treatment and treatment timing varied according to the practices of individual physicians and surgeons. The number of patients and the follow-up period of 7 years might not be sufficient to provide definitive results.

Conclusion

ACS did not have a negative impact on early and late outcomes after CABG in patients with LMD.

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Disclosure Statement

There are no conflicts of interest.

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