Benefits of Off-Pump Coronary Artery Bypass Grafting in High-Risk Patients

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**Background**—The benefits of off-pump coronary artery bypass graft (OPCAB) compared with conventional on-pump coronary artery bypass graft (CCAB) remain controversial. Thus, it is important to investigate which patient subgroups may benefit the most from OPCAB rather than CCAB.

**Methods and Results**—Among the patients undergoing first coronary revascularization enrolled in the CREDO-Kyoto Registry (a registry of first-time percutaneous coronary intervention and coronary artery bypass graft patients in Japan), 2468 patients undergoing coronary artery bypass graft were entered into the study (mean age, 67±9 years). Predicted risk of operative mortality (PROM) of each patient was calculated by logistic EuroSCORE. Patients were divided into tertile based on their PROM. Mortality rates and the incidences of cardiovascular events were compared between CCAB and OPCAB within each PROM tertile using propensity score analysis. A total of 1377 patients received CCAB whereas 1091 received OPCAB. Adjusted 30-day mortality was not significantly different between CCAB and OPCAB patients regardless of their PROM range. However, the odds ratio of 30-day stroke in CCAB compared with OPCAB in the high-risk tertile was 8.30 (95% confidence interval, 2.25–30.7; \( P < 0.01 \)). Regarding long-term outcomes, hazard ratio of stroke in CCAB compared with OPCAB in the high-risk tertile was 1.80 (95% confidence interval, 1.07–3.02; \( P = 0.03 \)). Nevertheless, hazard ratio of overall mortality in the high-risk tertile was 1.44 (95% confidence interval, 0.98–2.11; \( P = 0.06 \)), indicating no statistically significant difference between the 2 procedures.

**Conclusions**—OPCAB as opposed to CCAB is associated with short-term and long-term benefits in stroke prevention in patients at higher risk as estimated by EuroSCORE. No survival benefit of OPCAB was shown regardless of preoperative risk level. (*Circulation. 2012;126[suppl 1]:S151–S157.)*

**Key Words:** coronary artery bypass graft ■ high-risk populations ■ off-pump surgery

As awareness of the potential morbidity of cardiopulmonary bypass and aortic manipulation increased and as surgical tools and techniques were improved, off-pump coronary artery bypass grafting (OPCAB) gained widespread acceptance and entered the mainstream of clinical practice.1 OPCAB is part of the procedural armamentarium of a growing proportion of surgeons worldwide.

The advantages of OPCAB compared with conventional on-pump coronary artery bypass graft (CCAB) remain a source of controversy, however. Several randomized controlled trials (RCT) have been conducted over the past decade to compare the outcomes of these 2 procedures. Equivalent short-term and long-term angiographic graft patency has been demonstrated, but the benefits of OPCAB with regard to mortality and morbidity remain unclear.2-5 Several retrospective studies have reported that OPCAB is associated with lower incidences of death and stroke.6-11 This finding may result, at least partially, from the fact that the benefits of OPCAB are not prominent in RCT that excluded high-risk patients. Thus, it is important to investigate which patient subgroups may benefit the most from OPCAB rather than CCAB. In addition, OPCAB is used more frequently in Japan than it is in the United States or Europe, which may enable a more reliable comparison between CCAB and OPCAB using Japanese data.12-14

The Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) is a multicenter registry in Japan enrolling 9877 consecutive patients undergoing first percutaneous coronary intervention or coronary artery bypass graft (CABG).15 In the present study, we sought to investigate...
the benefits of OPCAB using the data from the CREDO-Kyoto registry. The purpose of the present study was to stratify the patients into subgroups according to the logistic European Systems for Cardiac Operative Risk Evaluation (EuroSCORE)16,17 and to investigate which patient subgroups can be expected to benefit the most from OPCAB rather than CCAB.

Patients and Methods

Study Population

The CREDO-Kyoto is a multicenter registry in Japan that enrolls consecutive patients undergoing first percutaneous coronary intervention or CABG and that excludes those patients with acute myocardial infarction within 1 week before the index procedure.15 This study was approved by the Institutional Review Boards or Ethics Committees of all participating institutions. Because the subjects were retrospectively enrolled, written informed consent was not obtained, in accordance with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare of Japan. However, 73 patients were excluded because of their refusal to participate in the study when contacted for follow-up.15

Between January 2000 and December 2002, 9877 patients were identified as having undergone either percutaneous coronary intervention (6878 patients) or CABG (2999 patients) without history of coronary revascularization. Among the 2999 patients undergoing CABG, 484 patients undergoing concomitant valvular, left ventricular, or major vascular operations were excluded from the current analysis. In addition, 47 patients whose records lacked the data required to calculate the logistic EuroSCORE were also excluded. Therefore, the study group comprised 2468 patients undergoing first isolated CABG.

Data Collection and Definitions

Demographic, angiographic, and procedural data were collected from hospital charts or databases at the various centers by independent clinical research coordinators according to prespecified definitions. Baseline clinical characteristics, such as myocardial infarction, heart failure, diabetes, hypertension, current smoker status, atrial fibrillation, chronic obstructive lung disease, and malignancy were regarded as present when these diagnoses were recorded in the hospital charts. Left ventricular ejection fraction was measured either by contrast left ventriculography or by echocardiography. Chronic kidney disease was regarded as present when creatinine clearance estimated according to the Cockcroft–Gould formula was <60 mL/min. Anemia was defined as a blood hemoglobin level <12 g/dL, as previously described.15

End Points

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.15 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 neurological deficit that could not be attributed to other neurological 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 end point was death from any cause. Secondary end points were cardiovascular death, stroke, myocardial infarction, composite cardiovascular event (cardiovascular death, stroke, or myocardial infarction), and need for any revascularization procedures (CCAB or OPCAB) during the follow-up period.

Risk Stratification by Logistic EuroSCORE

EuroSCORE was used to calculate predicted risk of mortality (PROM).17,18 Based on their PROM, patients were stratified into low-risk (PROM <3%), intermediate-risk (PROM 3% to <6%), and high-risk (PROM ≥6%) tertiles.

Statistical Analyses

All continuous variables were expressed as the mean±standard deviation. Differences in baseline characteristics between the 2 groups were examined by unpaired t test and Fisher exact test.

Outcomes after CCAB or OPCAB according to tertiles of PROM were compared by the propensity score-adjusted logistic regression or Cox proportional hazard models.19 These analyses were performed according to the intent-to-treat principle. The PROM of each patient was calculated based on the logistic EuroSCORE and used to divide patients into tertiles. Propensity scores, ie, the probability that a patient would undergo CCAB or OPCAB, were calculated for each.
Baseline Characteristics and Operative Outcomes

Of the 2468 patients in the CREDO-Kyoto registry, 1377 patients (56%) received CCAB and 1091 (44%) received OPCAB. Baseline characteristics of the patients in the 2 groups are presented in Table 1. The OPCAB group included more high-risk patients, such as those with older age, heart failure, history of stroke, and peripheral arterial disease. The Figure shows the Kaplan–Meier curves for all-cause mortality and stroke stratified by PROM. The 3 groups had similarly in both groups. However, arterial grafts in such vessels as the right internal thoracic artery and the gastroepiploic artery were used more commonly in the OPCAB group.

Results

The average number of anastomotic sites per patient was 3.3±1.0 in the CCAB group and 3.2±1.3 in the OPCAB group (Table 2). Left internal thoracic artery grafts were used more frequently in the OPCAB group. Baseline characteristics of the patients in the 2 groups are presented in Table 1. The OPCAB group included more high-risk patients, such as those with older age, heart failure, history of stroke, and peripheral arterial disease. The number of diseased vessels per patient was typically higher in the CCAB group. The number of patients with left main disease was similar between the groups.

The 30-Day Outcomes

Unadjusted 30-day mortality was 2.2% in the CCAB group and 0.82% in the OPCAB group. A comparison of 30-day outcomes in the CCAB and OPCAB groups, categorized according to PROM tertile, is presented in Table 3. Propensity-adjusted 30-day mortality was not significantly different between the groups regardless of the PROM range. Proportions of 30-day stroke were similar between the 2 groups in the low-risk and intermediate-risk tertiles, but the odds ratio of 30-day stroke in CCAB compared with OPCAB was 8.30 (95% confidence interval [CI], 2.25–30.7; P<0.01). Proportions of 30-day myocardial infarction were similar between the 2 groups in the high-risk tertile. Those composite cardiovascular events were also similar between the 2 groups in the low-risk tertile, but the odds ratio of composite event was 2.72 (95% CI, 1.10–6.72; P=0.03) in the intermediate-risk tertile and 2.58 (95% CI, 1.27–5.23; P=0.01) in the high-risk tertile.

Long-Term Outcomes

Clinical follow-ups were completed for 98% of the cases at 1 year and for 95% of the cases at 2 years. The median follow-up period was 1314 days. Unadjusted overall mortality rates in the CCAB and OPCAB groups were 4.9% and 4.1% at 1 year, and 14.6% and 14.9% at 5 years, respectively. The Figure shows the Kaplan–Meier curves for all-cause mortality and stroke stratified by PROM. The 3 groups had significantly different rates of all-cause death and stroke (P<0.01, respectively).

A comparison of long-term outcomes in the CCAB and OPCAB groups, categorized according to PROM tertile, is presented in Table 4. Propensity-adjusted overall mortality was not significantly different between the CCAB and OPCAB groups regardless of the PROM range, although mortality after CCAB tended to be higher in the high-risk tertile (1.44; 95% CI, 0.98–2.11; P=0.06). Adjusted incidence of myocardial infarction was similar between the procedures except in the intermediate-risk tertile. Adjusted incidence of any revascularization was similar between the 2 groups regardless of the PROM range. Adjusted incidence of stoke was similar between the 2 groups in the low-risk and intermediate-risk tertiles, but the hazard ratio of the incidence of stroke in CCAB compared with OPCAB in high-risk tertile was 1.80 (95% CI, 1.07–3.02; P=0.03). In addition, the hazard ratios of the incidence of composite cardiovascular events in CCAB compared with OPCAB in the intermediate-risk and high-risk tertiles were 1.68 (95%
CI, 1.07–2.66; \( P = 0.03 \) and 1.46 (95% CI, 1.03–2.08; \( P = 0.03 \)), respectively.

**Discussion**

**Principal Findings**

Because the benefits of OPCAB compared with CCAB remain controversial, the present study was designed to identify the patient subgroups that are likely to benefit the most from OPCAB rather than CCAB. Patients were divided into tertiles (low-risk, intermediate-risk, and high-risk) based on their PROM as calculated using the logistic EuroSCORE.

Thirty-day outcomes revealed no significant difference in survival between the CCAB and OPCAB groups regardless of the PROM range. In the high-risk tertile, however, OPCAB was associated with lower incidence of stroke and composite cardiovascular event. Long-term outcomes likewise revealed no significant difference in survival between the CCAB and OPCAB groups regardless of preoperative risk level. In the high-risk tertile, however, stroke rate was significantly higher

![Figure](http://circ.ahajournals.org/)

**Figure.** Kaplan–Meier curves for all-cause death and stroke stratified by predicted risk of operative mortality (PROM). **A**, All-cause death. **B**, Stroke.
after CCAB, whereas in both intermediate-risk and high-risk patients the incidence of composite cardiovascular events was higher after CCAB. These results indicate that OPCAB improves both early and late stroke outcomes compared with CCAB in high-risk patients. Still, OPCAB may not be associated with any survival benefit even in high-risk patients.

In the present study, we could not show that OPCAB was associated with survival benefit even in high-risk patients. Although mortality tended to be higher after CCAB in both 30-day and long-term outcomes ($P=0.10$ and $P=0.06$, respectively). In addition, the incidence of myocardial infarction was similar between the 2 groups in the low-risk and high-risk tertiles but was higher after CCAB in the intermediate-risk tertile. This trend was different from those of other end points. These outcomes might have been influenced by sample size or numbers of events.

**CCAB vs OPCAB: RCT and Meta-Analysis**

Although a number of RCT comparing CCAB and OPCAB have been performed, until recently, these were not of sufficient size to show statistically significant differences. Several recent studies have been of sufficient size but have failed to demonstrate the superiority of OPCAB compared with CCAB. OPCAB may reduce bleeding or atrial fibrillation, but it is not associated with any significant difference in the incidences of death, myocardial infarction, or stroke.2–5 A large RCT by Shroyer et al4 demonstrated that patients undergoing OPCAB had worse composite outcomes and poorer graft patency compared with patients undergoing CCAB. There was no difference in neurocognitive outcomes.

To compensate for the shortcomings of RCT, several meta-analyses also have been performed. Like the RCT, most of these meta-analyses have concluded that mortality, stroke, and myocardial infarction were not reduced in OPCAB.3,20–22 Moller et al23 reported that there were no significant differences in mortality, myocardial infarction, stroke, or renewed revascularization in a meta-analysis of 66 RCT. However, Sedrakyan et al24 reported that OPCAB was associated with benefits in terms of stroke prevention. Another recent large meta-analysis by Afilao et al20 which included 59 RCT, compared in-hospital and 30-day outcomes after CCAB and OPCAB, and reported that OPCAB did not reduce mortality or myocardial infarction compared with CCAB. OPCAB was associated with a 30% reduction in stroke, but meta-regression analysis showed that the benefits of OPCAB with

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**Table 4. Propensity Score Analysis of Long-Term Outcomes in 2468 Patients Undergoing Coronary Artery Bypass Graft**

<table>
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<tr>
<th>Subgroup by EuroSCORE</th>
<th>N</th>
<th>Events (CCAB vs OPCAB)</th>
<th>Hazard Ratio (CCAB vs OPCAB)</th>
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<th>P</th>
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<td>&lt;3%</td>
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<td>3%–6%</td>
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<td>≥6%</td>
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<td>1.44</td>
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<td>&lt;3%</td>
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<td>1.29</td>
<td>0.68</td>
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<td>3%–6%</td>
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<td>1.68</td>
<td>1.07</td>
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<td>≥6%</td>
<td>815</td>
<td>108 78</td>
<td>1.46</td>
<td>1.03</td>
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<td><strong>Myocardial infarction</strong></td>
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<td>≥6%</td>
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<td><strong>Stroke</strong></td>
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<td>&lt;3%</td>
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<td>3%–6%</td>
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<td>3%–6%</td>
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<td>0.75</td>
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<td>≥6%</td>
<td>815</td>
<td>40 48</td>
<td>0.74</td>
<td>0.45</td>
<td>1.22</td>
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CCAB indicates conventional on-pump coronary artery bypass graft; CI, confidence interval; OPCAB, off-pump coronary artery bypass graft.

The confounders used to calculate propensity scores are as follows: age; gender; body mass index; emergency procedure; critical preoperative state; previous myocardial infarction; congestive heart failure; stroke; peripheral arterial disease; cardiac artery disease; atrial fibrillation; chronic obstructive pulmonary disease; malignancy; hypertension; diabetes; hemodialysis; chronic kidney disease; anemia; current smoker status; left ventricular ejection fraction; total occlusion; proximal left anterior descending artery disease; triple-vessel disease; left main disease; and use of left internal thoracic artery, right internal thoracic artery, gastroepiploic artery, radial artery, or saphenous vein.

*Composite event: cardiovascular death, stroke, or myocardial infarction.
regard to prevention of death, myocardial infarction, and stroke were similar to those of CCAB regardless of patient age, gender, number of grafts, and trial publication date.

**CCAB vs OPCAB: Registry**

However, several large registry data analyses, including the present study, have provided compelling evidence in favor of OPCAB. Puskas et al. reported that OPCAB provides significant early mortality and morbidity advantages, especially for women; over the course of 10 years of follow-up, however, OPCAB and CCAB result in similar survival rates, regardless of gender. Hannan et al. reported that OPCAB is associated with lower in-hospital mortality and complication rates than CCAB, but long-term outcomes are comparable between the 2 groups, except with regard to the rate of revascularization. An intention-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.

The reasons for these differences in outcomes between the RCT data and the registry data are unclear. The greater technical difficulty of OPCAB may make it difficult to compare the outcomes of CCAB and OPCAB; in comparison with CCAB, OPCAB is a more technically demanding procedure, especially when it involves branches of the circumflex territory or the peripheral right coronary artery territory. Complete revascularization sometimes may be difficult for inexperienced surgeons. Moreover, the limitations of RCT are attributable, in part, to the limitations involved in patient selection for enrollment. “Truly high-risk” patients are often excluded from such comparisons for ethical reasons. Thus, a comparison of the RCT data with the registry data may play an important role in clarifying the true differences between the 2 procedures and/or the true benefits of OPCAB. Regarding observational studies, the impact of selection bias in determining the operative technique to be used for any given patient in these series may be a confounding variable.

**Benefits of OPCAB in High-Risk Patients**

As shown in the present study, OPCAB may be associated with better outcomes, particularly in high-risk populations. The observational study by Puskas et al. reported that OPCAB as opposed to CCAB is associated with lower operative mortality in higher-risk patients as stratified by The Society of Thoracic Surgeons score (>0.025), and that this benefit increases with increasing predicted risk of mortality. Similarly, Li et al. reported that OPCAB is associated with a significantly lower postoperative stroke rate compared with CCAB for older and high-risk patients. The Best Bypass Surgery Trial, a randomized study that compared 30-day outcomes in high-risk patients (EuroSCORE ≥5 and 3-vessel disease) undergoing CCAB or OPCAB, indicated that both procedures can be performed in high-risk patients with a low risk of short-term complications. Because of its small sample size (n = 341), however, the study could not reveal any small but clinically relevant differences between the procedures.

Because OPCAB has been performed more frequently in Japan than in European countries or in the United States, Japanese surgeons have accumulated more experience with the OPCAB technique. In 2009, ~63% of CABG in Japan were conducted without cardiopulmonary bypass, and the 30-day mortality associated with primary elective OPCAB was not >0.6%. The JOCRI study, an RCT conducted in Japan, revealed that OPCAB with multiple arterial grafts was as safe as CCAB, with similar completeness of revascularization and early graft patency. Japanese surgeons’ greater familiarity with the OPCAB techniques may enable them to focus more on the advantages of OPCAB in high-risk patients than on the technical difficulty of the procedure. Nevertheless, to clarify the impact of OPCAB compared with CCAB in high-risk patients, further studies must focus on improving research methodology, recruiting high-risk patients, and collecting long-term data.

**Study Limitations**

There are several important limitations to this study. First, several biases may exist, affecting such matters as indication for revascularization strategy and the level of expertise at CABG for each institution and surgeon involved in the registry. Propensity score analysis may not adequately adjust for these biases. Second, trends in the incidence of myocardial infarction (eg, risk of myocardial infarction in the intermediate-risk tertile) were somewhat different from those in other outcomes. These trends would be adjusted and more strongly supported in a study with a larger sample size. Finally, manipulation and clamping of the aorta is a well-known risk factor for stroke, but we did not have data on whether this was performed in particular patients.

**Conclusions**

OPCAB as opposed to CCAB is associated with short-term and long-term benefits in terms of stroke prevention in higher-risk patients as estimated based on EuroSCORE. Survival outcomes, however, were not significantly different between CCAB and OPCAB, even in high-risk patients. Further studies are warranted.

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**Disclosures**

None.

**References**


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**SUPPLEMENTAL MATERIAL**

**Significant Change using Tukey-Kramer post hoc analysis**

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Supplementary Table 1: Pairwise comparisons evaluated using Tukey-Kramer post hoc analysis. Arrows indicate a significance level of 5% and the direction of change.