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Cardiac Surgery

Long-Term Survival Following Coronary Artery Bypass Grafting

Off-Pump Versus On-Pump Strategies

Joon Bum Kim, MD, PHD,* Sung-Cheol Yun, PHD,† Jae Wong Lim, MD,* Soo Kyung Hwang, MD,* Sung-Ho Jung, MD,* Hyun Song, MD, PHD,‡ Cheol Hyun Chung, MD, PHD,* Jae Won Lee, MD, PHD,* Suk Jung Choo, MD, PHD*

Seoul, South Korea

Objectives This study sought to compare long-term survival after off- and on-pump coronary artery bypass grafting (CABG).

Background Although several large-scale clinical trials have compared the surgical outcomes between off- and on-pump CABG, the long-term survival has not been compared between the 2 surgical strategies in a reasonably sized cohort.

Methods We evaluated long-term survival data in 5,203 patients (age 62.9 ± 9.1 years, 1,340 females) who underwent elective isolated CABG (off-pump: n = 2,333; on-pump: n = 2,870) from 1989 through 2012. Vital statuses were validated using the Korean National Registry of Vital Statistics. Long-term survival was compared with the use of propensity scores and inverse probability weighting to adjust selection bias.

Results Patients undergoing on-pump CABG had a higher number of distal anastomoses than those undergoing off-pump CABG (3.7 ± 1.2 vs. 3.0 ± 1.1; $p < 0.001$). Survival data were complete in 5,167 patients (99.3%), with a median follow-up duration of 6.4 years (interquartile range: 3.7 to 10.5 years; maximum 23.1 years). During follow-up, 1,181 patients (22.7%) died. After adjustment, both groups of patients showed a similar risk of death at 30 days (odds ratio: 0.70; 95% confidence interval [CI]: 0.35 to 1.40; $p = 0.31$) and up to 1 year (hazard ratio [HR]: 1.11; 95% CI: 0.74 to 1.65; $p = 0.62$). For overall mortality, however, patients undergoing off-pump CABG were at a significantly higher risk of death (HR: 1.43; 95% CI: 1.19 to 1.71; $p < 0.0001$) compared with those undergoing on-pump CABG. In subgroup analyses, on-pump CABG conferred survival benefits in most demographic, clinical, and anatomic subgroups compared with off-pump CABG.

Conclusions In patients undergoing elective isolated CABG, on-pump strategy conferred a long-term survival advantage compared with off-pump strategy. (J Am Coll Cardiol 2014;63:2280–8) © 2014 by the American College of Cardiology Foundation

After the revival of the off-pump technique for coronary artery bypass grafting (CABG) in the early 1990s, a number of observational studies had shown the potential benefits of off-pump CABG over on-pump surgery. These benefits included superior neurocognitive outcomes, preservation of renal function, and reduction in surgical bleeding and transfusion-related complications (1–5). The enthusiasm for off-pump technique consequently followed, especially in eastern Asian countries: more than 60% of CABG is being conducted with the off-pump technique in South Korea and in Japan (6,7).

Recently, large-scale, prospective randomized trials have been conducted that showed trends toward reduced risks of early surgical complications with off-pump CABG, but these early benefits failed to prove to be significant in longer-term follow-up (8–10). Moreover, off-pump CABG had shown worse outcomes in terms of graft patency and the requirement for coronary reintervention compared with conventional on-pump CABG up to 1 year after surgery (10,11). To date, results of randomized trials are limited to within 1 year of surgery; therefore, the long-term comparative data regarding clinical outcomes between the 2 strategies are currently unavailable. Considering that the benefits of CABG most likely appear throughout a long-term period, the 2 operative strategies for CABG need to be compared using long-term follow-up data in a reasonably sized cohort to allow adequate statistical power.

From the *Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; †Division of Biostatistics, Center for Medical Research and Information, University of Ulsan College of Medicine, Seoul, South Korea; and the ‡Department of Thoracic and Cardiovascular Surgery, Seoul Saint Mary's Hospital, College of Medicine, Catholic University of Korea, Seoul, South Korea. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Kim and Yun contributed equally to this work.

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In this study, we sought to compare long-term survival after off- and on-pump CABG under adequate statistical risk adjustments through a large institutional database linked with the National Population Registry of the Korea National Statistical Office.

Methods

Patients. All patients undergoing cardiac surgery are prospectively registered in our institution's database, which records baseline patient characteristics, detailed information on surgery, and perioperative outcomes (12). A total of 6,658 patients who underwent CABG between April 1989 and April 2012 were identified, and of them, we excluded patients who underwent concomitant valvular or aortic surgery (n = 1,123) and those who had emergent or urgent surgeries (n = 332), thus including patients who underwent isolated elective CABG only. Finally, 5,203 patients who met the enrollment criteria formed the study population; of these, 2,333 patients (44.8%) underwent off-pump CABG whereas 2,570 (55.2%) underwent on-pump CABG. Patients who were initially intended to undergo off-pump CABG but were converted to on-pump CABG intraoperatively (n = 46, 0.9% of all patients, 2% of off-pump patients) were regarded as having underwent off-pump CABG for the purposes of the intension-to-treat analyses.

The decision to perform off- or on-pump CABG was influenced by several demographic (diabetes, renal function) and clinical (coronary lesion category, cardiac functions) risk profiles and years of surgery, but was finally at the discretion of the attending surgeon; the authors of this study had different attitudes regarding the use of cardiopulmonary bypass (CPB) during CABG.

This study was approved by our institutional Ethics Committee/Review Board, and the board waived the requirement for informed patient consent due to the retrospective nature of the study.

Surgical procedures and medication. Most patients (96.6%) were operated on through a median sternotomy, whereas some of the patients receiving single- or double-vessel off-pump CABG (n = 177, 3.4%) were operated on through mini-thoracotomy approaches. Internal thoracic arteries (ITAs) were dissected in either a pedicled or skeletonized fashion according to the surgeon preferences. All saphenous grafts were harvested by the open technique. The pedicled radial artery was harvested with the use of a harmonic scalpel or electrocautery in an open fashion. To prevent arterial graft spasm after harvesting, a vasodilatory cocktail was applied topically and injected intraluminally. In cases of on-pump CABG, intermittent, antegrade blood cardioplegic infusion (22°C to 32°C) was the principal strategy for myocardial protection during aortic cross clamping. The left ITA was used to bypass the left anterior descending artery whenever possible. Choices of conduits and their configurations for other coronary territories were determined on the basis of conduit availability, number of distal targets, the target territory (right coronary vs. left circumflex territories), and the surgeon's preference.

Statin medications and aspirin were routinely prescribed to all of the patients starting from postoperative day 1 or 2 and were continued indefinitely, if not contraindicated, through the 6-month interval outpatient clinic visits. The dose of statin medication was adjusted for a target low-density lipoprotein level of <100 mg/dl.

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CI = confidence interval
CPB = cardiopulmonary bypass
HR = hazard ratio
IPTW = inverse-probability-of-treatment weighting
ITA = internal thoracic artery
LV = left ventricular

Study endpoints. The primary endpoint was defined as all-cause mortality, because it is the most robust and unbiased index, requiring no adjudication to avoid inaccurate or biased documentation and clinical assessments (13). For validation of complete follow-up data regarding mortality, information about vital status was obtained through November 30, 2012, from the National Population Registry of the Korea National Statistical Office through the use of a unique personal identification number.

Statistical analysis. Categorical variables, presented as frequencies and percentages, were compared using the chi-square or Fisher exact test. Continuous variables, expressed as mean ± SD or median with range, were compared using the Student unpaired *t* test or the Mann-Whitney *U* test, as appropriate. Survival curves were constructed using Kaplan-Meier estimates and compared with the log-rank test.

To reduce the effect of treatment selection bias and potential confounding, we adjusted for differences in baseline characteristics by weighted Cox proportional-hazards regression models with inverse-probability-of-treatment weighting (IPTW) (14,15). With that technique, weights for patients receiving off-pump CABG were the inverse of the propensity score, and weights for patients receiving on-pump CABG were the inverse of 1 − propensity score. The propensity score is the probability given baseline variables that any patient in either group would be selected for receiving off-pump CABG. The propensity scores were estimated without regard to outcomes by multiple logistic regression analysis. A full nonparsimonious model was developed that included variables shown in Table 1. Model discrimination was assessed with C-statistics (C = 0.869), and model calibration was assessed with Hosmer-Lemeshow statistics (p = 0.497). The results of IPTW were verified by those of propensity score matching. The propensity score–matched pairs were created by matching between off- and on-pump CABG subjects on the logit of the propensity score using calipers of width equal to 0.2 of the SD of the logit of the propensity score (16). After propensity score matching, we examined the similarity of off- and on-pump CABG subjects in the propensity score–matched sample by calculating SDs for each of the baseline variables listed in

Table 1 Baseline Characteristics of Patients

	Overall Cohort					Propensity Score–Matched		
	Off-Pump (n = 2,333)	On-Pump (n = 2,870)	p Value	SD of Mean	IPTW p Value	Off-Pump (n = 1,070)	On-Pump (n = 1,070)	SD of Mean
Age, yrs	63.1 ± 9.3	62.8 ± 9.0	0.25	3.2%	0.37	63.1 ± 8.9	63.1 ± 9.0	1.0%
Female	576 (24.7)	764 (26.6)	0.11	4.4%	0.41	256 (24.0)	274 (25.6)	3.9%
Diabetes mellitus	547 (23.4)	498 (17.4)	<0.001	15.2%	0.51	257 (24.0)	250 (23.4)	1.5%
Hypertension	646 (27.7)	492 (17.1)	<0.001	25.5%	0.58	262 (24.5)	253 (23.6)	2.0%
Atrial fibrillation	19 (0.8)	39 (1.4)	0.063	5.3%	0.87	14 (1.3)	9 (0.8)	4.5%
Coronary lesion category			<0.001		0.008			
Single-vessel disease	148 (6.3)	24 (0.8)		29.9%		19 (1.8)	21 (2)	1.4%
Double-vessel disease	428 (18.3)	598 (20.8)		6.3%		209 (19.5)	230 (21.5)	4.9%
Triple-vessel disease	1,757 (75.3)	2,248 (78.3)		7.2%		842 (78.7)	819 (76.5)	5.2%
Left main involvement	559 (24.0)	648 (22.6)	0.24	3.3%	0.71	250 (23.4)	259 (24.2)	2.0%
Echocardiographic parameters								
LV ejection fraction, %	57.1 ± 10.1	56.4 ± 11.0	0.030	6.0%	0.59	56.0 ± 11.6	56.7 ± 10.3	6.1%
LV systolic dimension, mm	33.1 ± 7.6	34.2 ± 7.8	<0.001	13.1%	0.88	33.9 ± 8.1	33.5 ± 7.8	5.3%
Systolic PAP, mm Hg	27.3 ± 6.0	27.1 ± 5.7	0.17	3.8%	0.55	27.5 ± 6.0	27.3 ± 6.0	3.5%
MR ≥ moderate	31 (1.3)	47 (1.6)	0.36	2.6%	0.50	15 (1.4)	25 (2.3)	6.9%
TR ≥ moderate	5 (0.2)	10 (0.4)	0.37	2.5%	>0.99	3 (0.3)	3 (0.3)	0.0%
eGFR, ml/min/1.73 m^2	74.2 ± 26.2	72.1 ± 21.2	0.002	8.7%	0.92	73.0 ± 22.0	73.0 ± 26.7	0.1%
Operator			<0.001		<0.001			
A	963 (41.3)	299 (10.4)		75.3%		322 (30.1)	299 (27.9)	4.7%
B	579 (24.8)	24 (0.8)		76.8%		20 (1.9)	24 (2.2)	2.6%
C	191 (8.2)	1171 (40.8)		82.0%		187 (17.5)	173 (16.2)	3.5%
D	461 (19.8)	712 (24.8)		12.2%		431 (40.3)	458 (42.8)	5.1%
E	107 (4.6)	659 (23.0)		55.3%		105 (9.8)	111 (10.4)	1.9%
F	32 (1.4)	5 (0.2)		13.7%		5 (0.5)	5 (0.5)	0.0%

Values are mean ± SD or n (%), unless otherwise specified.
eGFR = estimated glomerular filtration rate; IPTW = inverse-probability-treatment-weighting; LV = left ventricle; MR = mitral regurgitation; PAP = pulmonary artery pressure; TR = tricuspid regurgitation.

Table 1. All of the SDs for each of the baseline variables were <0.10 (10%).

The operative year was found to be a strong discriminator in the decision of CPB strategies for CABG. For further adjustment for the operative years, patients were divided into quintiles according to the operative years, then the treatment effect was estimated separately within each quintile using the propensity score matching, and finally, quintile estimates were combined to measure an overall estimate of the treatment effect (17).

For subgroup analyses, a new propensity score for off-pump CABG versus on-pump CABG was calculated in each subgroup, and the individual propensity score was incorporated into the Cox regression model as a covariate and type of CABG to calculate the propensity-adjusted hazard ratio (HR). All statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, North Carolina). A 2-tailed p value <0.05 was considered to be statistically significant.

Results

Baseline characteristics and coronary grafting profiles. The baseline demographic and clinical characteristics of the patients are shown in Table 1 (left columns). Patients who underwent off-pump CABG were more likely to have diabetes, hypertension, and single-vessel coronary disease than those who underwent on-pump CABG. Left ventricular (LV) ejection fraction was higher, LV systolic dimension was smaller, and renal function was superior in the off-pump than in the on-pump CABG group. In the selection of CABG strategy, there were significant influences of the surgeon factor and surgical years (Fig. 1). After adjustment of the baseline profiles with the use of IPTW, there were no significant inter-group differences in baseline covariates except for coronary lesion category and operator, whereas propensity score matching yielded a cohort that was well balanced for all baseline covariates (Table 1, right columns).

Regarding the coronary bypass grafting profiles, patients undergoing off-pump CABG had fewer distal anastomoses, but more frequently had the use of arterial conduits, including higher rates of total arterial grafting and bilateral ITA grafting, compared with those undergoing on-pump CABG (Table 2).

Unadjusted mortality. The 30-day mortality rates were 0.9% (n = 21) in the off-pump CABG group and 1.4% (n = 41) in the on-pump CABG group (p = 0.095). Follow-up data regarding mortality was complete in 99.3% of patients (n = 5,167), with a median follow-up duration of 6.4 years (interquartile range: 3.7 to 10.5 years; maximum 23.1 years). During this period, 1,181 patients (22.7%) died. The Kaplan-Meier curve did not show a significant difference in mortality up to 1 year (Fig. 2A); however, in the

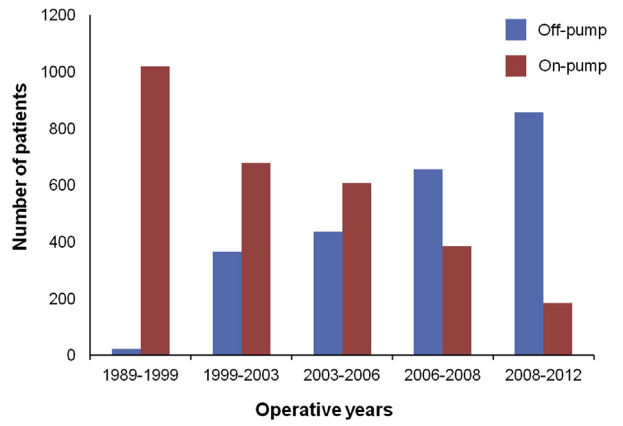

Figure 1 Trends in Cardiopulmonary Bypass Strategies for CABG

Trends in cardiopulmonary bypass strategies for coronary artery bypass grafting (CABG) during the study period at the Asan Medical Center, Seoul, Korea.

overall follow-up period, it showed a significant difference in favor of on-pump CABG over off-pump CABG (Fig. 2B).

Adjusted mortality. After adjustment with IPTW, there was no significant difference in the death rate at 30 days (odds ratio: 0.70; 95% CI: 0.35 to 1.40; p = 0.31) and up to 1 year (HR: 1.11; 95% CI: 0.74 to 1.65; p = 0.62). For overall mortality, off-pump CABG showed a higher risk of death (HR: 1.43; 95% CI: 1.19 to 1.71; p < 0.0001) compared with on-pump CABG. When the adjustment (IPTW) was further augmented by multivariable analyses (IPTW + multivariable analyses) including 2 baseline variables that were significantly different after IPTW (coronary lesion category and operator), off-pump CABG still showed a higher risk of death than on-pump CABG. Results from the propensity score–matched cohort were also similar for all of the outcomes of 30-day (p = 0.59), 1-year (p = 0.18), and overall mortality (p < 0.0001) as those of the IPTW (Table 3). Adjusted outcomes by various statistical methods are detailed in Table 3, showing consistent results in favor of on-pump CABG in long-term survival regardless of the statistical methods used.

Because the operative year had a strong determinant in the selection of operative strategy (Fig. 1), further adjustments for the operative years were performed through stratification methods. Consequently, the higher risk of death in patients undergoing off-pump CABG was still observed in the overall cohort and in propensity score–matched patients compared with those undergoing on-pump CABG (Table 4).

Subgroup analyses. Figure 3 reveals adjusted HRs for all-cause mortality in off-pump CABG compared with on-pump CABG in various demographic and clinical risk subgroups. The poorer survival for off-pump CABG was observed in most subgroups; the only exception was patients with single-vessel coronary disease.

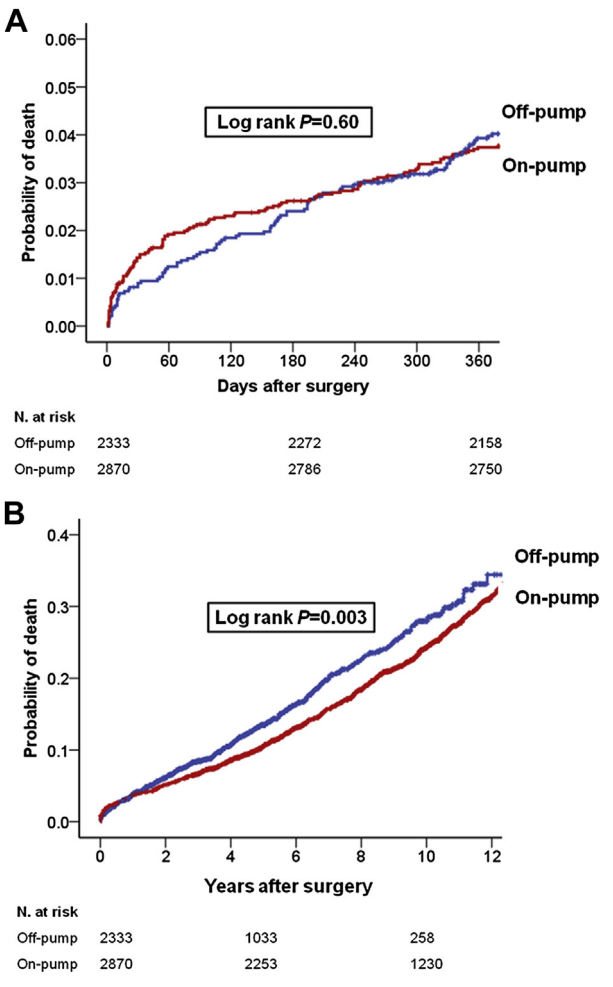

Figure 2 Unadjusted Kaplan-Meier Curves for Death

Up to 1 year, there is no significant difference between the on- and off-pump groups **(A)**; however, the difference becomes significant later in favor of on-pump surgery compared with off-pump surgery **(B)**.

Table 2 Coronary Grafting Profiles

	Off-Pump (n = 2,333)	On-Pump (n = 2,870)	p Value
Number of distal anastomoses	3.0 ± 1.1	3.7 ± 1.2	<0.001
1	245 (10.5)	47 (1.6)	
2	508 (21.8)	398 (13.9)	
3	820 (35.1)	896 (31.2)	
≥4	760 (32.6)	1,529 (53.3)	
Use of bilateral ITA	292 (12.5)	131 (4.6)	<0.001
No use of ITA	62 (2.7)	212 (7.4)	<0.001
Total arterial grafting in multivessel disease	869/2,113 (41.1)	630/2,669 (23.6)	<0.001
Use of radial artery	1,341 (57.5)	1,444 (50.3)	<0.001
Use of gastroepiploic artery	120 (5.1)	238 (8.3)	<0.001
Use of saphenous vein	1,283 (55.0)	2,212 (77.1)	<0.001

Values are mean ± SD, n (%), or n/N (%).
ITA = internal thoracic artery.

Table 3 Adjusted HRs for Death Following Off-Pump CABG Compared With On-Pump CABG

Outcomes	OR or HR	95% CI	p Value
30-day mortality			
Crude	0.63	0.37–1.06	0.084
IPTW	0.70	0.35–1.40	0.31
IPTW + multivariable*	0.67	0.41–1.09	0.11
Propensity score matching	0.82	0.41–1.67	0.59
1-yr mortality			
Crude	1.05	0.79–1.39	0.75
IPTW	1.11	0.74–1.65	0.62
IPTW + multivariable*	1.05	0.66–1.66	0.83
Propensity score matching	1.33	0.88–2.01	0.18
Overall death			
Crude	1.22	1.07–1.38	0.0035
IPTW	1.43	1.19–1.71	<0.0001
IPTW + multivariable*	1.47	1.30–1.67	<0.0001
Propensity score matching	1.48	1.23–1.79	<0.0001

Odds ratios (ORs) are listed for 30-day mortality, and hazard ratios (HRs) are listed for 1-year mortality and overall death. *Weighted Cox proportional hazards regression models incorporated coronary lesion category and operator.

CABG = coronary artery bypass grafting; CI = confidence interval; IPTW = inverse-probability-treatment-weighting.

When the analyses were further stratified according to grafting profiles and operator, the higher risk of death in the off-pump CABG group was consistently observed regardless of whether total arterial grafting was performed, bilateral ITA was used, or no ITA was used, although there was a significant interaction in the influence of CABG strategy on mortality according to the operators (Table 5).

Discussion

The results of the present study showed that, despite similar early mortality between off- and on-pump CABG, on-pump CABG conferred a superior survival benefit over off-pump CABG in the long term. These results are derived from a large set of data to compare the outcomes of the 2 strategies, and rigorous statistical adjustments were conducted considering the "surgeon factor" and the "year of operation" as well as other important covariates in the statistical models. It is a noteworthy fact that these results were obtained from one of the most enthusiastic centers to perform off-pump CABG in the world.

There has been a resurgence in off-pump CABG in the 1990s on the basis of the various purported advantages attributed to avoiding extracorporeal circulation during CABG. The most notable merits, as suggested by several observational studies, included avoiding embolic stroke induced by invasive aortic manipulation and reducing coagulopathy and renal dysfunction (4,5). The advent of all-arterial left ITA-composite bypass grafting and the implications for avoiding aortic manipulation has spurred the enthusiasm for off-pump CABG as a means of reaping the full benefits of both strategies. In North America, approximately 10% to 20% of all CABGs have been steadily performed by off-pump CABG (18). In Japan, however, over 60% of the cases were reported to be performed by off-pump CABG in the 2000s (6). Similarly, there has been a steep acceptance of off-pump CABG in the last decade in Korea beginning in 2000, when 24.5% of the cases used the off-pump technique, to 2008, when 66.2% of cases were off-pump CABG (7). Keeping pace with these trends, off-pump CABG has also been enthusiastically embraced in our institution, with an eventual reversal in the numbers of on-pump CABG by off-pump CABG. Of note, among patients who underwent CABG in our center from January 2011 through April 2012, 94.2% of patients (293 of 311) underwent off-pump CABG.

With increasing volumes of off-pump CABG, numerous studies have attempted to assess if off-pump CABG was actually superior to on-pump surgery. Takagi et al. (19) showed a survival benefit of on- over off-pump CABG through a meta-analysis of 18 randomized controlled trials assessing the mean 1-year follow-up results, in which there was a 35% greater late mortality associated with off-pump CABG over on-pump CABG (odds ratio: 1.35; 95% CI: 1.07 to 1.70; p = 0.01). The ROOBY (Veterans Affairs Randomized On/Off Bypass) trial, one of the largest published randomized controlled studies comparing the outcome of on- and off-pump CABG, also showed greater adverse composite outcomes of all-cause mortality, revascularization, and nonfatal myocardial infarction with

Table 4 HRs for Death Following Off-Pump CABG Compared With On-Pump CABG: Stratified Analysis Based on Operative Years in Quintiles

	All Cohort					Propensity Score Matching				
Death	On-Pump	Off-Pump	HR	95% CI	p Value	On-Pump	Off-Pump	HR	95% CI	p Value
q1 (1989–1999)	471/1,018	12/22	1.57	0.88–2.78	0.12	9/21	11/21	1.28	0.62–2.63	0.51
q2 (1999–2003)	162/678	104/364	1.26	0.98–1.61	0.069	30/138	43/138	1.67	1.07–2.61	0.024
q3 (2003–2006)	113/606	100/435	1.42	1.08–1.86	0.011	27/123	31/123	1.30	0.76–2.225	0.34
q4 (2006–2008)	49/385	99/655	1.22	0.87–1.72	0.25	21/173	33/173	1.77	1.01–3.11	0.046
q5 (2008–2012)	16/183	55/857	0.88	0.50–1.53	0.64	14/144	14/144	1.10	0.50–2.39	0.81
Summary*	811/2,870	370/2,333	1.29	1.11–1.50	0.0012	101/599	132/599	1.48	1.14–1.90	0.0028

Values are n/N unless otherwise indicated. *Likelihood ratio test for homogeneity; p = 0.57 for overall cohort, p = 0.80 for propensity score-matched cohort.

q = quintile; other abbreviations as in Table 3.

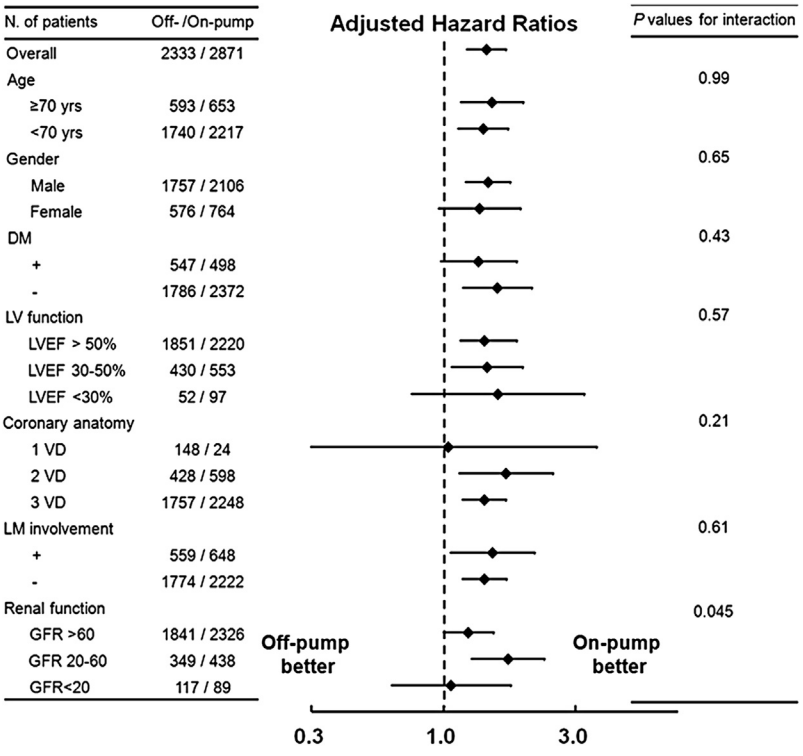

Figure 3 Hazard Ratios for Mortality in Off-Pump Surgery Compared With On-Pump Surgery

Adjusted hazard ratios for mortality in off-pump surgery compared with on-pump surgery according to various risk subgroups. DM = diabetes mellitus; GFR = glomerular filtration rate; LM = left main; LV = left ventricular; LVEF = left ventricular ejection fraction; VD = vessel disease.

off-pump CABG (10). However, neither the ROOBY trial nor the DOORS (Danish On-Pump versus Off-Pump Randomization Study), consisting of 900 patients, was sufficiently powered to support the between-group clinical differences with respect to death (10,20). Furthermore, because the largest-scale studies have been limited to 1-year outcome analysis, the long-term differences in adverse outcomes between the 2 strategies have not been evaluated appropriately (8–10).

Criticisms for the ROOBY trial in particular included a possible bias toward including relatively low-risk patients, an excessively high on-pump conversion rate (12.4%), and a

Table 5 Adjusted HRs for Death Following Off-Pump CABG Compared With On-Pump CABG: Stratified by Operators and Grafting Profiles

	Off-Pump	On-Pump	HR	95% CI	p Value	p Value for Interaction
Multivessel grafting						0.54
Use of venous grafts	172/1,072	582/2,039	1.64	1.31–2.05	<0.001	
Total arterial grafting	153/869	112/630	1.56	1.14–2.14	0.006	
Use of BITA in multivessel grafting						0.93
+	55/292	23/131	1.34	0.75–2.39	0.33	
−	270/1,821	671/2,538	1.42	1.21–1.65	<0.001	
Use of ITA						0.64
+	356/2,271	694/2,658	1.31	1.15–1.51	<0.001	
−	14/62	117/212	1.30	0.69–2.45	0.42	
Operator						0.003
A	168/963	98/299	1.14	0.86–1.50	0.36	
B	55/579	4/24	0.99	0.33–2.96	0.99	
C	53/191	417/1,171	1.63	1.20–2.22	0.002	
D	66/461	120/712	1.83	1.30–2.57	<0.001	
E	28/107	170/659	1.46	0.94–2.29	0.095	

Values are number of deaths divided by number of patients (n/N) unless otherwise indicated.
BITA = bilateral internal thoracic artery; ITA = internal thoracic artery; other abbreviations as in Table 3.

relatively small sample size (n = 2,203). To address these issues, a large international trial that enrolled 4,752 patients, CORONARY (CABG Off or On Pump Revascularization Study), was conducted (8,9). A strict criterion was applied to include only experienced surgeons (21). The adequacy of surgeon experience and expertise was determined according to the criteria outlined in the expertise-based, randomized controlled trial described previously. The 1-year results showed no significant differences between the 2 groups with regard to death, nonfatal stroke, nonfatal myocardial infarction, or renal failure. Therefore, unlike the ROOBY trial, the outcomes clearly did not support on-pump CABG as being superior to off-pump CABG and perpetuated the controversy regarding the question of which of the 2 strategies is superior.

In the present study, 5,203 elective coronary bypass surgery patients were divided into 2 groups on the basis of the cardiopulmonary support strategy. The patient population size was adequate to power the statistical analysis. Propensity scoring and IPTW were used to match the important differences in the baseline risk profiles that may otherwise have affected the outcomes. Due to the participation by multiple surgeons, rigorous statistical adjustments were made to eliminate the effects of the individual surgeon factor on the outcome. The participation of highly experienced and skilled surgeons is a notable strength of this study. The results showed no significant differences in the 30-day and 1-year mortality outcomes, although there was a slight tendency to favor the off-pump CABG group in this early period. The long-term survival rate beyond the first year, as illustrated in the Kaplan-Meier survival curves, however (Fig. 2B), was more favorable to patients receiving on-pump CABG, and suggested a sustained negative independent impact by off-pump CABG on the long-term outcome. This study is 1 of few large-scale clinical studies comparing the long-term outcomes of off- versus on-pump CABG, and the results were consistent with the recent Veterans Affairs study reported by Bakaeen et al. (22), which found no significant differences in the earlier survival outcome up to 3 years but a significant increase in the risk-adjusted mortality in the off-pump CABG group at 5 and 10 years. In light of the intuitive expectations that were generally held for off-pump CABG, the inferior outcomes by off-pump CABG in our and other studies were all the more remarkable and surprising.

Significantly more target vessel bypasses were performed in the on-pump group: 3.7 ± 1.2 versus 3.0 ± 1.1 in the off-pump CABG group ($p < 0.001$). A greater number of bypasses and subsequently a higher complete revascularization rate were also reported in the on-pump group in the ROOBY trial. Previous studies have reported that the completeness of revascularization was important in enhancing patient survival (23,24). We also attributed the superior long-term survival rate in the on-pump CABG group to the higher rate of complete revascularization. Although the significantly higher prevalence of single-vessel disease patients in the off-pump CABG group is arguably a factor that may lower the mean number of target vessel bypasses, the number was too small and, furthermore, it should have rather acted to enhance the survival outcomes in the off-pump CABG group.

Complete data regarding graft patency on the basis of angiographic or computed tomography imaging studies have not been available in this study, but major clinical trials including the ROOBY trial have shown superior long-term graft patency and quality of graft patency after on-pump CABG. Superior graft patency status and a higher Fitz-Gibbon A patency were observed throughout the spectrum of graft conduits used in the on-pump CABG patients. These findings were consistent with other similar trials showing superior graft patency with on-pump CABG (25–27). This may explain the higher repeat revascularization rate in the off-pump CABG group in the ROOBY and other large nonrandomized trials (11,28,29).

The adjusted HRs for all of the risk groups for mortality in the present study overwhelmingly favored on- over off-pump CABG (Fig. 3). These results clearly showed that any risks associated with CPB were limited to the early post-operative period. The significantly decreased long-term survival associated with off-pump CABG in the Veterans Affairs study was consistent with other large single-center observational studies (22,30,31). Based on the results of our trial and other large-scale clinical trials, the benefits of avoiding extracorporeal circulation with off-pump CABG do not seem to be long-lasting, and they are unable to offset the greater long-term risks of mortality associated with off-pump CABG. Therefore, it seems reasonable to suggest that the enthusiasm for off-pump CABG as the CABG strategy of choice should be reappraised.

Emergency cross-over from off- to on-pump CABG is known to increase the risks of early mortality and morbidity (32). If the 2 strategies were compared "as treated," there would have been critical errors in categorizing "on-pump conversion" patients to the "on-pump" group. The study results would have been misleading, as the early surgical results of the nonconverted off-pump CABG patients would have been more favorable than the subgroup of patients that had undergone pump conversion. This is why the comparison of the 2 CABG strategies in the present study was conducted as an "intention-to-treat" rather than "as treated" analysis. Our institutional database contained the critical information needed to determine the initial and actual CABG CPB strategy that was employed; 46 patients had converted to on-pump CABG intraoperatively from a failed initial off-pump attempt. These patients were correctly assigned to the off-pump group for the purposes of the present study. Consequently, the early mortality rate, which was 6.5% (3 of 46) in the patients who experienced such conversion, was significantly higher than in those who were able to complete the surgery as initially planned (mortality rate: 0.7% [17 of 2,286]; p = 0.006). Furthermore, long-term survival was also compromised in these on-pump

conversion patients, as evidenced by the 5-year survival rate of 70.7 ± 0.8%, which was significantly lower than the 86.8 ± 0.8% in those patients that had not undergone such conversion ($p = 0.001$).

Study limitations. This study is subject to the limitations inherent to a retrospective analysis of observational data. The decision to perform off- versus on-pump CABG was strongly affected by the surgeons' preferences and the years of the operation, as well as several other important baseline demographic and clinical profiles. Although we tried to rigorously adjust selection bias using multiple sophisticated statistical methods, such as propensity score-based analyses, unmeasured confounders, procedure bias, or detection bias may have affected our results.

All-cause mortality has been used as the primary outcome of interest in a number of studies on cardiovascular disease as it is regarded as the most robust and unbiased index. The present study also used this index to avoid potentially inaccurate or biased documentation and clinical assessments. The availability of survival data, which we obtained from the Korea National Statistical Office, was nearly 100% complete. However, obtaining detailed, complete clinical follow-up data regarding other outcomes, such as cardiac death, stroke, repeat revascularization, and myocardial infarction, in our large set of data was, for all practical purposes nearly impossible. Therefore, one of the major limitations of this study is that we did not evaluate such outcomes.

Conclusions

Off-pump CABG was associated with increased long-term mortality compared with on-pump CABG. This finding was consistent when the analyses were further stratified by grafting results, and the higher risk of death with off-pump CABG appeared in most risk subgroups. Further studies are needed to improve our understanding of the mechanism by which on-pump CABG confers enhanced long-term survival, as well as to identify the subsets of patients in which the benefits of this technique can be maximized.

Reprint requests and correspondence: Dr. Suk Jung Choo, Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Pungnap-dong Songpa-gu, Seoul 138-736, South Korea. E-mail: sjchoo@amc.seoul.kr.

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