

## ORIGINAL ARTICLE

# Five-Year Outcomes after On-Pump and Off-Pump Coronary-Artery Bypass

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## ABSTRACT

**BACKGROUND**

Coronary-artery bypass grafting (CABG) surgery may be performed either with cardiopulmonary bypass (on pump) or without cardiopulmonary bypass (off pump). We report the 5-year clinical outcomes in patients who had been included in the Veterans Affairs trial of on-pump versus off-pump CABG.

**METHODS**

From February 2002 through June 2007, we randomly assigned 2203 patients at 18 medical centers to undergo either on-pump or off-pump CABG, with 1-year assessments completed by May 2008. The two primary 5-year outcomes were death from any cause and a composite outcome of major adverse cardiovascular events, defined as death from any cause, repeat revascularization (CABG or percutaneous coronary intervention), or nonfatal myocardial infarction. Secondary 5-year outcomes included death from cardiac causes, repeat revascularization, and nonfatal myocardial infarction. Primary outcomes were assessed at a P value of 0.05 or less, and secondary outcomes at a P value of 0.01 or less.

**RESULTS**

The rate of death at 5 years was 15.2% in the off-pump group versus 11.9% in the on-pump group (relative risk, 1.28; 95% confidence interval [CI], 1.03 to 1.58;  $P=0.02$ ). The rate of major adverse cardiovascular events at 5 years was 31.0% in the off-pump group versus 27.1% in the on-pump group (relative risk, 1.14; 95% CI, 1.00 to 1.30;  $P=0.046$ ). For the 5-year secondary outcomes, no significant differences were observed: for nonfatal myocardial infarction, the rate was 12.1% in the off-pump group and 9.6% in the on-pump group ( $P=0.05$ ); for death from cardiac causes, the rate was 6.3% and 5.3%, respectively ( $P=0.29$ ); for repeat revascularization, the rate was 13.1% and 11.9%, respectively ( $P=0.39$ ); and for repeat CABG, the rate was 1.4% and 0.5%, respectively ( $P=0.02$ ).

**CONCLUSIONS**

In this randomized trial, off-pump CABG led to lower rates of 5-year survival and event-free survival than on-pump CABG. (Funded by the Department of Veterans Affairs Office of Research and Development Cooperative Studies Program and others; ROOBY-FS ClinicalTrials.gov number, NCT01924442.)

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**I**N THE 1990S, ENTHUSIASM REEMERGED for performing coronary-artery bypass grafting (CABG) surgery on a beating heart without the use of cardiopulmonary bypass (off pump).<sup>1-5</sup> Patients with poor cardiac function or complex coexisting conditions (e.g., lung disease or stroke) initially appeared to have better early clinical outcomes when off-pump CABG was performed than when on-pump CABG was performed.<sup>5,6</sup> However, data from randomized trials were limited.

In 2009, the results of the original Randomized On/Off Bypass (ROOBY) trial were reported, providing insight into the comparative effectiveness of these two surgical approaches.<sup>7</sup> The two primary outcomes of that trial included a short-term composite outcome consisting of 30-day or in-hospital mortality or morbidity and an interim composite outcome consisting of death from any cause within 1 year, nonfatal acute myocardial infarction between 30 days and 1 year, or repeat revascularization procedure (i.e., CABG or percutaneous coronary intervention [PCI]) between 30 days and 1 year. There were no significant treatment-related differences with regard to the short-term clinical outcomes, but patients in the off-pump group had a higher rate of the 1-year composite outcome than did those in the on-pump group (9.9% vs. 7.4%,  $P=0.04$ ).<sup>7</sup> No clinically relevant differences were found between treatment groups with regard to changes from baseline to 1 year of follow-up in neurocognitive status or health-related quality of life.<sup>8,9</sup> No advantage of off-pump surgery was found for any high-risk subgroup of patients (e.g., patients with chronic obstructive pulmonary disease or diabetes).<sup>10,11</sup> On the basis of the number of grafts completed being less than planned, incomplete revascularization was more frequent with off-pump surgery than with on-pump surgery (17.8% vs. 11.1%,  $P<0.001$ ). In addition, angiography at 1 year of follow-up revealed a lower rate of graft patency in the off-pump group than in the on-pump group (of the total grafts placed, 82.6% vs. 87.8% of the grafts were patent;  $P<0.001$ ).<sup>12</sup>

Recently, the international CABG Off or On Pump Revascularization Study (CORONARY) showed no significant treatment-related differences between off-pump and on-pump CABG with regard to any 5-year outcomes.<sup>13</sup> As the United States–based counterpart of that trial, the ROOBY Follow-up Study (ROOBY-FS) of the Department of Veterans Affairs (VA) Cooperative

Studies Program (CSP) compared 5-year outcomes between off-pump CABG and on-pump CABG. The primary outcomes after CABG in our follow-up study were death and a composite outcome consisting of major adverse cardiovascular events (MACE), defined as death, repeat revascularization (CABG or PCI), or nonfatal myocardial infarction. Secondary outcomes after CABG in the follow-up study included death from cardiac causes, repeat revascularization, nonfatal myocardial infarction, and a secondary composite outcome consisting of death from cardiac causes, repeat revascularization, or nonfatal myocardial infarction.

## METHODS

### STUDY DESIGN

The design and results of the original ROOBY trial have been published previously.<sup>7,14</sup> The original trial was a randomized, controlled, single-blind trial that enrolled veterans and was conducted at 18 VA medical centers from February 2002 through June 2007, with 1-year assessments completed by May 2008. In January 2013, the members of the ROOBY-FS executive committee and planning committee designed this 5-year follow-up study. The follow-up study was scientifically reviewed and approved by the VA Clinical Merit Review Board with separate funding from the VA CSP, and the primary aim of ROOBY-FS was to examine 5-year clinical outcomes in the patients who had undergone randomization in the original trial (see the protocol, available with the full text of this article at NEJM.org). Approvals (including waivers of informed consent and Health Insurance Portability and Accountability Act [HIPAA] authorizations) were obtained from the institutional review boards associated with the Denver VA Medical Center, Stanford University, and the Northport VA Medical Center. Clinical data were extracted from VA medical records by national nurse reviewers. The Health Economics Resource Center coordinated VA and non-VA database matches and merges. The end-points committee adjudicated all 5-year outcomes, and differences between medical-chart review and database extracts were reconciled appropriately.

### STUDY OUTCOMES

Five-year mortality was initially assessed by matching the participants in the follow-up study

to data in the VA Vital Status File and the National Death Index, which provided cause-of-death codes according to the *International Classification of Diseases, 10th Revision*. Nonfatal myocardial infarctions and repeat revascularization procedures were identified by means of chart review and database merges with the VA National Patient Care Database, VA Patient Treatment File, VA-purchased care files, and Medicare Part A and Part B records.

Of the 2203 patients included in the follow-up study, only 11 had no verified VA or non-VA encounters within the 180 days before the 5-year follow-up. In the records for these 11 patients, no significant treatment-related difference was found ( $P=0.55$ ). Assuming that no adverse events had occurred in these 11 patients at 5 years, we included all 2203 records in this report.

The two primary outcomes, monitored from the date of surgery up to 5 years after CABG, were death from any cause and MACE (a composite outcome of death from any cause, repeat revascularization [CABG or PCI], or nonfatal myocardial infarction). For these two outcomes, the time to event was also compared between off-pump and on-pump treatments. Secondary outcomes included the 5-year rates of death from cardiac causes, repeat revascularization, and nonfatal myocardial infarction. An additional secondary 5-year composite outcome of death from cardiac causes (rather than death from any cause), repeat revascularization, or myocardial infarction was also assessed.

An independent end-points committee — consisting of cardiologists, cardiac surgeons, and the national nurse coordinator, all of whom were unaware of the treatment assignments — reviewed all the trial outcomes (see the protocol for the procedures and definitions used by the end-points committee). The end-points committee initially assigned the cause of death to cardiac, noncardiac, or unknown categories on the basis of data from the medical chart. After this initial classification, the end-points committee-assigned cause of death was subsequently compared with the cause-of-death coding in the National Death Index, and a final classification for the cause of death in each record was determined. In cases in which insufficient data were available for the end-points committee to assign a cause of death (26% of cases), the National Death Index coding (based on the death certificate) was used. With 99.5% of the 5-year follow-

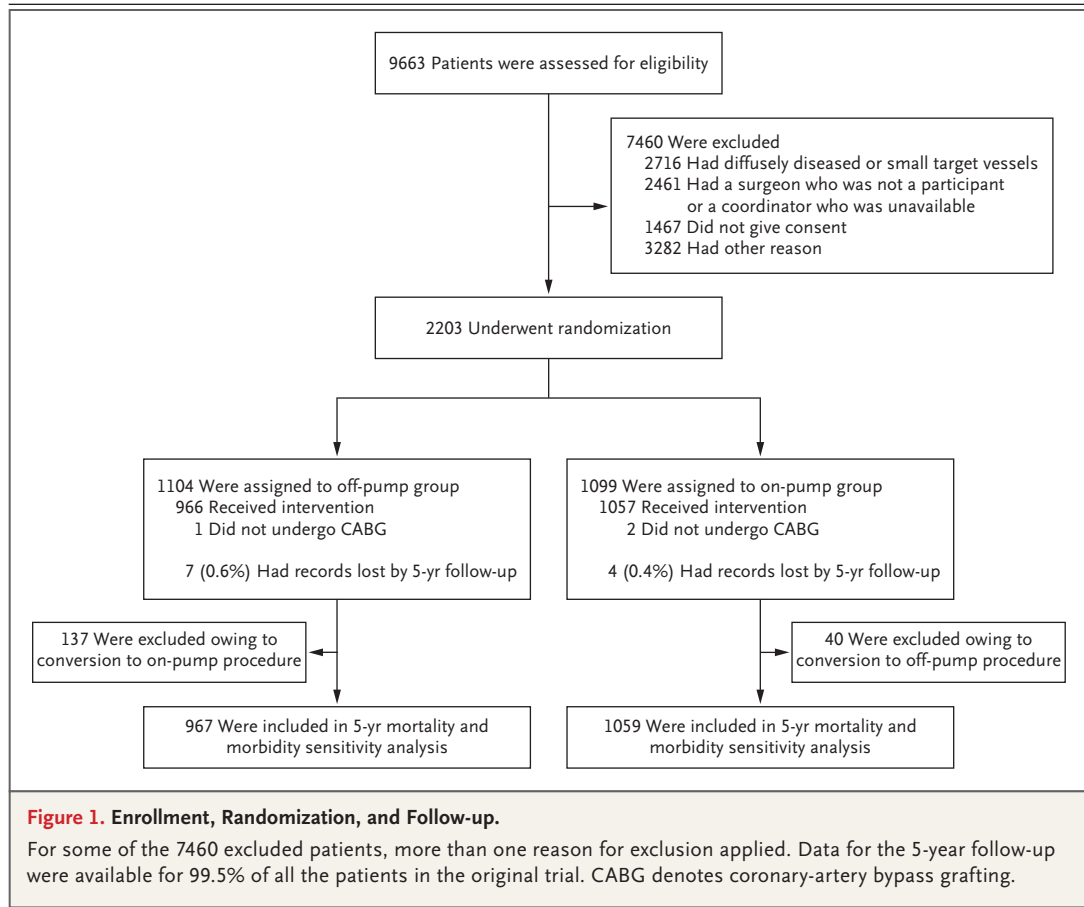
ups coordinated in the study, the end-points committee reconciled all discrepancies that were identified between medical-chart review and database-extract findings.

#### STATISTICAL ANALYSIS

The original trial reported 1-year findings in 2203 participants (1104 patients in the off-pump group and 1099 in the on-pump group). With death at 5 years as one of the two primary outcomes in the follow-up study, it was expected that the on-pump group would have 10% mortality. In order to detect an absolute difference of 5 percentage points at the 5-year follow-up (i.e., 10% vs. 15%), a power of greater than 90% with the significance level set to a  $P$  value of 0.05 or less was verified to be feasible. Assuming a 5-year mortality of 10% in the on-pump group, we estimated that the follow-up study would have at least 80% power to find an absolute difference between the groups of 4 percentage points (10% vs. 14%) in mortality. For the primary composite MACE outcome at 5 years, it was estimated that the rate in the on-pump group would be 20%. Therefore, we estimated that the follow-up study would have at least 80% power to detect an absolute difference of 5 percentage points in the rate of the primary composite outcome at 5 years.

Since the characteristics of the patients at baseline were balanced in the two treatment groups in the original trial, the follow-up study used bivariate statistical comparisons for the testing of the primary and secondary hypotheses. Chi-square tests or Fisher's exact tests were used to compare treatments for categorical outcomes. Continuous variables were compared with the use of Student's  $t$ -tests or Wilcoxon rank-sum analyses. For the time-to-event analyses, log-rank tests and Kaplan–Meier curves were used.

The ROOBY-FS protocol prespecified that the two primary hypotheses (death and the MACE composite) would be tested independently for significance at a  $P$  value of 0.05 or less; the secondary hypotheses would be tested at a  $P$  value of 0.01 or less to determine statistical significance. Above these two thresholds, slightly higher  $P$  values (i.e., up to  $P\leq 0.15$ ) were evaluated to potentially guide future research.<sup>15</sup> Because our previous article had shown that the rate of survival at 1 year was lower among patients who had their procedures converted (either off-to-on-pump conversion or on-to-off-pump conver-



sion) than among those who did not have their procedure converted, a sensitivity analysis was performed that excluded all the patients with conversion to ensure that the conclusions of the follow-up study were robust.<sup>16</sup> Finally, the performance of the primary surgeon was compared (resident vs. attending surgeon), after the exclusion of two medical centers that did not have participating graduate medical education trainees, to evaluate for an effect of the surgeon's experience.<sup>17,18</sup>

## RESULTS

### RISK CHARACTERISTICS OF PATIENTS AT BASELINE

With 5-year follow-up data available for more than 99% of the patients, 2203 patients (1104 patients in the off-pump group and 1099 in the on-pump group) in the follow-up study were monitored after having undergone randomization (Fig. 1). The demographic characteristics and the risk characteristics at baseline did not

differ significantly between the off-pump group and the on-pump group (Table 1). In brief, the patients were predominantly men (99.4%), and the mean age of the patients was 62.7 years. The majority of patients had two-vessel or three-vessel disease (94.1%), hypertension (86.2%), and normal or mildly depressed left ventricular ejection fraction (among patients with available data, 82.3% had a left ventricular ejection fraction  $\geq 45\%$ ). The patients were representative of the populations of male veterans who underwent CABG with coronary disease of mild-to-moderate severity and multiple coexisting conditions.<sup>7</sup> The original operative details of the trial, according to treatment group, are described in Table S1 in the Supplementary Appendix, available at NEJM.org.

### STUDY OUTCOMES

There were a total of 299 deaths (13.6% of the patients) at 5 years of follow-up, including 128 patients (5.8%) who had a cardiac-related death.

**Table 1. Characteristics of the Patients.\***

Characteristic	Off-Pump Group (N=1104)	On-Pump Group (N=1099)
Age		
Mean — yr	63.0±8.5	62.5±8.5
Distribution — no. (%)		
<55 yr	163 (14.8)	185 (16.8)
≥55 to <65 yr	509 (46.1)	514 (46.8)
≥65 to <75 yr	304 (27.5)	289 (26.3)
≥75 yr	128 (11.6)	111 (10.1)
Male sex — no./total no. (%)	1097/1104 (99.4)	1092/1098 (99.5)
Race or ethnic group — no./total no. (%)†		
Black	77/1104 (7.0)	93/1098 (8.5)
Hispanic	71/1104 (6.4)	52/1098 (4.7)
White	931/1104 (84.3)	926/1098 (84.3)
Other	25/1104 (2.3)	27/1098 (2.5)
Marital status — no./total no. (%)		
Married	628/1102 (57.0)	642/1096 (58.6)
Divorced or separated	328/1102 (29.8)	308/1096 (28.1)
Other	146/1102 (13.2)	146/1096 (13.3)
Urgent status — no. (%)	179 (16.2)	156 (14.2)
Chronic obstructive pulmonary disease — no. (%)	220 (19.9)	238 (21.7)
Creatinine level >1.5 mg/dl — no. (%)‡	94 (8.5)	79 (7.2)
Stroke — no. (%)	82 (7.4)	88 (8.0)
Peripheral vascular disease — no. (%)	179 (16.2)	163 (14.8)
Diabetes — no. (%)	470 (42.6)	491 (44.7)
Hypertension — no. (%)	948 (85.9)	952 (86.6)
Left ventricular ejection fraction — no./total no. (%)		
<35%	61/1065 (5.7)	61/1062 (5.7)
35 to 44%	122/1065 (11.5)	132/1062 (12.4)
45 to 54%	249/1065 (23.4)	253/1062 (23.8)
>54%	633/1065 (59.4)	616/1062 (58.0)
History of depression — no./total no. (%)	146/792 (18.4)	120/785 (15.3)
Estimated risk of death within 30 days after the procedure — %§	1.9±1.8	1.8±1.8

\* Plus–minus values are means ±SD. There were no significant differences between the two groups at baseline.

† Race or ethnic group was reported by the research nurse on the basis of the medical records or information from the patient or family.

‡ To convert the values for creatinine to micromoles per liter, multiply by 88.4.

§ The estimated risk of death within 30 days after the procedure was the calculated risk according to the Department of Veterans Affairs Surgical Quality Improvement Program.<sup>19</sup>

A total of 239 patients (10.8%) had a nonfatal myocardial infarction, and 276 (12.5%) had a repeat revascularization procedure (21 patients had a repeat CABG and 258 had a PCI procedure after CABG) (Table 2).

#### PRIMARY OUTCOMES

The 5-year rate of death of 15.2% in the off-pump group was significantly higher than the rate of 11.9% in the on-pump group ( $P=0.02$ ) (Table 2). The rate of the primary composite



**Table 2. Five-Year Follow-up Assessments, According to Treatment Group, in All the Patients in the Follow-up Study.\***

Outcome	Off-Pump Group (N=1104)	On-Pump Group (N=1099)	Absolute Difference (95% CI)	Relative Risk (95% CI)	P Value
	number (percent)		percentage points		
<b>Primary outcomes at 5 yr</b>					
Death	168 (15.2)	131 (11.9)	3.3 (0.4 to 6.2)	1.28 (1.03 to 1.58)	0.02
Composite MACE outcome with death	342 (31.0)	298 (27.1)	3.9 (0.1 to 7.6)	1.14 (1.00 to 1.30)	0.046
<b>Secondary outcomes at 5 yr</b>					
Death from cardiac causes	70 (6.3)	58 (5.3)	1.1 (-0.9 to 3.0)	1.20 (0.86 to 1.68)	0.29
Acute myocardial infarction	134 (12.1)	105 (9.6)	2.6 (0.0 to 5.2)	1.27 (1.00 to 1.62)	0.05
Repeat revascularization procedure	145 (13.1)	131 (11.9)	1.2 (-1.6 to 4.0)	1.10 (0.88 to 1.37)	0.39
Percutaneous coronary intervention	131 (11.9)	127 (11.6)	0.3 (-2.4 to 3.0)	1.03 (0.82 to 1.29)	0.82
Repeat CABG	16 (1.4)	5 (0.5)	1.0 (0.2 to 1.8)	3.19 (1.17 to 8.67)	0.02
Composite MACE outcome with death from cardiac causes	270 (24.5)	234 (21.3)	3.2 (-0.3 to 6.7)	1.15 (0.98 to 1.34)	0.08

\* The primary 5-year composite outcome of major adverse cardiovascular events (MACE) was death from any cause, acute myocardial infarction, or any repeat revascularization procedure. The secondary 5-year composite MACE outcome was death from cardiac causes, acute myocardial infarction, or any repeat revascularization procedure. Values for absolute differences may not sum as expected because of rounding. The P values are equivalent for both the absolute percentage differences and the relative risks reported. To evaluate for statistical significance, a P value of 0.05 or less was used for the two primary outcomes, and a P value of 0.01 or less was used for the secondary outcomes. CABG denotes coronary-artery bypass grafting, and CI confidence interval.

MACE outcome at 5 years differed significantly between the off-pump group and the on-pump group (31.0% vs. 27.1%,  $P=0.046$ ). The Kaplan-Meier curves separated before 1 year after CABG with regard to both death and the composite MACE outcome, with continued separation over the 5-year follow-up ( $P=0.02$  for the 5-year outcome of death and  $P=0.03$  for the 5-year outcome of MACE) (Fig. 2).

#### SECONDARY OUTCOMES

None of the secondary outcomes in the follow-up study met the prespecified threshold of a P value of 0.01 or less for statistical significance. The 5-year rate of death from cardiac causes did not differ significantly between the off-pump group and the on-pump group (6.3% and 5.3%, respectively;  $P=0.29$ ). The 5-year rate of nonfatal myocardial infarction was 12.1% in the off-pump group and 9.6% in the on-pump group ( $P=0.05$ ). There was no significant difference between the off-pump group and the on-pump group in the overall rate of repeat revascularization at 5 years (13.1% and 11.9%, respectively;  $P=0.39$ ) or in the rate of PCI (11.9% and 11.6%, respectively;  $P=0.82$ ). Repeat CABG occurred in 1.4% of the

patients in the off-pump group and in 0.5% in the on-pump group ( $P=0.02$ ) (Table 2).

#### SENSITIVITY ANALYSES

Since the primary analysis was based on the intention-to-treat principle, a sensitivity analysis was performed that excluded patients who had conversion to the other treatment.<sup>16</sup> Among patients who did not have conversion to the other treatment (967 patients in the off-pump group and 1059 in the on-pump group), the rate of death at 5 years was 13.5% in the off-pump group and 11.0% in the on-pump group ( $P=0.09$ ). Among patients who did not have conversion to the other treatment, the rate of the primary composite MACE outcome was 29.1% in the off-pump group and 26.5% in the on-pump group ( $P=0.21$ ) (Table 3).

Attending surgeons had somewhat higher 5-year rates of patients with repeat revascularization in the off-pump group than did residents ( $P=0.07$ ), most likely because attending surgeons selected the most difficult surgical procedures.<sup>17,18</sup> Landmark analyses were performed that compared treatments during the follow-up period between 1 year and 5 years (Tables S2 and

S4 in the Supplementary Appendix). Within this limited period, no primary or secondary outcomes had a significant treatment-related difference identified (see the Supplementary Appendix).

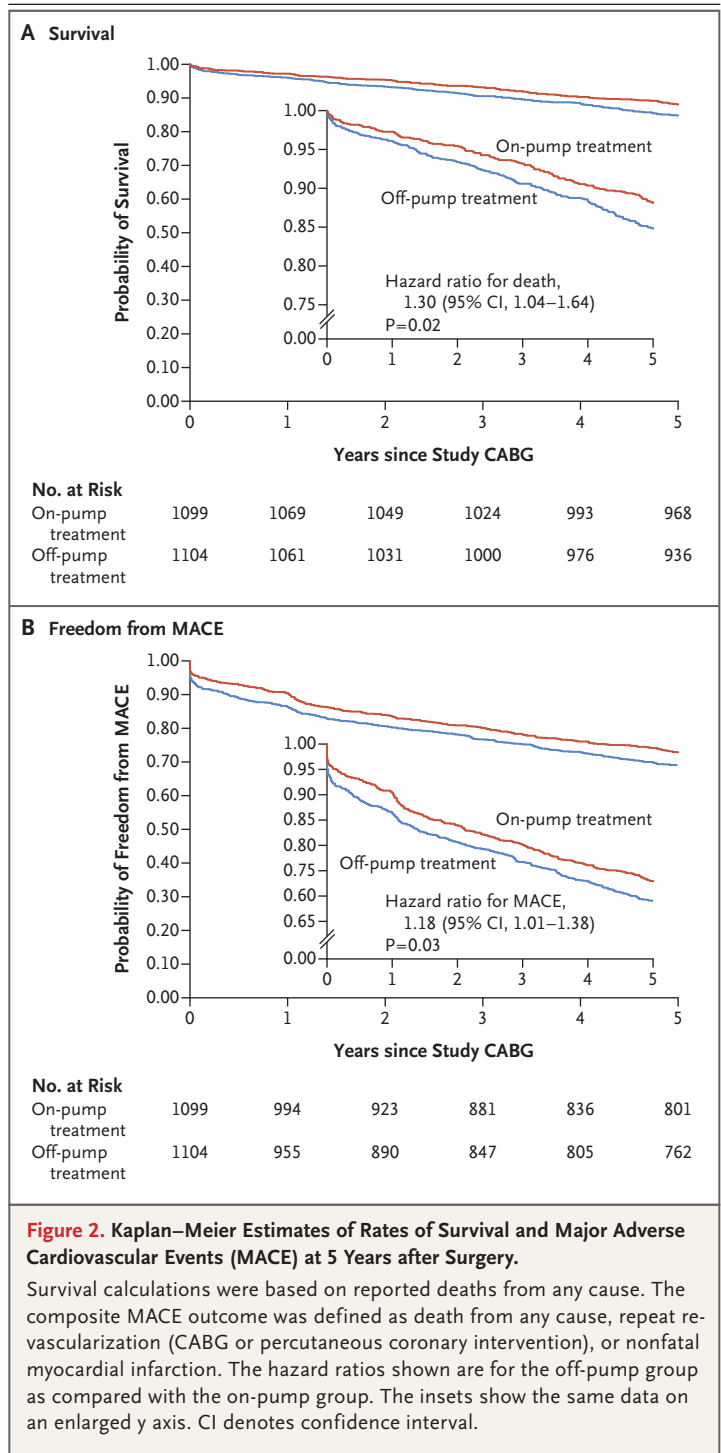
DISCUSSION

This study was a United States–based, large-scale, multicenter trial comparing 5-year clinical outcomes in patients who had been randomly assigned to undergo off-pump or on-pump surgery. At 5 years, on-pump CABG was superior to off-pump CABG with regard to death from any cause and the primary composite MACE outcome. Across all 5-year clinical outcomes that were evaluated, the off-pump approach did not confer any advantage over on-pump CABG procedures.

The patients in our trial tended to have slightly higher rates of hypertension, peripheral vascular disease, and atrial fibrillation than did the patients in the CORONARY trial; the patients in our trial also had lower rates of urgent status, diabetes, and female sex. However, the rates of death at 5 years in our trial and in the CORONARY trial were similar (13.6% and 14.1%, respectively).<sup>13</sup>

Although the difference was not significant, the original ROOBY trial showed higher 1-year mortality with off-pump procedures than with on-pump procedures.<sup>7</sup> For the 5-year ROOBY-FS cumulative follow-up period, a significant 28% higher risk of death from any cause was observed after off-pump surgery than after on-pump surgery (15.2% vs. 11.9%,  $P=0.02$ ). Between 1 year and 5 years, the survival curves in the ROOBY-FS study continued to separate; the landmark analysis showed that the rate of death was 11.8% in the off-pump group and 9.4% in the on-pump group ( $P=0.08$ ).

Historically, questions have been raised regarding the participating surgeons' off-pump experience in the ROOBY trial. The prestudy off-pump case experience of the surgeons involved in this trial averaged 120 cases (median, 50 cases). In comparison, in CORONARY, the surgeons performing off-pump procedures were required to have more than 2 years of experience and to have completed more than 100 procedures. In the German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE) trial, the median experience was 322 off-pump surgeries. Despite



**Figure 2. Kaplan–Meier Estimates of Rates of Survival and Major Adverse Cardiovascular Events (MACE) at 5 Years after Surgery.**

Survival calculations were based on reported deaths from any cause. The composite MACE outcome was defined as death from any cause, repeat revascularization (CABG or percutaneous coronary intervention), or nonfatal myocardial infarction. The hazard ratios shown are for the off-pump group as compared with the on-pump group. The insets show the same data on an enlarged y axis. CI denotes confidence interval.

the selection of surgeons who were highly experienced with regard to off-pump procedures, the CORONARY and GOPCABE trials showed no benefit of an off-pump approach with respect to

**Table 3. Sensitivity Analysis of 5-Year Follow-up Assessments, According to Treatment Group, among Patients Who Did Not Have Conversion to Other Treatment.\***

Outcome	Off-Pump Group (N = 967)	On-Pump Group (N = 1059)	Absolute Difference (95% CI)	Relative Risk (95% CI)	P Value
	number (percent)		percentage points		
<b>Primary outcomes at 5 yr</b>					
Death	131 (13.5)	117 (11.0)	2.5 (-0.4 to 5.4)	1.23 (0.97 to 1.55)	0.09
Composite MACE outcome with death	281 (29.1)	281 (26.5)	2.5 (-1.4 to 6.4)	1.09 (0.95 to 1.26)	0.21
<b>Secondary outcomes at 5 yr</b>					
Death from cardiac causes	55 (5.7)	51 (4.8)	0.9 (-1.1 to 2.8)	1.18 (0.82 to 1.71)	0.38
Acute myocardial infarction	108 (11.2)	99 (9.3)	1.8 (-0.8 to 4.5)	1.19 (0.92 to 1.55)	0.18
Repeat revascularization procedure	130 (13.4)	127 (12.0)	1.4 (-1.5 to 4.4)	1.12 (0.89 to 1.41)	0.33
Percutaneous coronary intervention	117 (12.1)	123 (11.6)	0.5 (-2.3 to 3.3)	1.04 (0.82 to 1.32)	0.74
Repeat CABG	15 (1.6)	5 (0.5)	1.1 (0.2 to 2.0)	3.29 (1.20 to 9.01)	0.014

\* The primary 5-year composite MACE outcome was death from any cause, acute myocardial infarction, or any revascularization procedure. The P values are equivalent for both the absolute percentage differences and the relative risks reported. To evaluate for statistical significance, a P value of 0.05 or less was used for the two primary outcomes, and a P value of 0.01 or less was used for the secondary outcomes.

any of their primary 30-day or 1-year outcomes, with CORONARY showing no benefit up to 5 years.<sup>13,20-22</sup>

To date, other single-center or small, prospective, randomized studies have shown no long-term mortality advantages to off-pump treatment.<sup>23-25</sup> Among the earliest randomized, controlled trials were the Beating Heart against Cardioplegic Arrest Studies (BHACAS 1 and 2), which were two studies from a single center that were combined into one report involving 401 patients who underwent randomization.<sup>24</sup> At 6 to 8 years of follow-up, there was no significant difference between off-pump surgery and on-pump surgery with regard to the rates of death from any cause or death from cardiac causes.<sup>24</sup> Similarly, the MASS III single-center trial did not show any significant differences between off-pump treatment and on-pump treatment with regard to the primary composite 5-year outcome of death, myocardial infarction, stroke, or repeat revascularization.<sup>25</sup> The trial was limited by a small sample of 308 patients; the rates of death of 8.4% in the off-pump group and 5.2% in the on-pump group did not differ significantly, and the rate of acute myocardial infarction was 6.5% in the off-pump group versus 1.9% in the on-pump group (P=0.05).<sup>25</sup> The OCTOPUS trial, a randomized, multicenter trial involving 281 low-risk patients,

also showed no significant difference in the rate of death from any cause at 5 years (7.0% in the off-pump group and 4.3% in the on-pump group, P=0.44).<sup>26</sup>

In a randomized trial involving 341 high-risk patients who underwent CABG and had three-vessel coronary disease and a European System for Cardiac Operative Risk Evaluation (EuroSCORE) grade of 5% or more (scores are calculated by means of a logistic-regression equation and range from 0 to 100%, with higher scores indicating greater risk), the rate of death during the median 3.7 years of follow-up was 24% with off-pump CABG, which was significantly higher than the rate of 15% with on-pump CABG (P=0.04).<sup>27</sup> As in our study, this trial showed no between-group difference in the rate of death from cardiac causes.<sup>27</sup> Even single-site reports from very experienced centers have shown no advantage of off-pump treatment with regard to outcomes such as death, reintervention, or myocardial ischemia at 3 to 8 years of follow-up.<sup>28,29</sup>

Over time, the use of off-pump procedures has decreased in the United States. The rate of off-pump CABG procedures declined from 23% in 2002 to 17% in 2012.<sup>30</sup> In a recent Society of Thoracic Surgeons annual report, the 2016 rate of off-pump CABG was 13.1% in the United States and Canada.<sup>31</sup> Reasons for this decline are



unclear, but multiple studies have shown that off-pump CABG results in less complete revascularization and worse graft patency than the on-pump approach.<sup>32-34</sup> Less complete revascularization is known to decrease long-term survival, and this may be a mechanism for the shorter survival that has been observed among patients who have undergone an off-pump procedure.<sup>35</sup>

In combination with findings from other randomized trials and a 2012 Cochrane systematic review,<sup>32</sup> the 5-year outcomes in our study support the conclusion that off-pump CABG does not offer any substantial advantages over on-pump CABG except possibly in unusual situations such as, for example, in patients with an extensively calcified (porcelain) aorta, in whom the off-pump technique may result in less manipulation of the aorta, potentially decreasing the risk of aortic emboli or stroke. In light of the low rates of use of off-pump CABG in the United States, the findings in our trial may provide more of a real-world experience than those in the CORONARY and GOPCABE trials, which required surgeons with a very high volume of experience with off-pump procedures, as compared with the ROOBY trial and with most other surgeons who are based in the United States.

The patients in our follow-up study were predominantly male veterans (99.5%) who had multiple coexisting conditions, so the findings may not be applicable to female patients or to patients who are not veterans.<sup>7</sup> Given the combination of chart review with national database analyses, the follow-up assessments in this trial approached 100% completeness. In spite of this very low rate of loss to follow-up, there may have been missed events of nonfatal myocardial infarction in the younger cohort of veterans (i.e., those not yet eligible for Medicare) receiving care at non-VA centers.

Although the CORONARY and GOPCABE trials required more stringent off-pump experience of their participating surgeons, the primary-outcome rates in the ROOBY trial were lower than the

corresponding primary-outcome rates reported in either of these two international trials. The rates of adverse outcomes (i.e., death and MACE) and treatment conversions in our trial lie within the prevailing surgical standards.<sup>20-22,28-30,32</sup>

The significant difference in the rate of death between treatments was not correspondingly reflected in the comparison of death from cardiac causes. In this study, the end-points committee had to rely exclusively on death-certificate information from the National Death Index to assign the cause of death in 26% of the records. Because death from cardiac causes is always challenging to adjudicate, the reliability of assessing cardiac-related causes of death has been much debated. Thus, total death (from any cause) was the primary death-related outcome that was evaluated in the follow-up study.

In conclusion, in this follow-up study, we investigated the 5-year mortality and major morbidity outcomes of a large, United States–based, multicenter, randomized trial that compared off-pump CABG with on-pump CABG. Given the results, it appears that innovative surgical approaches — such as the more technically demanding off-pump procedure — may not always provide superior clinical outcomes. Additional long-term follow-up, evaluating these same outcomes rigorously at 10 years after CABG, appears to be warranted. Future research may identify the risk factors of the patients and the cardiac surgical processes of care that affect longer-term outcomes of coronary revascularization procedures, with the goal of increasing the rate of long-term event-free survival.

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