ORIGINAL ARTICLE

# Off-Pump versus On-Pump Coronary-Artery Bypass Grafting in Elderly Patients

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## ABSTRACT

### BACKGROUND

The benefits of coronary-artery bypass grafting (CABG) without cardiopulmonary bypass in the elderly are still undetermined.

### METHODS

We randomly assigned patients 75 years of age or older who were scheduled for elective first-time CABG to undergo the procedure either without cardiopulmonary bypass (off-pump CABG) or with it (on-pump CABG). The primary end point was a composite of death, stroke, myocardial infarction, repeat revascularization, or new renal-replacement therapy at 30 days and at 12 months after surgery.

### RESULTS

A total of 2539 patients underwent randomization. At 30 days after surgery, there was no significant difference between patients who underwent off-pump surgery and those who underwent on-pump surgery in terms of the composite outcome (7.8% vs. 8.2%; odds ratio, 0.95; 95% confidence interval [CI], 0.71 to 1.28; P=0.74) or four of the components (death, stroke, myocardial infarction, or new renal-replacement therapy). Repeat revascularization occurred more frequently after off-pump CABG than after on-pump CABG (1.3% vs. 0.4%; odds ratio, 2.42; 95% CI, 1.03 to 5.72; P=0.04). At 12 months, there was no significant between-group difference in the composite end point (13.1% vs. 14.0%; hazard ratio, 0.93; 95% CI, 0.76 to 1.16; P=0.48) or in any of the individual components. Similar results were obtained in a per-protocol analysis that excluded the 177 patients who crossed over from the assigned treatment to the other treatment.

### CONCLUSIONS

In patients 75 years of age or older, there was no significant difference between on-pump and off-pump CABG with regard to the composite outcome of death, stroke, myocardial infarction, repeat revascularization, or new renal-replacement therapy within 30 days and within 12 months after surgery. (Funded by Maquet; GOPCABE ClinicalTrials.gov number, NCT00719667.)

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*A complete list of investigators in the German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE) study is provided in the Supplementary Appendix, available at NEJM.org.

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There is an ongoing debate about the benefits and shortcomings of coronary-artery bypass grafting (CABG) without cardiopulmonary bypass (off-pump CABG). Cardiopulmonary bypass can have detrimental effects.[1-4] Initial trials have shown that off-pump CABG is feasible in selected low-risk patients and offers results similar to those of CABG performed with the conventional on-pump technique (on-pump CABG). In institutions with experience in off-pump CABG, the rate of major adverse events and the rates of complete revascularization and graft patency have been similar to those with on-pump CABG.[5-7] These positive results have been called into question by reports of inferior graft patency and higher rates of repeat target-vessel revascularization associated with off-pump CABG.[8-10] The Randomized On/Off Bypass (ROOBY) trial[11] showed that among low-risk patients, the rate of death or major adverse events at 30 days after surgery was similar with off-pump and on-pump CABG, but off-pump CABG was associated with a higher rate of incomplete revascularization and an inferior outcome at 1 year. Short-term mortality and morbidity after off-pump and on-pump CABG were similar in a recent trial involving 4752 patients with a mixed operative-risk profile (the CABG Off or On Pump Revascularization Study [CORONARY]).[12]

The German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE) study focused exclusively on patients 75 years of age or older. Considering the high incidence of coexisting conditions in this population, we anticipated that this trial would clarify the potential benefit of off-pump CABG in high-risk patients.

## Methods

### Study Design and Oversight

The GOPCABE study was a randomized, controlled, multicenter trial conducted at 12 German institutions. The study was designed by the first and last authors and was approved by a certified ethics committee. The study sponsor was the German Society for Thoracic and Cardiovascular Surgery. Funding was provided by an unrestricted grant from Maquet, which otherwise had no role in the conduct of the study or the analysis or reporting of data. There was no confidentiality agreement regarding data use.

Data collection and site management were handled by the Institute for Clinical Cardiovascular Research (IKKF, Munich, Germany). The trial was monitored by an independent data and safety monitoring board. The first draft of the manuscript was written by the first and third-to-last authors; all the authors provided revisions and comments. All the authors vouch for the accuracy and completeness of the report, as well as for the fidelity of the report to the study protocol, which is available with the full text of this article at NEJM.org. The participating centers, the principal investigators, the participating surgeons, and the members of the safety committee are listed in the Supplementary Appendix, available at NEJM.org.

### Study Population

Patients who were scheduled for isolated, first-time CABG were eligible if they were at least 75 years of age. Exclusion criteria were any additional cardiovascular disease necessitating concomitant surgery, previous pericardiotomy, any condition requiring immediate surgery (i.e., within 24 hours after hospital admission), planned minimally invasive direct coronary-artery bypass procedure (CABG with the use of left anterior thoracotomy), and the inability or unwillingness of the patient to provide consent. The baseline characteristics of potentially eligible but excluded patients were recorded in a screening log. All patients provided written informed consent.

### Randomization and Treatment

Eligible patients were randomly assigned to off-pump CABG or on-pump CABG. Randomization was performed after the baseline data, including information about the target vessels, had been entered into a central, Internet-based, password-protected database with the use of a template. Treatment assignments were performed in a blinded manner according to a blocked randomization scheme with a block size of eight, stratified according to the participating center.

Off-pump CABG was routinely performed at all participating centers before the trial was initiated. Participating centers nominated individual study surgeons for each surgical technique. Study surgeons were required to be established experts in the performance of either off-pump or on-pump CABG. The average number of CABG surgeries performed before the study was 514 off-

pump surgeries (median, 322) for the off-pump CABG surgeons and 1378 on-pump surgeries (median, 578) for the on-pump CABG surgeons. In both groups, the technical details were left to the discretion of the operating surgeon. In all off-pump procedures, commercially available stabilizers were used to provide a motionless surgical field.

### STUDY END POINTS

The primary end point was a composite of death or a major adverse event (myocardial infarction, stroke, acute renal failure requiring renal-replacement therapy, or repeat revascularization) within 30 days and within 12 months after surgery. Definitions of these end-point events are provided in the Supplementary Appendix. Secondary end points included operative time, duration of mechanical ventilation, length of stay in the intensive care unit (ICU), length of hospital stay, and transfusion requirements.

### STATISTICAL ANALYSIS

At study conception, the participating centers reported an approximate 15% rate of the composite primary end point for patients 75 years of age or older undergoing first-time CABG. We calculated that a sample of 2000 patients would provide a power of 90% to detect a relative risk reduction of 33% (odds ratio, 0.63) with the off-pump technique, assuming a balanced crossover rate of 5%. After the enrollment of 500 patients, a planned, blinded interim analysis showed a total event rate of 11%. In order to maintain a power of 90% with an odds ratio of 0.63, the sample size was increased to 2500 patients.

Analysis was performed on a modified intention-to-treat basis, with all randomly assigned patients who underwent isolated CABG by the assigned surgeon included (Fig. 1). Baseline characteristics and operative characteristics were compared with the use of the chi-square test, t-test, or Kruskal–Wallis test, as appropriate. Dichotomous data are presented as numbers and percentages. Continuous data are presented as means and standard deviations or medians and interquartile ranges. The continuity-corrected chi-square test was used for comparison of the 30-day end point. Mantel–Haenszel chi-square tests were used to adjust for study-center effects. Treatment effects at 30 days are expressed as odds ratios and 95% confidence intervals. For the 12-month end point, Kaplan–Meier curves were constructed, and the study groups were compared with use of the log-rank test. Hazard ratios and 95% confidence intervals derived from the Cox proportional-hazards model are provided for the composite outcome and individual components. All statistical analyses were performed with the use of SPSS software, version 20.0 (IBM). Forest plots were depicted with the use of Review Manager software from the Cochrane Library (RevMan, version 5.1).

## RESULTS

### ENROLLMENT AND RANDOMIZATION

Between June 25, 2008, and September 9, 2011, a total of 4355 patients who were scheduled for first-time isolated CABG and who were at least 75 years of age were screened for enrollment. Of these, 1816 patients were excluded for the reasons shown in Figure 1. A total of 2539 patients (68.9% of the 3683 who were assessed for eligibility) were included in the study and randomly assigned to off-pump CABG (1271 patients) or on-pump CABG (1268 patients).

After randomization, 80 patients in the off-pump group and 56 patients in the on-pump group were excluded. Reasons for exclusion were the necessity for another cardiovascular procedure in addition to CABG, the need for immediate surgery with unavailability of the assigned study surgeon, a decision not to perform surgery, withdrawal of consent, missing consent form, death before surgery, or miscellaneous reasons (Fig. 1). The remaining 1191 patients in the off-pump group and 1212 patients in the on-pump group underwent isolated CABG by the assigned surgeon.

After surgery, 2 patients withdrew consent and 7 patients were lost to follow-up at 30 days. There were 1187 patients in the off-pump group and 1207 patients in the on-pump group available for analysis of the 30-day end point. At 12 months, an additional 23 patients were lost to follow-up and 1 patient had withdrawn consent. A total of 1179 patients assigned to off-pump CABG and 1191 patients assigned to on-pump CABG were available for analysis of the 12-month end point.

### CHARACTERISTICS OF THE PATIENTS

Baseline demographic and clinical characteristics were well balanced between the two treatment groups (Table 1). The mean age was 78 years

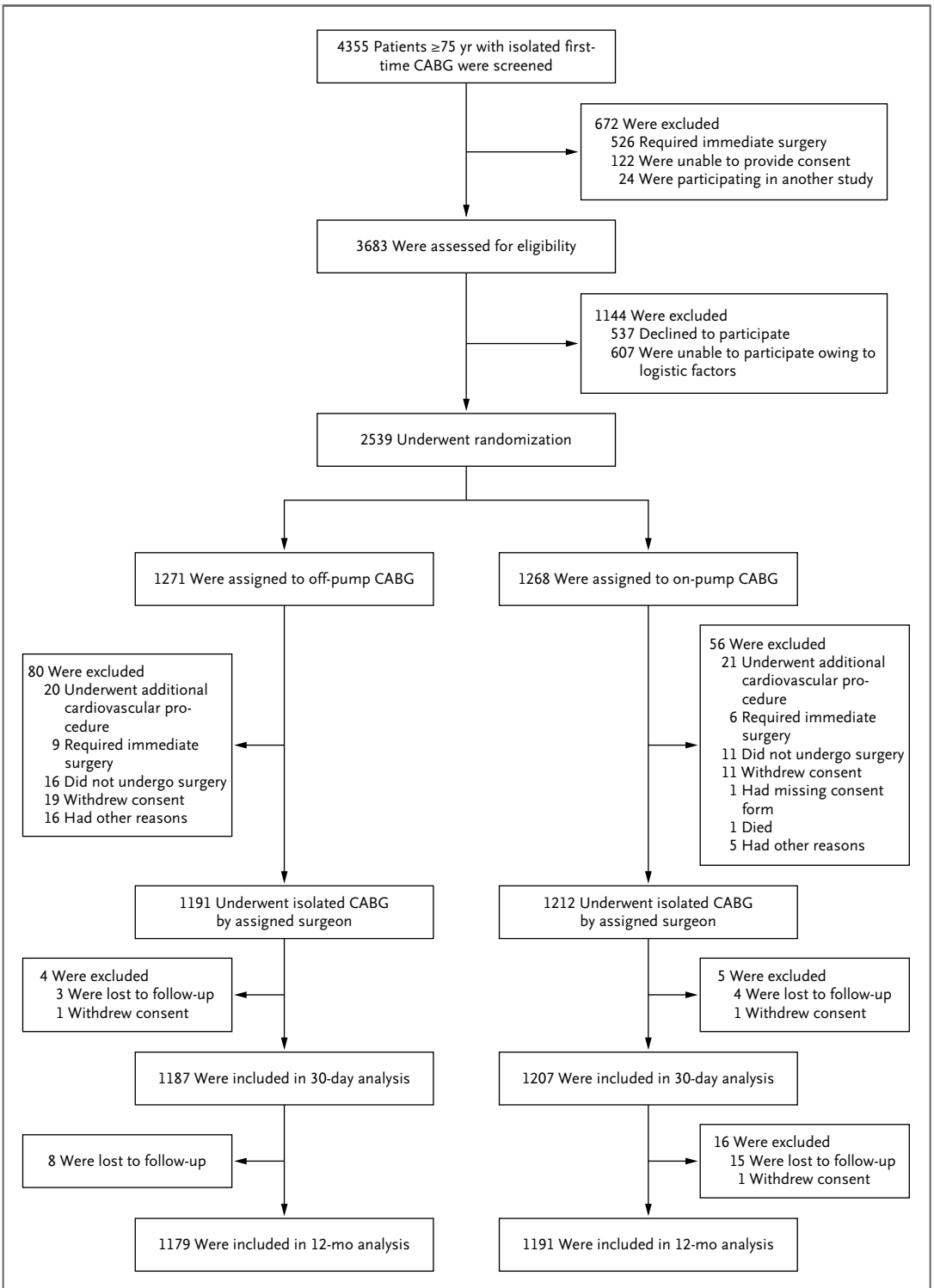



**Figure 1. Trial Enrollment, Randomization, and Follow-up.**
CABG denotes coronary-artery bypass grafting.

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

| Characteristic | Off-Pump CABG (N=1187) | On-Pump CABG (N=1207) |
|---|---|---|
| Female sex — no. (%) | 366 (30.8) | 389 (32.2) |
| Age — yr | 78.6±3.0 | 78.4±2.9 |
| Body-mass index† | 27.8±4.1 | 27.8±4.1 |
| Insulin-dependent diabetes mellitus — no. (%) | 179 (15.1) | 166 (13.8) |
| Chronic obstructive pulmonary disease — no. (%) | 127 (10.7) | 118 (9.8) |
| Previous stroke — no. (%) | 121 (10.2) | 95 (7.9) |
| Peripheral vascular disease — no. (%) | 388 (32.7) | 392 (32.5) |
| Pulmonary arterial hypertension — no. (%)‡ | 39 (3.3) | 26 (2.2) |
| History of myocardial infarction — no. (%) | 427 (36.0) | 456 (37.8) |
| History of percutaneous coronary intervention — no. (%) | 268 (22.6) | 263 (21.8) |
| History of atrial fibrillation — no. (%) | 177 (14.9) | 190 (15.7) |
| Implanted pacemaker — no. (%) | 31 (2.6) | 33 (2.7) |
| Left ventricular ejection fraction — no. (%) | | |
| <30% | 25 (2.1) | 39 (3.2) |
| 30–50% | 365 (30.7) | 341 (28.3) |
| >50% | 797 (67.1) | 827 (68.5) |
| CCS angina class — no. (%)§ | | |
| I | 224 (18.9) | 230 (19.1) |
| II | 396 (33.4) | 425 (35.2) |
| III | 523 (44.1) | 496 (41.1) |
| IV | 44 (3.7) | 56 (4.6) |
| Extent of coronary artery disease — no. (%) | | |
| One-vessel disease | 23 (1.9) | 14 (1.2) |
| Two-vessel disease | 119 (10.0) | 106 (8.8) |
| Three-vessel disease | 712 (60.0) | 730 (60.5) |
| Left main coronary artery disease plus disease of one to three vessels | 333 (28.1) | 357 (29.6) |
| Creatinine level — no. (%)¶ | | |
| ≤2.3 mg/dl | 1150 (96.9) | 1169 (96.9) |
| >2.3 mg/dl | 26 (2.2) | 27 (2.2) |
| Renal-replacement therapy — no. (%) | 11 (0.9) | 11 (0.9) |
| Critical condition — no. (%)‖ | 22 (1.9) | 36 (3.0) |
| Logistic euroSCORE** | 8.3±7.2 | 8.2±6.6 |
| Koronarchirurgie score** | 3.8±4.0 | 3.8±3.5 |

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between the two groups. CABG denotes coronary-artery bypass grafting.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Pulmonary arterial hypertension was defined as a systolic pulmonary-artery pressure higher than 60 mm Hg.

§ Classes of angina on the Canadian Cardiovascular Society (CCS) scale range from I to IV, with higher classes indicating greater limitations on physical activity owing to angina.

¶ Data on creatinine were missing for 11 patients in each group. To convert the values to micromoles per liter, multiply by 88.4.

‖ Critical condition was defined as the presence of one or more of the following: cardiogenic shock or resuscitation within 48 hours before hospital admission, mechanical ventilation, inotropic support, or intraaortic balloon pump.

** Both the logistic European System for Cardiac Operative Risk Evaluation (euroSCORE)[13] and the Koronarchirurgie score[14] indicate the percent risk of death within 30 days after surgery. Both scores are calculated with multivariable models that incorporate clinical predictors to estimate the operative mortality for any given patient. The euroSCORE was developed in 1998 from data on cardiac surgery in eight European countries. The Koronarchirurgie scale is constructed on a yearly basis with the use of current registry data for all CABG procedures in Germany.

(range, 75 to 90), and approximately one third of the patients were women. A total of 36.9% of patients had had a previous myocardial infarction, and 32.2% had impaired left ventricular function (ejection fraction ≤50%). Most of the patients (89.1%) had severe coronary artery disease — that is, either three-vessel disease or left main coronary artery involvement. The predicted in-hospital mortality according to the Koronarchirurgie score was 3.8% in both groups (Table 1).

Baseline characteristics of 1028 of the 1144 excluded but potentially eligible patients are shown in Table S1 in the Supplementary Appendix. Comparison with the study population revealed that these patients were slightly older, were more likely to have angina at rest, and were more likely to have an ejection fraction below 30%. The percentage of patients in critical condition before surgery was more than three times as high in this group. A total of 46.0% of the excluded patients (473 of 1028) underwent off-pump CABG (data not shown).

### SURGERY

Before randomization, the anticipated number of grafts and information about the corresponding target vessels were required to be entered into the Internet-based data template. The majority of procedures were planned to include two or three coronary anastomoses (79.4% of the procedures in the off-pump group and 78.1% of those in the on-pump group), with a similar number of anastomoses planned in the two groups. During surgery, fewer grafts were performed in the off-pump group than in the on-pump group. The average number of coronary anastomoses was 2.7 in the off-pump group and 2.8 in the on-pump group (P<0.001). The proportion of patients with fewer grafts than anticipated was higher in the off-pump group (34.0%, vs. 29.3% in the on-pump group), and the proportion of patients with more grafts than anticipated was lower in the off-pump group (10.2% vs. 16.7%) (Table 2).

Crossover from the assigned treatment occurred more often in the off-pump group (9.7%, vs. 5.1% in the on-pump group). Treatment crossover before skin incision was predominantly due to logistic factors (e.g., the study surgeon was unavailable) in both groups. After the skin incision, the most common reason for conversion from on-pump to off-pump CABG was a calcified ascending aorta, precluding aortic manipulation with cannulation and aortic cross-clamping. Conversion from off-pump to on-pump CABG was primarily due to hemodynamic instability, highly calcified coronary arteries, and inadequate target-vessel exposure. The timing and the reasons for treatment crossover are shown in Figure S1 in the Supplementary Appendix.

### PRIMARY END POINT

The composite end point of death, stroke, myocardial infarction, repeat revascularization, or new renal-replacement therapy within 30 days after surgery occurred in 93 patients (7.8%) in the off-pump group and 99 patients (8.2%) in the on-pump group (odds ratio with off-pump CABG vs. on-pump CABG, 0.95; 95% confidence interval [CI], 0.71 to 1.28; P=0.74) (Table 3). Patients in the off-pump group were more likely than those in the on-pump group to undergo a repeat revascularization procedure within 30 days after the initial surgery (15 patients [1.3%] vs. 5 patients [0.4%]; odds ratio, 2.42; 95% CI, 1.03 to 5.72; P=0.04). The primary end point occurred in both treatment groups with a similar probability across all participating centers (Fig. S2 in the Supplementary Appendix).

At 12 months, the composite end point of death, stroke, myocardial infarction, repeat revascularization, or new renal-replacement therapy had occurred in 154 patients (13.1%) assigned to off-pump CABG as compared with 167 patients (14.0%) assigned to on-pump CABG (hazard ratio, 0.93; 95% CI, 0.76 to 1.16; P=0.48) (Table 3 and Fig. 2). No significant between-group differences were observed at 12 months for any of the individual components of the primary end point (Table 3). Between 30 days and 1 year after surgery, 52 patients assigned to off-pump CABG and 61 patients assigned to on-pump CABG died. Mortality at 1 year was 7.0% with off-pump CABG and 8.0% with on-pump CABG (hazard ratio, 0.88; 95% CI, 0.65 to 1.18; P=0.38) (Table 3, and Fig. S3 in the Supplementary Appendix). There was no significant difference between the two groups with respect to rates of revascularization at 1 year (Table 3, and Fig. S3 in the Supplementary Appendix).

The primary analysis was based on the modified intention-to-treat principle. A supplementary per-protocol analysis, excluding the 177 patients who crossed over from the assigned treatment, yielded similar results (Table S2 in the Supple-

**Table 2. Operative Variables and Use of Resources.***

| Variable | Off-Pump CABG (N=1187) | On-Pump CABG (N=1207) |
|---|---|---|
| **Operative variables†** | | |
| Mean no. of anticipated grafts‡ | 2.9 | 3.0 |
| Anticipated no. of grafts — no. of patients (%) | | |
| 1 | 28 (2.4) | 12 (1.0) |
| 2 | 242 (20.4) | 260 (21.5) |
| 3 | 700 (59.0) | 683 (56.6) |
| 4 | 197 (16.6) | 222 (18.4) |
| >4 | 20 (1.7) | 30 (2.5) |
| Mean no. of performed grafts§ | 2.7 | 2.8 |
| No. of performed grafts — no. of patients (%)§ | | |
| 1 | 74 (6.2) | 44 (3.6) |
| 2 | 414 (34.9) | 382 (31.6) |
| 3 | 557 (46.9) | 551 (45.7) |
| 4 | 123 (10.4) | 187 (15.5) |
| >4 | 19 (1.6) | 43 (3.6) |
| Anticipated vs. performed grafts per patient — no. of patients (%)§ | | |
| No. anticipated = no. performed | 663 (55.9) | 651 (53.9) |
| No. anticipated < no. performed | 121 (10.2) | 202 (16.7) |
| No. anticipated > no. performed | 403 (34.0) | 354 (29.3) |
| Treatment crossover — no. of patients (%)§ | 115 (9.7) | 62 (5.1) |
| **Use of resources** | | |
| Allogeneic blood transfusion — no. of patients (%)§ | 668 (56.3) | 757 (62.7) |
| Units of transfused packed red cells§ | | |
| Mean | 2.0 | 2.4 |
| Median | 1 | 2 |
| Operative time — min | | |
| Mean | 175.5 | 174.3 |
| Median | 170 | 168 |
| Duration of mechanical ventilation — hr | | |
| Mean | 25.1 | 30.7 |
| Median | 12 | 12 |
| Postoperative length of ICU stay — days | | |
| Mean | 3.7 | 4.3 |
| Median | 2 | 2 |
| Postoperative length of hospital stay — days | | |
| Mean | 11.5 | 11.6 |
| Median | 9 | 9 |

* ICU denotes intensive care unit.
† Specification of the number and territory of anticipated bypass grafts was mandatory before randomization.
‡ $P<0.05$ for between-group comparisons.
§ $P<0.001$.

mentary Appendix). The 30-day composite end point occurred in 75 patients (7.0%) in the off-pump group as compared with 92 patients (8.0%) in the on-pump group (odds ratio, 0.87; 95% CI, 0.63 to 1.20; P=0.40). Additional revascularization procedures within 30 days after surgery were more frequent in the off-pump group than in the on-pump group (in 14 patients [1.3%] vs. 4 patients

**Table 3. Trial End Points (Modified Intention-to-Treat Analysis).***

| End Point | Off-Pump CABG | On-Pump CABG | Odds Ratio or Hazard Ratio (95% CI)† | P Value |
|---|---|---|---|---|
| | *no./total no. (%)* | | | |
| **At 30 days‡** | | | | |
| Primary composite end point§ | 93/1187 (7.8) | 99/1207 (8.2) | 0.95 (0.71–1.28) | 0.74 |
| Individual components | | | | |
| Death | 31/1187 (2.6) | 34/1207 (2.8) | 0.92 (0.57–1.51) | 0.75 |
| Myocardial infarction | 18/1187 (1.5) | 20/1207 (1.7) | 0.92 (0.51–1.66) | 0.79 |
| Stroke | 26/1187 (2.2) | 32/1207 (2.7) | 0.83 (0.50–1.38) | 0.47 |
| Repeat revascularization | 15/1187 (1.3) | 5/1207 (0.4) | 2.42 (1.03–5.72) | 0.04 |
| New renal-replacement therapy | 29/1187 (2.4) | 37/1207 (3.1) | 0.80 (0.49–1.29) | 0.36 |
| **At 12 mo¶** | | | | |
| Primary composite end point§ | 154/1179 (13.1) | 167/1191 (14.0) | 0.93 (0.76–1.16) | 0.48 |
| Individual components | | | | |
| Death | 83/1179 (7.0) | 95/1191 (8.0) | 0.88 (0.65–1.18) | 0.38 |
| Myocardial infarction | 25/1179 (2.1) | 28/1191 (2.4) | 0.90 (0.53–1.54) | 0.70 |
| Stroke | 41/1179 (3.5) | 52/1191 (4.4) | 0.79 (0.53–1.19) | 0.26 |
| Repeat revascularization | 36/1179 (3.1) | 24/1191 (2.0) | 1.52 (0.90–2.54) | 0.11 |
| New renal-replacement therapy | 34/1179 (2.9) | 42/1191 (3.5) | 0.82 (0.52–1.28) | 0.37 |

* CI denotes confidence interval.
† Odds ratios are reported for end points at 30 days after surgery, and hazard ratios are reported for end points at 12 months after surgery.
‡ Comparison of end points at 30 days was performed with the chi-square test.
§ The primary composite end point was death, myocardial infarction, stroke, repeat revascularization, or new renal-replacement therapy at 30 days and at 12 months after surgery.
¶ Comparison of end points at 12 months was performed with the log-rank test.

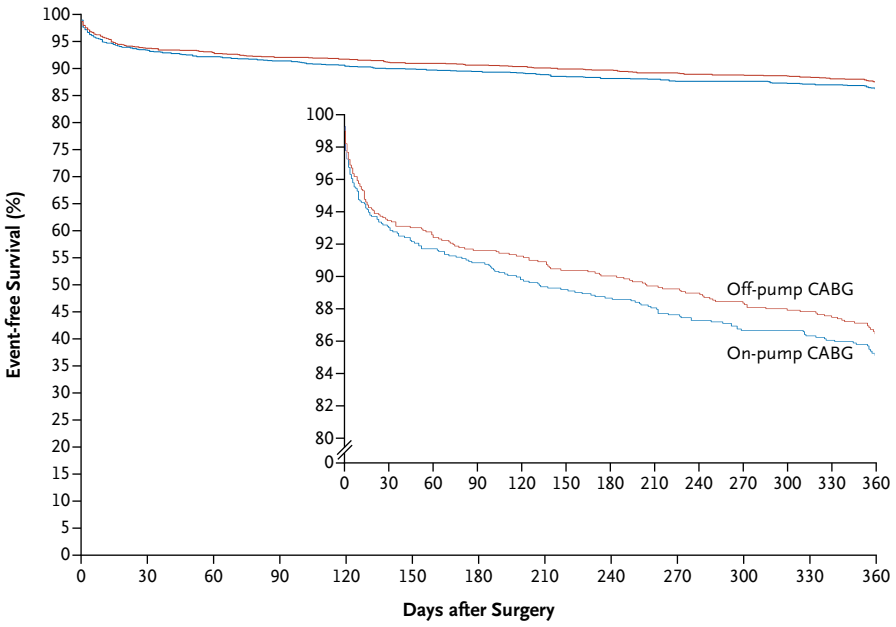
[0.3%]; odds ratio, 2.65; 95% CI, 1.10 to 6.40; P=0.03). The 12-month per-protocol analysis revealed no significant differences with regard to either the composite end point or its individual components. A sensitivity analysis was also performed in which patients excluded from the primary analysis after randomization were assumed to have systematically worse outcomes than those not excluded; even with this scenario, the result was unchanged (Table S2 in the Supplementary Appendix).

### SECONDARY END POINTS

As compared with patients in the on-pump group, those in the off-pump group required fewer transfusions of packed red cells and were less likely to have received blood products. Operative time, duration of mechanical ventilation, length of ICU stay, and length of hospital stay were similar in the two groups (Table 2).

## DISCUSSION

We found no significant difference between off-pump CABG and on-pump CABG, performed in elderly patients, with respect to the composite end point of death, stroke, myocardial infarction, repeat revascularization, or new renal-replacement therapy after surgery. With a mean age of 78 years and a predicted in-hospital mortality of 3.8%, the study cohort represents a patient population with an increased operative risk. The results of previous studies are inconsistent with regard to high-risk patients.[15-17] Our trial does not support the assumption that off-pump CABG can improve the early outcome in high-risk patients. This result is consistent with an American Heart Association scientific statement,[18] which concluded that both procedures may result in excellent outcomes and that other factors, such as the skill of the surgeon and the quality of the institution, are more likely




| No. at Risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| On-pump CABG | 1192 | 1112 | 1095 | 1083 | 1073 | 1065 | 1059 | 1053 | 1044 | 1039 | 1035 | 1030 | 1024 |
| Off-pump CABG | 1179 | 1103 | 1093 | 1079 | 1075 | 1066 | 1060 | 1053 | 1047 | 1041 | 1036 | 1032 | 1024 |

**Figure 2. Kaplan–Meier Cumulative Event Rates for the Primary End Point at 12 Months.**

The primary end point was a composite of death, stroke, myocardial infarction, repeat revascularization, or new renal-replacement therapy. The inset shows the same data on an enlarged y axis.

to influence the outcome than the choice of surgical technique.

In contrast to other trials,[11,12,19] the GOPCABE trial used an "all comers" approach, without any restrictions regarding coronary morphologic characteristics or left ventricular function. As a consequence, the results should be representative for a large and well-defined patient population. Another specific feature of the trial is the screening log for almost 90% of the excluded patients, providing the clinical data for a cohort parity analysis. It is notable that 46.0% of these potentially eligible but excluded patients underwent off-pump CABG, which indicates that these patients were not excluded because of a consistent preference for one surgical technique or the other.

Although different in design and patient population, the previous trials[11,12,19] were similar to the GOPCABE trial in several respects. Neither of the two techniques for CABG was superior to the other with regard to death or major complications within 30 days after surgery in any of the trials. As compared with on-pump CABG, off-pump CABG consistently resulted in fewer grafts and higher rates of treatment crossover, as well as more repeat revascularization procedures (a finding that may raise concern about possible adverse long-term outcomes). Yet in contrast to the ROOBY trial,[11] our study did not show a significant between-group difference in survival or major adverse events at 1 year after surgery. This difference may be a consequence of the requirement for substantially greater experience with off-pump CABG in the GOPCABE trial than in the ROOBY trial.

Several limitations of our trial should be noted. First, the study end points focused on major clinical events only. Other variables, such as angiographic assessment of graft patency, neurocognitive status, and quality of life were not investigated. Second, the primary-end-point events were not adjudicated by a blinded adjudication committee. All data were provided by the local

investigators according to the protocol definitions. However, the data monitoring performed by the IKKF, which periodically audited the study sites to assess the accuracy of the recorded data, should have prevented an underreporting of outcome events.

Third, the assignment of a specific study surgeon to each patient meant that randomization in the operating room just before surgery was not feasible. This organizational prerequisite resulted in an interval between randomization and surgery during which medical and logistic requirements (e.g., the need for an additional cardiovascular procedure, urgent surgery, and unavailability of the study surgeon) could override the randomized assignment. We therefore allowed for the exclusion of patients after randomization. This ultimately resulted in an imbalanced exclusion of patients assigned to off-pump CABG. Yet the similarity of the results obtained in the per-protocol analysis argues against a major bias.

In conclusion, our randomized trial of off-pump versus on-pump CABG in elderly patients did not show a significant benefit of either operative approach with respect to clinical outcomes at 30 days or 1 year.

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## REFERENCES

1. Pintar T, Collard CD. The systemic inflammatory response to cardiopulmonary bypass. Anesthesiol Clin North America 2003;21:453-64.
2. Selnes OA, Gottesman RF, Grega MA, Baumgartner WA, Zeger SL, McKhann GM. Cognitive and neurologic outcomes after coronary-artery bypass surgery. N Engl J Med 2012;366:250-7.
3. Diegeler A, Doll N, Rauch T, et al. Humoral immune response during coronary bypass grafting: a comparison of limited approach, "off-pump" technique, and conventional cardiopulmonary bypass. Circulation 2000;102:Suppl 3:III-95–III-100.
4. Diegeler A, Hirsch R, Schneider F, et al. Neuromonitoring and neurocognitive outcome in off-pump versus conventional bypass operation. Ann Thorac Surg 2000;69:1162-6.
5. Nathoe HM, van Dijk D, Jansen EW, et al. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. N Engl J Med 2003;348:394-402.
6. Widimsky P, Straka Z, Stros P, et al. One-year coronary bypass graft patency: a randomized comparison between off-pump and on-pump surgery: angiographic results of the PRAGUE-4 trial. Circulation 2004;110:3418-23.
7. Puskas JD, Williams WH, Mahoney EM, et al. Off-pump vs. conventional coronary artery bypass grafting: early and 1-year graft patency, cost, and quality-of-life outcomes: a randomized trial. JAMA 2004;291:1841-9.
8. Khan NE, De Souza A, Mister R, et al. A randomized comparison of off-pump and on-pump multivessel coronary-artery bypass surgery. N Engl J Med 2004;350:21-8.
9. Hannan EL, Wu C, Smith CR, et al. Off-pump versus on-pump coronary artery bypass graft surgery: differences in short-term outcomes and in long-term mortality and need for subsequent revascularization. Circulation 2007;116:1145-52.
10. Hattler B, Messenger JC, Shroyer AL, et al. Off-pump coronary artery bypass surgery is associated with worse arterial and saphenous vein graft patency and less effective revascularization: results from the Veterans Affairs Randomized On/Off Bypass (ROOBY) trial. Circulation 2012;125:2827-35.
11. Shroyer AL, Grover FL, Hattler B, et al. On-pump versus off-pump coronary-artery bypass surgery. N Engl J Med 2009;361:1827-37.
12. Lamy A, Devereaux PJ, Prabhakaran D, et al. Off-pump or on-pump coronary artery bypass grafting at 30 days. N Engl J Med 2012;366:1489-97.
13. Roques F, Michel P, Goldstone AR, Nashef SAM. The logistic EuroSCORE. Eur Heart J 2003;24:881-2.
14. Badreldin AMA, Kania A, Ismail MMA, et al. KCH, the German preoperative score for isolated coronary artery bypass surgery: is it superior to the logistic EuroSCORE? Thorac Cardiovasc Surg 2011;59:399-405.
15. Puskas J, Cheng D, Knight J, et al. Off-pump versus conventional coronary artery bypass grafting: a meta-analysis and consensus statement from the 2004 ISMICS Consensus Conference. Innovations 2005;1:3-27.
16. Kuss O, Börgermann J. Do higher-risk patients benefit from off-pump coronary artery bypass grafting? Evidence from an ecologic analysis of randomized trials. J Thorac Cardiovasc Surg 2011;142(3):e117-e122.
17. Møller CH, Perko MJ, Lund JT, et al. No major differences in 30-day outcomes in high-risk patients randomized to off-pump versus on-pump coronary bypass surgery: the Best Bypass Surgery Trial. Circulation 2010;121:498-504.
18. Sellke FW, DiMaio JM, Caplan LR, et al. Comparing on-pump and off-pump coronary artery bypass grafting: numerous studies but few conclusions: a scientific statement from the American Heart Association Council on Cardiovascular Surgery and Anesthesia in collaboration with the Interdisciplinary Working Group on Quality of Care and Outcomes Research. Circulation 2005;111:2858-64.
19. Houlind K, Kjeldsen BJ, Madsen SN, et al. On-pump versus off-pump coronary artery bypass surgery in elderly patients: results from the Danish on-pump versus off-pump randomization study. Circulation 2012;125:2431-9.