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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

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Background—Off-pump coronary artery bypass grafting compared with coronary revascularization with cardiopulmonary bypass seems safe and results in about the same outcome in low-risk patients. Observational studies indicate that off-pump surgery may provide more benefit in high-risk patients. Our objective was to compare 30-day outcomes in high-risk patients randomized to coronary artery bypass grafting without or with cardiopulmonary bypass.

Methods and Results—We randomly assigned 341 patients with a EuroSCORE ≥ 5 and 3-vessel coronary disease to undergo coronary artery bypass grafting without or with cardiopulmonary bypass. Patients were followed through the Danish National Patient Registry. The primary outcome was a composite of adverse cardiac and cerebrovascular events (ie, all-cause mortality, acute myocardial infarction, cardiac arrest with successful resuscitation, low cardiac output syndrome/cardiogenic shock, stroke, and coronary reintervention). An independent adjudication committee blinded to treatment allocation assessed the outcomes. Baseline characteristics were well balanced between groups. The mean number of grafts per patient did not differ significantly between groups (3.22 in off-pump group and 3.34 in on-pump group; $P=0.11$). Fewer grafts were performed to the lateral part of the left ventricle territory during off-pump surgery (0.97 versus 1.14 after on-pump surgery; $P=0.01$). No significant differences in the composite primary outcome (15% versus 17%; $P=0.48$) or the individual components were found at 30-day follow-up.

Conclusions—Both off- and on-pump coronary artery bypass grafting can be performed in high-risk patients with low short-term complications.

Clinical Trial Registration—clinicaltrials.gov. Identifier: NCT00120991.

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Key Words: cardiopulmonary bypass ■ high-risk patients ■ off-pump ■ OPCAB ■ revascularization

Previous randomized trials comparing coronary artery bypass grafting (CABG) with (on-pump CABG) versus without cardiopulmonary bypass (off-pump CABG) have included mainly low-risk patients (ie, patients with lower age, preserved left ventricular function, and without systemic comorbidity).¹⁻⁴ In these trials, off-pump CABG was shown to be a safe and effective procedure, but avoiding cardiopulmonary bypass and cardioplegic arrest did not result in a significant reduction in mortality, myocardial infarction, or stroke.⁵ However, these hard clinical outcomes are infrequent in the investigated patient population, and to show a difference requires a large sample size. This has not been reached

even in the latest meta-analysis of the topic including >5500 patients.⁵

Clinical Perspective on p 504

During the last decades, the preoperative risk profile of patients referred for CABG surgery has changed.⁶⁻⁹ Patients are now older, have more severe coronary disease, and have more comorbidity. These patients have a substantial risk of postoperative morbidity and mortality.^{10,11} Off-pump CABG in high-risk patients seems to reduce postoperative morbidity and mortality compared with on-pump CABG according to observational studies.^{8,12-14}

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To clarify the potential benefit of off-pump CABG in high-risk patients, we conducted a randomized trial comparing off-pump versus on-pump CABG in patients with 3-vessel coronary disease and a EuroSCORE ≥ 5 .¹⁵ The present article reports procedural results and the 30-day outcomes of the 2 treatment groups.

Methods

Trial Design

Details of the Best Bypass Surgery (BBS) trial have been reported elsewhere.¹⁵ In brief, the trial was a single-center trial in which patients were randomly assigned to undergo off-pump or on-pump CABG. Central randomization was performed by a press-button voice-response telephone randomization service. Random assignment 1:1 was permuted in varying blocks (6 or 8) and stratified by sex, age (55 to 65 years, >65 years), diabetes mellitus, and EuroSCORE (5 to 7, 8 to 10, 11 to 13, 14 to 16). An independent adjudication committee blinded to treatment allocation assessed all of the potential outcomes.

Patients

Patients referred for first-time isolated CABG (ie, no valve surgery) were eligible if they were >54 years of age, had a EuroSCORE ≥ 5 , had 3-vessel disease affecting a graftable marginal artery, were scheduled for elective or subacute operation, and provided written informed consent. Exclusion criteria were previous heart surgery, left ventricular ejection fraction $<30\%$, lack of informed consent, and unstable preoperative condition (eg, patients receiving continuous infusion of inotropics on the day of surgery). The Danish Regional Committee on Biomedical Research Ethics and the Danish Data Protection Agency approved the BBS trial (www.clinicaltrials.gov/ct2/show/NCT00120991), which was conducted in accordance with the International Conference on Harmonization on Good Clinical Practice Guidelines and the Declaration of Helsinki.

Surgical Technique

Surgical access to the heart was gained through a median sternotomy in all of the patients. Off-pump surgery was performed with the use of Octopus and Starfish heart stabilizers (Medtronic, Inc, Minneapolis, Minn). Patients were heparinized with 100 IU/kg intravenously to achieve activated clotting time >200 s. Normothermia was maintained with the use of a Bair Hugger system (Augustine Medical, Inc). A side-biting aorta clamp was usually used when proximal anastomoses were performed. Intracoronary shunts were not used routinely. On-pump surgery was performed in normothermia, with the use of aortic cross-clamping and cold cardioplegic arrest. Patients were heparinized with 300 IU/kg to achieve an activated clotting time >480 s. Heparin was neutralized with 1 mg protamine sulfate per 100 IU given. The quality of anastomoses was assessed at the end of operation with the use of a transit-time flow probe (MediStim A/S, Oslo, Norway). During the trial, there were no changes in the 2 surgical techniques. In our center, off-pump surgery had been performed routinely for >2 years before the launch of the trial, and each of the 3 participating surgeons performed at least 50% of their CABG procedures as off-pump procedures.

Follow-Up and Outcome Measures

Patients were followed up after discharge through the Danish National Patient Registry, which is a national database of all somatic hospital admissions in Denmark. Information about death came from the Danish Central Civil Register, which records the vital status of inhabitants. Registration in these registers is 100%. On the basis of the registers, we collected copies of hospital records and death certificates during the follow-up period. No follow-up visits were planned; however, patients were routinely seen by the referring cardiologist 1 month after the operation. Hospital records and death certificates were blinded for the allocated treatment and forwarded to 2 randomly selected members of the adjudication committee, who

assessed whether each of the prespecified outcomes had occurred. In case of disagreement, the 2 assessments together with a copy of the record of the event were sent to a third member, who had to select the most likely assessment.

The primary outcome was a composite of adverse cardiac and cerebrovascular events (ie, all-cause mortality, acute myocardial infarction, cardiac arrest with successful resuscitation, low cardiac output syndrome/cardiogenic shock, stroke, and coronary reintervention). Secondary outcomes were hyperdynamic shock, new onset of atrial fibrillation, need for pacing >24 hours, renal complications, reoperation, respiratory insufficiency requiring intubation >24 hours, pneumonia, length of stay in intensive care unit and hospital, and other serious adverse event. Myocardial infarction was defined as creatine kinase-MB increase >80 $\mu\text{g/L}$ or troponin T >3.0 $\mu\text{g/L}$ the first 48 hours after surgery. Hereafter, the definition was enzymatic elevation of creatine kinase-MB >10 $\mu\text{g/L}$ or troponin T >0.1 $\mu\text{g/L}$ together with at least 1 of the following findings: classic angina symptoms, ECG signs of necrosis or ischemia, or coronary reintervention. Low cardiac outcome syndrome was defined as need of intra-aortic balloon pumping or infusion of norepinephrine, epinephrine, milrinone, or dobutamine after the first hour postoperatively to maintain systolic blood pressure ≥ 90 mm Hg. Definition of stroke was global or focal neurological deficits persisting >24 hours and verified by a neurologist or brain computed tomography scan. Renal complications were defined as need of acute hemodialysis, blood creatinine level ≥ 200 $\mu\text{g/L}$, or blood creatinine 2 times the preoperative value.

Statistical Analysis

The sample size in the BBS trial was based on the ability to detect a 15% reduction in the primary outcome in the off-pump group compared with the on-pump group, assuming an event proportion after on-pump CABG of 40% and accepting a risk of type I and II errors of 5% and 20%, respectively. Consequently, at least 330 patients had to be included.¹⁵ For the primary outcome as well as other outcomes analyzed in the present 30-day follow-up, the actual event proportions were lower than the estimated proportions used for the sample size calculation. The sample size calculation was based on 1-year event rates, and therefore both significant and insignificant *P* values for the 30-day results should be interpreted conservatively.

All of the data were analyzed according to intention-to-treat (ie, based on treatment allocation). Because of some crossover patients in both groups, we also report "treatment-received" analysis according to the intervention actually received. Dichotomous data are presented as numbers with percentages and were compared with the χ^2 statistic. Means are presented with 1 SD and compared with a 2-sample *t* test. Nonnormally distributed continuous variables are presented as medians with the interquartile range and compared with a Mann-Whitney test. The primary outcome measure and its individual components were analyzed with χ^2 statistic or Fisher exact test and expressed as relative risk with 95% confidence interval.

Results

Patient Characteristics and In-Hospital Outcomes

From April 2002 through March 2006, 2578 patients were referred for isolated CABG at Rigshospitalet. Of these, 341 patients were included in the trial. The reasons for exclusion are shown in the Figure. Two randomized patients never underwent CABG. One declined treatment and was discharged without coronary intervention. The other was diagnosed as having lung cancer on the day of randomization. Both patients were excluded in the data analysis without violating the intention-to-treat principle.¹⁶

Preoperative characteristics were well balanced across the 2 intervention groups (Table 1). Only 5 patients were younger than 65 years. Nearly 20% had diabetes mellitus, and more than one third were women. The mean EuroSCORE was 6.9

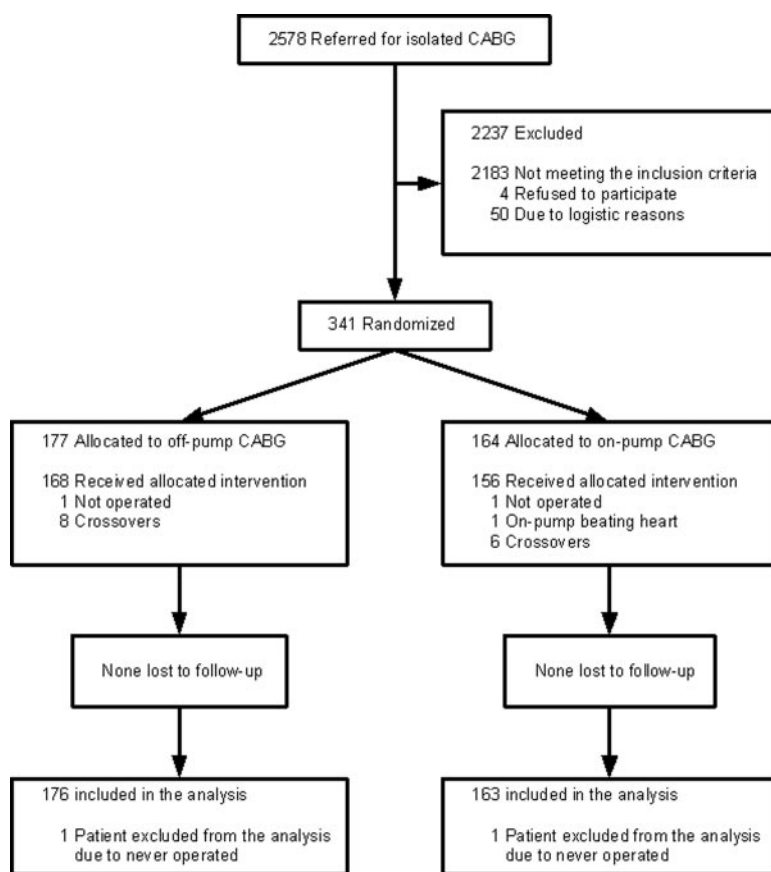


Figure. Flow diagram of BBS trial.

in both groups, and 80% in both groups had a score >5 , indicating high risk. The predicted 30-day mortality according to the Society of Thoracic Surgeons risk score was 3.1% in the off-pump group and 3.0% in the on-pump group.

Eight patients (4.5%) allocated to off-pump CABG crossed over to on-pump CABG. The reasons were as follows: unstable hemodynamic ($n=3$), intraoperative transesophageal echocardiography showing aortic valve disease requiring repair ($n=1$), intraoperative recognition of left ventricular aneurysm requiring surgical repair ($n=1$), not operated on by a trial surgeon because of logistics ($n=2$), and anesthesiologist unwilling to participate in off-pump surgery ($n=1$). In the on-pump group, 6 patients (3.7%) crossed over and were operated on with the use of the off-pump technique, and 1 patient was operated on with the on-pump technique but without aortic cross-clamping and cardioplegic arrest (on-pump beating heart). In all 7 patients, the reason for conversion was intraoperative discovery of a too-heavy calcified ascending aorta, making it too hazardous to cross-clamp.

Table 2 reveals that the mean number of grafts per patient was not significantly different between the 2 groups (3.22 versus 3.34; mean difference, -0.13 ; 95% confidence interval, -0.28 to 0.03); however, significantly fewer grafts were performed to the lateral territory of the left ventricle in the off-pump group compared with the on-pump group (mean difference, -0.16 ; 95% confidence interval, -0.29 to -0.04 ; $P=0.01$). Completeness of revascularization did not differ significantly between the 2 intervention groups.

Thirty-day postoperative complications did not differ significantly between the 2 groups (Table 3). New-onset atrial

fibrillation occurred in nearly half of the patients in both groups. No significant differences in time to extubation, prolonged ventilation, or length of stay in the hospital were observed. Eleven percent in the off-pump group versus 15% in the on-pump group stayed >1 day in the intensive care unit. This difference was insignificant.

Primary Outcome

No significant difference was found in the composite primary outcome after 30 postoperative days (Table 4), nor were any of the individual components of the primary outcome significantly different. Treatment-received analysis did not change our results noticeably.

The number of patients with myocardial infarction was nearly doubled in the on-pump group (15 versus 9); however, only 6 patients in the on-pump group versus 5 patients in the off-pump group underwent postoperative coronary angiography because of increased cardiac enzymes. In both groups, 2 patients had graft occlusions.

We also analyzed exclusively patients with a EuroSCORE >5 . This did not in any way change our results (online-only Data Supplement).

Discussion

In the BBS trial, patients with a EuroSCORE ≥ 5 and 3-vessel disease were randomly assigned to undergo off-pump versus on-pump CABG. The primary outcome at 30-day follow-up was not significantly influenced by the type of operation. In agreement with previous randomized trials of off-pump

Table 1. Preoperative Data*

Variable	Off-Pump (n=176)	On-Pump (n=163)
Age, mean (SD), y	76.1 (5.2)	75.6 (4.9)
Age >65 y	172 (98)	162 (99)
Body mass index, mean (SD)	26.3 (4.1)	27.1 (4.5)
Women	62 (35)	59 (36)
Hypertension	84 (48)	87 (53)
Diabetes mellitus	31 (18)	30 (18)
Myocardial infarction within 90 d	98 (56)	94 (58)
Extracardiac arteriopathy†	55 (31)	53 (33)
COPD	19 (11)	13 (8.0)
Current smoker	36 (21)	27 (17)
Stroke	21 (12)	28 (17)
Transient ischemic attack	10 (5.7)	7 (4.3)
Renal failure	8 (4.5)	5 (3.1)
Ejection fraction		
Good (>50%)	89 (51)	83 (51)
Moderate (30%–50%)	87 (49)	80 (49)
EuroSCORE, mean (SD), %	6.9 (1.7)	6.9 (1.6)
STS risk score, mean (SD), %	3.1 (1.4)	3.0 (1.4)
Angioplasty	9 (5.1)	7 (4.3)
Stent	5 (2.8)	4 (2.5)
CCS class 3/4	49 (28)	43 (26)
NYHA class III/IV	51 (29)	48 (29)

COPD indicates chronic obstructive pulmonary disease; STS, Society of Thoracic Surgeons; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association.

*Values are numbers (percentages) unless stated otherwise.

†Any 1 or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries, or carotids.

versus on-pump CABG in lower-risk patients, we found no significant difference in mortality, myocardial infarction, or stroke.^{2,17–19} A relatively high rate of postoperative complications occurred in our high-risk patients, but off-pump CABG did not result in a significant reduction in postoperative morbidity. The average number of grafts per patients was similar after off-pump and on-pump surgery (3.22 versus 3.34), but, in general, fewer grafts were performed to the lateral territory of the heart after off-pump surgery.

In several observational studies and registry data in which detailed statistical analyses were used, mortality and morbidity have been found to be significantly reduced after off-pump CABG compared with on-pump CABG in high-risk patients (eg, patients with advanced age or cardiac and systemic comorbidity).^{8,12–14,20} The results of our randomized trial are in contrast to these findings. Overall 30-day mortality in our trial was 4.4%, which was less than the predicted mortality rate of 7% according to the EuroSCORE but in agreement with the predicted 3.1% according to the Society of Thoracic Surgeons risk score. The operative mortality in the on-pump group in some observational studies was considerably higher than the 5.5% observed in our trial. Selection bias may be a potential reason for the difference between

Table 2. Intraoperative Data

Variable	Off-Pump (n=176)	On-Pump (n=163)	P
Crossover, n (%)	8 (4.5)	6 (3.7)	0.79
Operation time, mean (SD), min	162.7 (47.8)	156.9 (38.1)	0.22
ECC, mean (SD), min		64.6 (28.5)	
Cross-clamp, mean (SD), min		37.6 (10.7)	
Grafts per patient, mean (SD)	3.22 (0.72)	3.34 (0.76)	0.11
Graft per territory			
Anterior wall, mean (SD)	1.36 (0.51)	1.32 (0.52)	0.42
Lateral wall, mean (SD)	0.97 (0.58)	1.14 (0.58)	0.01
Posterior wall, mean (SD)	0.88 (0.47)	0.89 (0.54)	0.87
LIMA to LAD, %	95	93	0.65
Complete revascularization, %	65.3	67.5	0.73

ECC indicates extracorporeal circulation; LIMA, left internal mammary artery; LAD, left anterior descending coronary artery.

off-pump and on-pump surgery seen in the observational studies. Our findings underscore the potential dangers in using observational studies to try to determine the benefits of interventions.

Postoperative stroke is a serious complication after CABG. In both observational studies and a meta-analysis of randomized trials, off-pump surgery has been associated with a decrease in postoperative stroke.^{5,13,20} The meta-analysis of randomized trials has included mainly patients with 1- and 2-vessel disease. Because all of the patients included in our

Table 3. 30-Day Postoperative Outcomes*

Variable	Off-Pump (n=176)	On-Pump (n=163)	P
Hyperdynamic shock	0	0	1.00
Postoperative need for inotropics	39 (22)	35 (22)	0.90
Need of intra-aortic balloon pump	1 (0.6)	0 (0.0)	1.00
Need for pacing >24 h	12 (6.8)	13 (8.0)	0.84
New onset of atrial fibrillation	75 (43)	71 (44)	0.91
Renal complication	21 (12)	20 (12)	1.00
Hemodialysis	7 (4.0)	8 (4.9)	0.79
Reoperation during index admission			
Reoperation for bleeding	9 (5.1)	4 (2.4)	0.26
Reoperation for other causes	5 (2.8)	7 (4.3)	0.56
Pneumonia	16 (9.1)	16 (9.8)	0.86
Prolonged ventilation†	7 (4.0)	11 (6.7)	0.34
Time to extubation, median (IQR), h	8 (6–13)	9 (6–13)	0.70
Length of stay in ICU >1 d	20 (11)	25 (15)	0.34
Length of stay in hospital, median (IQR), d	7 (6–9)	7 (6–9)	0.57

IQR indicates interquartile range; ICU, intensive care unit.

*Values are numbers (percentages) unless stated otherwise.

†Respiratory insufficiency requiring intubation >24 h.

Table 4. Primary Outcome After 30 Days

Variable	Off-Pump (n=176)	On-Pump (n=163)	RR	95% CI	P
Composite primary outcome*	27 (15)	30 (18)	0.83	0.52–1.34	0.47
All-cause mortality	6 (3.4)	11 (6.7)	0.51	0.19–1.34	0.21
Myocardial infarction	9 (5.1)	15 (9.2)	0.56	0.25–1.24	0.20
Cardiac arrest with successful resuscitation	2 (1.1)	3 (1.8)	0.62	0.10–3.65	0.67
Low cardiac output syndrome	7 (4.0)	10 (6.1)	0.65	0.25–1.66	0.46
Stroke	7 (4.0)	6 (3.7)	1.08	0.37–3.15	1.00
Coronary reintervention†	1 (0.6)	3 (1.8)	0.31	0.03–2.94	0.36

Values are numbers (percentages). RR indicates relative risk; CI, confidence interval.

*All-cause mortality, acute myocardial infarction, cardiac arrest with successful resuscitation, low cardiac output syndrome/cardiogenic shock, stroke, and coronary reintervention.

†Coronary artery bypass grafting or percutaneous coronary intervention.

trial had 3-vessel disease, manipulation of the heart and aorta may have been more extensive in the off-pump group. In addition, proximal anastomoses were usually performed with the use of the site-biting aorta clamp, which may explain the apparent absence of benefit after off-pump surgery. A subgroup of 120 patients underwent neurocognitive testing.²¹ These results have been reported previously; however, after 3 months, no significant difference in cognitive dysfunction was observed in off-pump versus on-pump CABG patients.²¹

The number of patients with postoperative myocardial infarction was higher than reported in observational studies of high-risk patients, which is probably explained by differences in definitions.^{12,20} In a propensity-matched study of 1020 high-risk patients (EuroSCORE ≥ 6), Calafiore et al²⁰ reported a 30-day event rate of myocardial infarction of 2% after off-pump and 2.5% after on-pump CABG. Myocardial infarction was defined as enzymatic elevation, ECG sign of necrosis, new akinetic segment(s) at echocardiogram, and non-K-related ventricular arrhythmias. Al-Ruzzeh et al¹² retrospectively studied 1398 high-risk patients (EuroSCORE ≥ 5) and found that 0.7% in the off-pump group compared with 3.4% in the on-pump group had myocardial infarction. Definition of myocardial infarction was new Q waves in ECG, creatine kinase-MB >50 $\mu\text{g/L}$ with ECG changes, or creatine kinase-MB >70 $\mu\text{g/L}$ without ECG changes. Compared with these studies, our definition of myocardial infarction seemed more sensitive, especially beyond the first 48 hours after the operation. In accordance with these studies as well as others, we observed a trend toward a reduction in myocardial infarction after off-pump surgery.^{12,13,20}

Avoidance of cardiopulmonary bypass and thereby non-pulsatile flow to the kidney did not result in a reduction in renal insufficiency or hemodialysis in the off-pump group. This may be due to the increased risk of hemodynamic instability during off-pump surgery seen in high-risk patients with 3-vessel disease, generalized vascular disease, and reduced left ventricular function.

In accordance with the results from randomized trials by van Dijk et al,¹⁷ Al-Ruzzeh et al,¹ and Puskas et al,¹⁹ the incidence of postoperative atrial fibrillation did not differ significantly between the 2 operation groups. In these trials, atrial fibrillation was experienced by 20% of the patients. In our trial, however, nearly half of the patients experienced an

episode with postoperative atrial fibrillation. This difference may well be explained by the difference in patient population because a predictor of postoperative atrial fibrillation is advanced age.²² In contrast, the most recent meta-analysis found that off-pump CABG significantly reduced postoperative atrial fibrillation.⁵

We found that median hospital length of stay was 7 days in both intervention groups. In previous randomized trials, off-pump CABG reduced hospitalization by ≈ 1 day, but mean length of stay was different in all of the trials.^{1,17,19} This indicates either difference in patient population or more likely that indications for discharge are subjective and driven by tradition. Five percent of the off-pump patients underwent reoperation for bleeding, which was double the rate of the on-pump patients. Heparin was not routinely reversed with protamine sulfate, which may explain the increase in reoperation for bleeding in the off-pump group.

Debate about whether off-pump CABG results in inadequate revascularization compared with on-pump CABG is ongoing.²³ The average number of grafts per patient has been shown in some randomized trials to be similar,^{17,19,24} but a meta-analysis of all randomized trials found that off-pump CABG resulted in significantly fewer grafts.⁵ It is troublesome to perform anastomosis to the lateral territory of the left ventricle during off-pump surgery; however, in most randomized trials, patients with the need for grafts to the marginal branches were excluded or underrepresented. We found that patients undergoing off-pump CABG had significantly fewer grafts performed to the lateral territory. Because all of the patients in the trial ought to have a graftable marginal branch as judged by the preoperative coronary angiography, the difference observed must relate to the operative procedure. Whether surgeons performing off-pump surgery in general have a tendency to assess a coronary artery unfeasible for grafting due to severe atherosclerosis or desist from grafting for technical reasons is unclear.

The BBS trial has several strengths. First, the background for conducting the trial was recently highlighted in a systematic review.⁵ Second, the protocol has been described in detail in a design article.¹⁵ Third, we used central and stratified randomization. Fourth, $\approx 85\%$ of eligible patients were randomized and included in the trial. Fifth, outcomes were assessed by an independent adjudication committee blinded

to allocated treatment, and data analysis and conclusions were drawn before blinding was broken.²⁵ This reduces the risk of bias seen in trials with an open-label design.²⁶ Furthermore, no patients were lost to follow-up.

Although the BBS trial was designed with high methodological quality and hence low risk of systematic errors (bias),²⁷ it does have limitations. The trial was a single-center trial, and all of the operations were performed by 3 surgeons highly experienced in both off-pump and on-pump surgery. This may influence the generalizability, but it also increases internal validity. We cannot exclude that our results are under the influence of some degree of performance bias because surgeons had to remain unblinded and because we chose to inform both patients and healthcare providers about the treatment allocation. Because of the limited sample size, we were not able to reveal small but clinically relevant differences between the procedures. Furthermore, our results represent only 30-day postoperative results, and long-term follow-up should be performed.¹⁵

In conclusion, off-pump CABG seems to be a safe procedure even in high-risk patients with no significant difference in 30-day mortality and other outcomes compared with on-pump CABG. Any expected short-term benefits from off-pump CABG were not evident from this trial. Off-pump CABG may carry a risk of incomplete revascularization of the lateral territory of the left ventricle, which could affect long-term prognosis.

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Disclosures

None.

References

1. Al-Ruzzeh S, George S, Bustami M, Wray J, Ilsley C, Athanasios M, Amrani M. Effect of off-pump coronary artery bypass surgery on clinical, angiographic, neurocognitive, and quality of life outcomes: randomised controlled trial. *BMJ*. 2006;332:1365.
2. Angelini GD, Taylor FC, Reeves BC, Ascione R. Early and midterm outcome after off-pump and on-pump surgery in Beating Heart Against Cardioplegic Arrest Studies (BHACAS 1 and 2): a pooled analysis of two randomised controlled trials. *Lancet*. 2002;359:1194–1199.
3. Nathoe HM, van Dijk D, Jansen EW, Suyker WJ, Diephuis JC, van Boven WJ, de la Riviere AB, Borst C, Kalkman CJ, Grobbee DE, Buskens E, de Jaegere PP. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. *N Engl J Med*. 2003;348:394–402.
4. Puskas JD, Williams WH, Mahoney EM, Huber PR, Block PC, Duke PG, Staples JR, Glas KE, Marshall JJ, Leimbach ME, McCall SA, Petersen RJ, Bailey DE, Weintraub WS, Guyton RA. 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;291:1841–1849.
5. Moller CH, Penninga L, Wetterslev J, Steinbrüchel DA, Gluud C. Clinical outcomes in randomized trials of off- vs. on-pump coronary artery bypass surgery: systematic review with meta-analyses and trial sequential analyses. *Eur Heart J*. 2008;29:2601–2616.
6. Society of Thoracic Surgeons National Adult Cardiac Database: Spring Report 2007. Durham, NC: Duke Clinical Research Institute; June 2007.
7. Filsoofi F, Rahmanian PB, Castillo JG, Chikwe J, Adams DH. Excellent results of contemporary coronary artery bypass grafting with systematic application of modern perioperative strategies. *Heart Surg Forum*. 2007;10:E349–E356.
8. Gaudino M, Glieda F, Alessandrini F, Nasso G, Pragliola C, Luciani N, Morelli M, Possati G. High risk coronary artery bypass patient: incidence, surgical strategies, and results. *Ann Thorac Surg*. 2004;77:574–579.
9. Ohata T, Kaneko M, Kuratani T, Ueda H, Shimamura K. Using the EuroSCORE to assess changes in the risk profiles of the patients undergoing coronary artery bypass grafting before and after the introduction of less invasive coronary surgery. *Ann Thorac Surg*. 2005;80:131–135.
10. Tuman KJ, McCarthy RJ, Najafi H, Ivankovich AD. Differential effects of advanced age on neurologic and cardiac risks of coronary artery operations. *J Thorac Cardiovasc Surg*. 1992;104:1510–1517.
11. Nalysnyk L, Fahrbach K, Reynolds MW, Zhao SZ, Ross S. Adverse events in coronary artery bypass graft (CABG) trials: a systematic review and analysis. *Heart*. 2003;89:767–772.
12. Al Ruzzeh S, Nakamura K, Athanasios T, Modine T, George S, Yacoub M, Ilsley C, Amrani M. Does off-pump coronary artery bypass (OPCAB) surgery improve the outcome in high-risk patients? A comparative study of 1398 high-risk patients. *Eur J Cardiothorac Surg*. 2003;23:50–55.
13. Mack MJ, Pfister A, Bachand D, Emery R, Magee MJ, Connolly M, Subramanian V. Comparison of coronary bypass surgery with and without cardiopulmonary bypass in patients with multivessel disease. *J Thorac Cardiovasc Surg*. 2004;127:167–173.
14. Stamou SC, Jablonski KA, Hill PC, Bafi AS, Boyce SW, Corso PJ. Coronary revascularization without cardiopulmonary bypass versus the conventional approach in high-risk patients. *Ann Thorac Surg*. 2005;79:552–557.
15. Moller CH, Jensen BO, Gluud C, Perko MJ, Lund JT, Andersen LW, Madsen JK, Hughes P, Steinbrüchel DA. The Best Bypass Surgery Trial: rationale and design of a randomized clinical trial with blinded outcome assessment of conventional versus off-pump coronary artery bypass grafting. *Contemp Clin Trials*. 2007;28:540–547.
16. Fergusson D, Aaron SD, Guyatt G, Hebert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ*. 2002;325:652–654.
17. van Dijk D, Nierich AP, Jansen EW, Nathoe HM, Suyker WJ, Diephuis JC, van Boven WJ, Borst C, Buskens E, Grobbee DE, Robles de Medina EO, de Jaegere PP. Early outcome after off-pump versus on-pump coronary bypass surgery: results from a randomized study. *Circulation*. 2001;104:1761–1766.
18. Straka Z, Widimsky P, Jirasek K, Stros P, Votava J, Vanek T, Brucek P, Kolesar M, Spacek R. Off-pump versus on-pump coronary surgery: final results from a prospective randomized study PRAGUE-4. *Ann Thorac Surg*. 2004;77:789–793.
19. Puskas JD, Williams WH, Duke PG, Staples JR, Glas KE, Marshall JJ, Leimbach M, Huber P, Garas S, Sammons BH, McCall SA, Petersen RJ, Bailey DE, Chu H, Mahoney EM, Weintraub WS, Guyton RA. Off-pump coronary artery bypass grafting provides complete revascularization with reduced myocardial injury, transfusion requirements, and length of stay: a prospective randomized comparison of two hundred unselected patients undergoing off-pump versus conventional coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2003;125:797–808.
20. Calafiore AM, Di MM, Canosa C, Di GG, Iaco AL, Contini M. Early and late outcome of myocardial revascularization with and without cardiopulmonary bypass in high risk patients (EuroSCORE > or = 6). *Eur J Cardiothorac Surg*. 2003;23:360–367.
21. Jensen BO, Hughes P, Rasmussen LS, Pedersen PU, Steinbrüchel DA. Cognitive outcomes in elderly high-risk patients after off-pump versus conventional coronary artery bypass grafting: a randomized trial. *Circulation*. 2006;113:2790–2795.

22. Amar D, Shi W, Hogue CW Jr, Zhang H, Passman RS, Thomas B, Bach PB, Damiano R, Thaler HT. Clinical prediction rule for atrial fibrillation after coronary artery bypass grafting. *J Am Coll Cardiol*. 2004;44:1248–1253.
23. Briffa N. Off pump coronary artery bypass: a passing fad or ready for prime time? *Eur Heart J*. 2008;29:1346–1349.
24. Kobayashi J, Tashiro T, Ochi M, Yaku H, Watanabe G, Satoh T, Tagusari O, Nakajima H, Kitamura S. Early outcome of a randomized comparison of off-pump and on-pump multiple arterial coronary revascularization. *Circulation*. 2005;112:1338–1343.
25. Gotzsche PC. Blinding during data analysis and writing of manuscripts. *Control Clin Trials*. 1996;17:285–290.
26. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Ann Intern Med*. 2001;135:982–989.
27. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, Gluud C, Martin RM, Wood AJ, Sterne JA. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ*. 2008;336:601–605.

CLINICAL PERSPECTIVE

Observational studies comparing off-pump with on-pump coronary artery bypass grafting (CABG) have indicated that high-risk patients will benefit the most from avoiding cardiopulmonary bypass; however, this has not been assessed previously in a randomized trial. In the Best Bypass Surgery trial (n=341), off-pump compared with on-pump CABG in patients with 3-vessel disease and a EuroSCORE ≥ 5 did not result in a significant difference in the 30-day composite outcome including all-cause mortality, acute myocardial infarction, cardiac arrest with successful resuscitation, low cardiac output syndrome/cardiogenic shock, stroke, and coronary reintervention, nor were any of the individual components of the composite outcome significantly different. Off-pump CABG resulted in fewer grafts to the lateral territory of the left ventricle, although the overall number of grafts did not differ significantly between the 2 groups. The Best Bypass Surgery trial found that both off-pump and on-pump CABG can be performed in high-risk patients with low 30-day mortality and morbidity. Off-pump CABG seems to carry a risk of incomplete revascularization, and this may affect long-term mortality and morbidity.

SUPPLEMENTAL MATERIAL

Primary Outcome after 30 days in patients with EuroSCORE >5

Variable	Off-pump (n =140)		On-pump (n =130)		RR	95% CI	P
Composite primary outcome*	20	(14)	25	(19)	0.74	0.43-1.27	0.32
All-cause mortality	5	(3.6)	9	(6.9)	0.52	0.18-1.50	0.28
Myocardial infarction	6	(4.3)	12	(9.2)	0.46	0.18-1.20	0.14
Cardiac arrest with successful resuscitation	2	(1.4)	2	(1.5)	0.92	0.13-6.51	1.00
Low cardiac output syndrome	5	(3.6)	9	(6.9)	0.51	0.18-1.50	0.28
Stroke	6	(4.3)	6	(4.6)	0.93	0.31-2.81	1.00
Coronary reintervention [‡]	1	(0.7)	2	(1.5)	0.46	0.04-5.06	0.61

Values are numbers (percentages)

* All-cause mortality, acute myocardial infarction, cardiac arrest with successful resuscitation, low cardiac output syndrome/cardiogenic shock, stroke, and coronary reintervention

[‡] Coronary artery bypass surgery or percutaneous coronary intervention