Effect of off-pump coronary artery bypass surgery on clinical, angiographic, neurocognitive, and quality of life outcomes: randomised controlled trial

Sharif Al-Ruzzeh, Shane George, Mahmoud Bustami, Jo Wray, Charles Ilsley, Thanos Athanasiou, Mohamed Amrani

Abstract

Objective To compare the clinical, angiographic, neurocognitive, and quality of life outcomes of off-pump coronary artery bypass surgery with conventional coronary artery bypass grafting surgery using cardiopulmonary bypass.

Design Randomised controlled clinical trial.

Setting Tertiary cardiothoracic centre in Middlesex, England.

Participants 168 patients (27 women) requiring primary isolated coronary artery bypass grafting surgery.

Interventions Patients were randomised to conventional coronary artery bypass grafting surgery using cardiopulmonary bypass (n = 84) or off-pump coronary artery bypass surgery (n = 84), carried out by one surgeon. Angiographic examination was carried out at three months postoperatively. Neurocognitive tests were carried out at baseline and at six weeks and six months postoperatively.

Main outcome measures Clinical outcome, graft patency at three months, neurocognitive function at six weeks and six months, and health related quality of life.

Results Graft patency was evaluated by angiography in 151 (89.9%) patients and was similar between the cardiopulmonary bypass and off-pump groups (risk difference −1%, 95% confidence interval −5% to 4%), with the off-pump group considered the treatment group. Patients in the off-pump group required fewer blood transfusions (1.7 units vs 1.0 unit, P = 0.02), shorter duration of mechanical ventilation (7.7 hours vs 3.9 hours, P = 0.03), and shorter hospital stay (10.8 days vs 8.9 days). Scores for neurocognitive function showed a significant difference in three memory subtests at six weeks and two memory subtests at six months in favour of the off-pump group.

Conclusions Patients who underwent off-pump coronary artery bypass surgery showed similar patency of grafts, better clinical outcome, shorter hospital stay, and better neurocognitive function than patients who underwent conventional coronary artery bypass grafting surgery using cardiopulmonary bypass.

Introduction

Coronary artery bypass grafting surgery has classically been carried out through the median sternotomy approach using cardiopulmonary bypass with cardiac arrest. This method provides the most ideal operative field for a motionless and bloodless heart surface, with easy access to epicardial coronary arteries. Efforts were made to move to off-pump coronary artery bypass surgery because of well documented side effects of cardiopulmonary bypass. Concerns were raised, however, about the rate of graft patency and lack of uniformity in technical approach. Conflicting data from randomised controlled trials raised further controversies but did not tackle all the relevant aspects. A recent meta-analysis of randomised and observational studies concluded that the findings of randomised trials contradicted each other to some extent and, aside from atrial fibrillation, the statistically significant reductions in short term mortality and morbidity shown by observational studies could not be proved. These discrepancies could be attributed to differing patient selection or study methods and, more importantly, reliance on different surrogate end points.

In our centre we have used a systematic approach in adopting off-pump coronary artery bypass surgery. We shifted to the non-selective use of the off-pump technique for all patients requiring primary isolated coronary artery bypass grafting surgery and found similar clinical outcome with a low conversion rate. We further analysed the initial experience with off-pump coronary artery bypass surgery in the United Kingdom and showed a reduction in risk stratified morbidity and mortality at a multicentre level. We also retrospectively analysed our data on specific groups of patients, including elderly patients, high risk patients, and patients with ischaemic left ventricular dysfunction or sequential grafts. Having gone through the learning curve, we aimed, in this study, to compare the two techniques for clinical outcome, graft patency (evaluated by angiography), neurocognitive function, and health related quality of life.

Patients and methods

We prospectively randomised 168 patients to conventional coronary artery bypass grafting surgery using cardiopulmonary bypass (n = 84) or to off-pump coronary artery bypass grafting surgery (n = 84; figure). Randomisation used minimisation in an Excel program to balance the groups for the following factors: sex, left ventricular function, diabetes, and age. Assignment to either on-pump or off-pump, was done on the operation day with the surgeon being informed immediately before the procedure.

Blinding of the surgeon was not possible. All other staff were blinded: medical, paramedical, and nursing staff on the intensive therapy unit, the ward staff, and the study staff, including the cardiologist who carried out the angiography and commented on the angiograms and the psychologist who carried out the tests for neurocognitive function. Patients and their relatives were also
blinded to the procedure. Clinical decisions on patient management on the intensive therapy unit and the ward were taken by blinded staff and were based on local protocols and guidelines, including decisions on extubation, blood transfusion, and discharge. To ensure complete blinding the type of procedure was not stated in the clinical notes or in any correspondence. If a clinical necessity for disclosing information arose then the nominated principal investigator (SA) was contacted and given the name and study number of the patient. This was required on only one occasion, for a patient who died at six days postoperatively in the off-pump group.

We excluded patients with severe left ventricular dysfunction (ejection fraction < 30%), renal failure (serum creatinine ≥ 180 μmol or active renal replacement therapy), those who needed concomitant cardiac surgery using cardiopulmonary bypass, those who needed emergency surgery after angiographic intervention, those who were unable to effectively communicate in English (a requirement for neurocognitive testing), those who did not accept to undergo angiography after surgery, and those who had isolated single vessel disease requiring single coronary bypass.

The primary end points were angiographic graft patency (equivalence trial) and neurocognitive function (efficacy trial). The secondary end points were clinical outcome and health related quality of life.

Perioperative myocardial infarction was indicated by the presence of new Q waves on the electrocardiogram, a creatine kinase-muscle brain concentration > 50 ng/ml with electrocardiographic changes, or a creatine kinase-muscle brain concentration > 70 ng/ml without electrocardiographic changes. Atrial fibrillation was confirmed by 12 lead electrocardiography. A neurological deficit was considered to be a cerebrovascular accident if focal neurological signs and symptoms persisted for more than 24 hours and this was confirmed by computed tomography; but was considered a transient ischaemic attack if the focal neurological signs and symptoms lasted less than 24 hours. Renal impairment was diagnosed clinically on the basis of laboratory results or by the requirement of haemofiltration. Blood transfusion was given during hospital stay if the haemoglobin level was less than 80 g/l. Blood products, including fresh frozen plasma and platelets, were given as indicated by thromboelastography if the patient was bleedning on arrival at the intensive therapy unit.
Surgical technique
One surgeon (MA) carried out the operations in both arms of the study. Anaesthesia was induced using propofol 1-2 mg/kg, pancuronium 0.1 mg/kg, and fentanyl 8-15 μg/kg and maintained by air and oxygen and propofol 2-3 mg/kg/hour. Normothermia was maintained with warm intravenous fluids, a heating mattress, a humidified airway, and a warm operating theatre.

The heart was exposed using a standard midline sternotomy incision. After the internal thoracic arteries had been harvested the pericardium was opened using an inverted T-shaped incision. To minimise haemodynamic compromise the right pleural space was opened to create a space for the rotated and vertically positioned heart.

Either or both of the internal thoracic arteries was harvested as a wide pedicle including artery, vein, muscle, fascia, and adipose tissue and was sprayed with diluted papaverine solution (50 mg/20 ml normal saline). The left radial artery was used preferentially regardless of hand dominance, as this allows simultaneous harvesting of the left internal thoracic artery. In our hospital we use a flushing solution of 50 mg phenoxybenzamine, 20 ml of blood, and 2000 units of heparin.

Off-pump technique
The heart was stabilised using the suction-irrigation tissue stabilisation system Octopus 3 (Medtronic, Minneapolis, USA). A deep pericardial retraction suture helped position the heart for grafting. The technique is described in detail elsewhere. Anticoagulation was achieved with 150 U/kg of heparin. If required, heparin was supplemented to maintain the activated clotting time above 250 seconds and was reversed by protamine at the end of the procedure. Blood pressure was continually optimised during the procedure, and the mean arterial pressure was maintained above 50 mm Hg by repositioning the heart and by intravenous fluids or selective use of vasoconstrictors, or both.

Cardiopulmonary bypass technique
Cardiopulmonary bypass was instituted with a single right atrial two stage cannula and an ascending aorta perfusion cannula. Standard bypass management included membrane oxygenators, arterial line filters, systemic hypothermia down to 32°C, and non-pulsatile flow of 2.4 l/min/m², with a mean arterial pressure greater than 50 mm Hg. The myocardium was protected by using intermittent antegrade cold blood cardioplegia (4:1 blood to crystalloid ratio). Anticoagulation was achieved using 300 U/kg of heparin. If required, heparin was supplemented to maintain the activated clotting time above 480 seconds and was reversed by protamine at the end of the procedure.

Angiography
Participants were booked for angiography three months after surgery. Each of the grafts was engaged and two orthogonal views of each were obtained along with two orthogonal views of each of the coronary arteries. If an aortocoronary graft could not be identified, aortography was carried out. Subclavian arteriography was carried out if an internal thoracic artery graft could not be identified, aortography was carried out. Subclavian arteriography was performed if an internal thoracic artery graft could not be identified, aortography was carried out. Subclavian arteriography was carried out if an internal thoracic artery graft could not be identified. The angiographic patency of the grafts was graded as either patent (graft open all the way through) or occluded (graft completely blocked even if a patent stump was seen at the proximal end using subclavian arteriography or aortography). Angiograms were obtained and commented on by one cardiologist (MB), who was blinded to the study arm.

Neurocognitive function, mood state, and health related quality of life
The neurocognitive tests were planned in accordance with the statement of consensus of assessment of neurobehavioural outcomes after cardiac surgery. We used a battery composed of 11 memory subtests of the Wechsler memory scale (third edition) and two intelligence subtests of the Wechsler adult intelligence scale (third edition) to assess the neurocognitive performance of the two groups at three time points (day before surgery, six weeks postoperatively, six months postoperatively). The memory subsets comprised logical memory 1 (total and thematic), logical memory 2 (total and thematic), faces, family pictures, verbal paired associates, letter-number sequencing, digit span-forward, digit span-backward, mental control, trail A, and trail B. The intelligence subtests comprised vocabulary and block design.

The consensus also recommended an assessment of mood state as this is believed to influence neurocognitive performance. The hospital anxiety and depression scale was therefore administered with the neurocognitive tests. This scale consists of 14 items and was developed to assess anxiety and depression in an outpatients' setting irrespective of physical symptoms. Seven items measure anxiety and seven measure depression. Each item is scored from 0 to 3, with total scores ranging from 0 to 21 for the anxiety and depression subscales. Higher scores indicate greater anxiety and depression.

We assessed health related quality of life at the same time as the neurocognitive tests using the World Health Organization quality of life questionnaire. This questionnaire assesses 100 items in the six domains of physical health, psychological health, level of independence, social relationships, environment, and spirituality. Each item is scored from 0 to 5.

Statistical analysis
We designed our trial with adequate power (80%; alpha level of 0.05) to detect an absolute difference in angiographic patency as small as 5% between the two groups in either direction. We used the Blackwelder's method¹¹ for the power calculation, and baseline or expected patency rate was considered as high as 96%. This rate has been reported when arterial grafts were commonly used,¹² which has been the routine practice in our institution. Evidence from the literature suggested that a smaller number of patients would be required to show a difference in neurocognitive function between the two groups.¹³

We expressed continuous variables as means and standard deviations. To test for the correlation between these variables we used Pearson's correlation test. We compared categorical variables using Fisher's exact test or the χ² test, and we compared group means using Student's t test or the Mann Whitney U test.

To analyse scores on the hospital anxiety and depression scale and the World Health Organization quality of life questionnaire, we carried out repeated measures analysis. Analysis of covariance was used to analyse the neurocognitive test scores. Analysis of covariance has a high statistical power and adjusts each participant's follow-up measurement according to his or her baseline measurement.¹⁶ It also prevents regression to the mean, which can make natural variation in repeated data seem like a real change.¹⁷

We considered differences significant when P values were less than or equal to 0.05. We analysed data using SPSS version 12.0 for Windows and Intercooled Stata version 8.0 for Windows.
Results

Baseline characteristics were similar between patients assigned to conventional coronary artery bypass grafting surgery and those assigned to off-pump coronary artery bypass grafting surgery (table 1). No cross over occurred between the two groups. Table 2 shows the clinical outcome data, including morbidity and mortality. One patient allocated to off-pump surgery died in hospital six days after surgery due to pulmonary embolism (confirmed by postmortem examination). In-hospital mortality was equivalent to mortality at six weeks (42 days); no further patients died between the two time points.

Patients in the cardiopulmonary bypass group required significantly longer mechanical ventilation than patients in the off-pump group (7.7 hours vs 3.9 hours, \( P = 0.03 \)), significantly more blood transfusions (1.7 units vs 1.0 unit, \( P = 0.02 \)), and longer stay in hospital (10.8 days vs 8.9 days, \( P = 0.03 \)).

**Angiographic outcome**

Overall 151 (89.9%) patients underwent angiography three months postoperatively: 75 in the cardiopulmonary bypass group and 76 in the cardiopulmonary bypass group, providing 461 grafts for analysis (table 3). The blocked grafts are listed in brackets in table 3 after the total number of grafts to each particular target coronary artery of the heart.

In total, 17 of 229 (7.3%) grafts were blocked in the cardiopulmonary bypass group, and 18 of 229 (7.9%) grafts were blocked in the off-pump group. Thus, cardiopulmonary bypass group had an angiographic patency of 92.7% compared with 99.1% for the off-pump group (odds ratio 1.08, 95% confidence interval 0.54 to 2.15; risk difference = 1% – 5% to 4%), with the off-pump group considered the treatment group.

**Neurocognitive function, mood state, and health related quality of life**

At six weeks 159 patients completed the neurocognitive test (79 in the cardiopulmonary bypass group and 80 in the off-pump group) and at six months 145 patients completed the neurocognitive test (72 in the cardiopulmonary bypass group and 73 in the off-pump group; table 4). The off-pump group performed significantly better in three memory subtests at six weeks (verbal paired associates, \( P < 0.001 \); letter-number sequencing, \( P < 0.001 \); and trail A, \( P = 0.01 \)) and in two memory subtests at six months (letter-number sequencing, \( P < 0.001 \); and trail A, \( P < 0.001 \)).

Repeated measures analysis of scores on the hospital anxiety and depression scale at baseline, six weeks, and six months showed no significant difference in mood state (table 5). The repeated measures analysis of the World Health Organization quality of life scores at the same time points showed significant improvement in only social relationships (\( P = 0.04 \); table 5). Although a trend was seen for better scores in the off-pump group in the other five domains, this was not significant.

**Discussion**

Patients who underwent off-pump coronary artery bypass grafting surgery had similar graft patency rates to patients who underwent conventional coronary artery bypass grafting surgery using cardiopulmonary bypass. Patients in the off-pump group, however, needed a shorter stay in hospital, shorter duration of mechanical ventilation in the intensive therapy unit, and fewer blood transfusions, and had better preservation of neurocognitive function at six weeks and six months.

The finding of a significantly shorter period of mechanical ventilation in the off-pump group concurs with some randomised trials but not all. This could be due to several reasons, including statistical methods used for evaluation, the variability in local practice and protocols between centres and teams, and even differences in the type of patients randomised. Despite this contradiction, recent evidence suggests that this difference in ventilation requirements could be more related to myocardial damage, that is, some degree of pump failure, than...
to lung damage caused by cardiopulmonary bypass. The difference in ventilation time was not associated with a difference in stay in the intensive therapy unit. This could be because clinical decisions on discharge were made once or twice daily.

The off-pump group required significantly fewer blood transfusions than the cardiopulmonary bypass group. This was not correlated with blood loss through postoperative chest drainage in the first 24 hours as previously reported, but could be explained by dilution of the patient’s blood by the priming solution. The difference in requirements for blood transfusion between the two groups was not uniform in previous randomised trials, with some reporting a significant difference and others none. We showed that hospital stay was significantly shorter in patients in the off-pump group.

Using coronary angiography, the standard method for qualitative and quantitative assessment of bypass grafts, we showed that patients in the off-pump group had similar patency rates to patients in the cardiopulmonary bypass group. A discrepancy has been found in reported patency rates after off-pump surgery. Graft patency rates at three years were shown by one study to be lower in patients undergoing off-pump surgery. Patency rates of 92% and 54% for left internal thoracic artery and saphenous vein graft with cardiopulmonary bypass surgery compared with 41% and 23%, respectively, with off-pump surgery. These results were ascribed to the surgical technique, comprising occlusion of the coronary target proximal and distal to the anastomotic site using silicon rubber tapes and without adequate stabilisation. Another study showed a significantly lower patency rate for saphenous vein grafts (47.1%) than for internal thoracic arteries (95.7%) in patients followed-up for three years after off-pump surgery. A significantly lower patency of saphenous vein grafts has also been shown both early and at one year after off-pump surgery, but comparable patency of arterial grafts between the off-pump group and cardiopulmonary bypass group. These blocked saphenous vein grafts were explained mainly by the increased procogulant activity in the first 24 hours after off-pump surgery, which could contribute to the risk of venous thrombosis and blockage of aortocoronary grafts. Extending this to recently reported randomised trials, the discrepancy still exists: no difference in patency rates between the two groups (200 patients) at 30 days and one year, with operations carried out by one surgeon; no difference at one year in 70% (25%) patients in a multicentre trial, and a significant difference between the two groups (103 patients), with operations carried out by two surgeons. This was attributed to differences in experience of off-pump bypass surgery between

<table>
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<th>Variable</th>
<th>Left internal thoracic artery</th>
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<td>10</td>
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<td>9</td>
<td>13</td>
<td>24 (5)</td>
<td>77 (7)</td>
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<td>0</td>
<td>28 (5)</td>
<td>33 (3)</td>
<td>62 (8)</td>
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<td>50 (6)</td>
<td>68 (8)</td>
<td>232 (17)</td>
</tr>
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<tr>
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<td>9 (1)</td>
<td>13 (2)</td>
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<td>28 (2)</td>
<td>33 (7)</td>
<td>62 (9)</td>
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<tr>
<td>Total</td>
<td>76 (1)</td>
<td>37 (1)</td>
<td>55 (5)</td>
<td>61 (11)</td>
<td>229 (18)</td>
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</table>

Table 3 Analysis of distal anastomoses studied by angiography in patients assigned cardiopulmonary bypass or off-pump coronary artery bypass (the numbers of blocked grafts are listed in brackets after the total number of grafts to each particular target coronary artery of the heart)
the centres before and during the trials and the conduits used. For example, in the last trial more radial artery grafts were used in the off-pump group and at the time of angiography 24% of them were blocked compared with no blockages in similar grafts in the cardiopulmonary bypass group.10

To minimise or eliminate bias from differences in learning curves, surgeons, centres, and conduits, we gained experience, before starting the trial, from non-selective use of the off-pump technique in more than 500 unselected patients,7 using different types of arterial and venous grafts.11 12

We found that off-pump surgery was associated with better preservation of neurocognitive function at six weeks and six months after surgery. The difference between the two groups was statistically significant in three memory subtests at six weeks and two memory subtests at six months. This deterioration in neurocognitive function happened in the absence of any accompanying change in the mood state, which could have contributed to the difference in performance.9

Since the mid-1990s a fundamental change has occurred in the demographics of patients requiring cardiac surgery. Largely as a result of factors related to increasing age of this group, major neurological complications constituted a growing percentage of serious postoperative morbidity.13 Stroke occurs in 1-3% of patients undergoing cardiac surgery and is mainly due to embolisation by atheromatous debris during manipulation of the diseased aorta.14 However, cognitive impairment, which is predominantly caused by microembolisation of gaseous and particulate matter is a more common form of neurological injury related to coronary artery bypass surgery but at the same time more difficult to assess or quantify than stroke.15 Others have measured the occurrence of microemboli during cardiac surgery using transcranial Doppler ultrasonography, when the microemboli produce a characteristic high intensity transcranial signal.16 The increase in water content of the brain caused by cardiac surgery using transcranial Doppler ultrasonography, when the microemboli produce a characteristic high intensity transcranial signal.16 The increase in water content of the brain caused by cardiac surgery using transcranial Doppler ultrasonography, when the microemboli produce a characteristic high intensity transcranial signal.16

The increase in water content of the brain caused by cardiac surgery using transcranial Doppler ultrasonography, when the microemboli produce a characteristic high intensity transcranial signal.16

Table 5 Repeated measures analysis of scores on hospital anxiety and depression scale and World Health Organization quality of life questionnaire

<table>
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<th>P value</th>
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<td>Psychological</td>
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<td>Level of independence</td>
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<td>Environment</td>
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<td>0.07</td>
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<tr>
<td>Spirituality, religion, personal beliefs</td>
<td>3</td>
<td>0.09</td>
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<tr>
<td>Overall</td>
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normothermic, pH, and even the rate of rewarming, have been evaluated for their effect on neurocognitive performance.40-42 A longitudinal assessment of neurocognitive function in patients after cardiopulmonary bypass surgery showed that the cognitive decline could still be present in 42% at five years after surgery.43 Recent randomised trials comparing the neurocognitive performance of patients after off-pump surgery or cardiopulmonary bypass surgery have reported contradictory results. One trial of 281 patients reported no difference in cognitive outcome at three months, but in a separate report on 219 patients the authors still concluded that early cognitive decline at four days after surgery predicted cognitive outcome at three months more prominently in patients after cardiopulmonary bypass surgery.44 In contrast, two trials, recruiting fewer patients, reported significantly better neurocognitive performances in patients after off-pump surgery.13 45

The difference between those trials was attributed to differences in the statistical methods or tests of neurocognitive performance used.46 To overcome this problem, experts have recommended calculating score change from baseline and then using analysis of covariance to compare changes in mean scores between the group and a control group.47 The major disadvantages of the single case definitions, such as a decline of one standard deviation or 20% change, is that high performers at baseline will be more likely classified as having deteriorated, even in the absence of real change, because of regression to the mean.48 This concept has already been adopted and implemented in large multicentre trials.49

Limitations of the study

An important inherent limitation of our trial is the reliance on surrogate end points, such as graft patency and neurocognitive function, rather than patient outcomes such as myocardial infarction, stroke, and death.50 Carrying out a clinical randomised trial in one centre to assess such patient outcomes is, however, logistically challenging as it requires a large sample size or long patient follow-up, or both.51

Another limitation of our trial is that the power calculation was based on a relatively high expected patency rate (96%), which could have influenced the sample size required for this trial aimed to test equivalence rather than superiority. Despite the inherent weakness of this approach,11 we made every effort to minimise its effect.52

We thank Derek Robinson (Sussex University) for help with statistical planning.

Contributors: SA and CI were principal investigators. SG was responsible for anaesthetic management of the patients, MB carried out the angiography and commented on the angiograms, SA and JW carried out and analysed the neurocognitive tests. TA carried out the statistical analysis. MA was a principal investigator and carried out all the operations in the trial.

Competing interests: None declared.

Ethical approval: This study was approved by the Royal Brompton and Harefield research ethics committee.

5 Al-Ruzzeh S, Nakamura K, Athanasiou T, Moride T, George S, Yacoub M, et al. Does off-pump coronary artery bypass (OPCAB) surgery improve the outcome in high-risk...
What is already known on this topic
Cardiopulmonary bypass is suggested to be a contributing factor to neurocognitive dysfunction after conventional coronary artery bypass grafting surgery.

Concerns were raised about graft patency after off-pump coronary artery bypass grafting surgery, which is at least as safe as conventional coronary artery bypass grafting surgery for clinical outcome.

What this study adds
Rates of graft patency are similar between coronary artery bypass grafting surgery using cardiopulmonary bypass and off-pump coronary artery bypass grafting surgery

Patients in the off-pump bypass group showed better preservation of neurocognitive function at six weeks and six months and better clinical outcomes