

Coronary artery bypass grafting in high-RISk patients randomised to off- or on-Pump surgery: a randomised controlled trial (the CRISP trial)

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Scientific summary

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Scientific summary

Background

Despite advances in medical therapy and percutaneous coronary interventions (PCIs) there is good evidence that coronary artery bypass grafting (CABG) offers superior survival and freedom from repeat intervention in patients with multivessel coronary artery disease (CAD). Conventional CABG uses cardiopulmonary bypass (CPB) ('on-pump') to support the circulation while the heart is temporarily stopped. CPB causes a systemic inflammatory response syndrome, which can contribute to mortality and overt morbidity, particularly in higher-risk patients. Evidence from randomised controlled trials (RCTs) in low-risk populations shows that 'off-pump' CABG (OPCABG) on the beating heart is at least as safe as 'on-pump' CABG (ONCABG). There are consistent findings from large observational studies that OPCABG appears to reduce mortality and morbidity in high-risk patients.

Objectives

The Coronary artery bypass grafting in high-RISK patients randomised to off- or on-Pump surgery (CRISP) trial was set up to test the hypothesis that OPCABG in high-risk patients reduces mortality and morbidity, without causing a higher risk of reintervention.

Methods

Study design

An international, multicentre, open, parallel-group RCT of isolated OPCABG versus ONCABG in high-risk patients with an additive European system for cardiac operative risk evaluation score (EuroSCORE) of ≥ 5 .

Settings and participants

Specialist cardiac surgery centres in the UK and overseas. Patients with an additive EuroSCORE of ≥ 5 undergoing non-emergency isolated CABG surgery via a median sternotomy incision.

Interventions

Trial patients were randomised to

- (a) CABG without CPB (OPCABG) on the beating heart or
- (b) CABG with CPB (ONCABG) on a chemically arrested heart.

The anaesthetic technique and method of myocardial protection used was in accordance with established local protocols.

Randomisation

The preferred method of randomisation was expertise based, i.e. patients were randomised to surgery carried out by an experienced OPCABG surgeon or to an experienced ONCABG surgeon. Surgeons were eligible if they had a stated preference and were sufficiently experienced in their preferred technique (had performed at least 100 operations).

Allocations were concealed and stratified by centre and cohort minimisation was used to minimise imbalance of key prognostic factors across the groups. Patients were randomly assigned in a 1 : 1 ratio.

Outcomes

The primary outcome was a composite end point of death or serious morbidity within 30 days of surgery. The components were (1) all-cause mortality, (2) new-onset renal failure, (3) myocardial infarction (MI), (4) stroke, (5) prolonged initial ventilation and (6) sternal wound dehiscence. New-onset renal failure was defined as a postoperative creatinine level of $> 200 \mu\text{mol/l}$, a percentage increase from preoperative creatinine of $\geq 40\%$ and the need for renal replacement therapy (RRT). Blood test results (of troponin I, troponin T or creatine kinase MB isoenzyme) and the pre- and postoperative electrocardiographs were adjudicated by an independent committee who were blinded to the allocation of OPCABG or ONCABG, and MI was defined on consensus of the adjudicators. Stroke was defined as new, acute, focal neurological deficit thought to be of vascular origin with signs or symptoms lasting longer than 24 hours and confirmed by a neurologist. Prolonged ventilation was defined as ≥ 96 hours, excluding any periods of reintubation. Sternal wound dehiscence was defined as requiring non-pharmacological intervention (e.g. V.A.C.® dressing or reoperation).

Secondary outcomes were:

- (a) quality-of-life (QoL) assessment at recruitment and 4–8 weeks after surgery, measured using the Rose Angina Questionnaire, Canadian Cardiovascular Society (CCS) angina class, European QoL-5 Dimensions (EQ-5D) and Coronary Revascularisation Outcome Questionnaire (CROQ)
- (b) resource utilisation, determined by hospital resources during index admission.

Follow-up

All patients were followed up 4–8 weeks after surgery.

Sample size

The study sample size was set at 5418 patients (2709 per group). The expected incidence of the composite primary outcome, based on data from the Bristol and Oxford cardiac databases, was 9.3%. A sample size of 5418 patients had 90% power to detect a 30% reduction in relative risk (RR) with 5% statistical significance (two tailed).

Statistical analyses

Analyses were carried out on the basis of intention to treat. All treatment comparisons are presented as effect sizes with 95% confidence intervals (CI) and p -values of < 0.05 were considered statistically significant. All models were adjusted for age, sex and operative priority as fixed effects and surgeon as a random effect. Adverse events (AEs) were grouped by the treatment received, rather than by the treatment allocated.

Results

Patient screening

From October 2009 to March 2011, a total of 787 patients were assessed for potential inclusion in the trial. Six hundred and eighty-one were excluded: 523 were ineligible, 82 were eligible but not approached, 74 did not consent and two were omitted for other reasons. The main reasons for non-consent were 'personal' or wanting a specific type of surgery or surgeon.

Recruitment

A total of 106 patients were recruited from eight centres in the UK and one centre in Kolkata, India. Patient follow-up was completed in June 2011. A total of 39 surgeons participated: 19 were ONCABG specialists and 20 were OPCABG specialists. It was estimated that each centre would recruit at least six patients per month. However, this target was not met at any participating centre and the study was closed to recruitment in March 2011 at the request of the funder.

Barriers to recruitment

Five key barriers to recruitment were identified:

1. The number of participating surgeons. Recruitment using an expertise-based randomisation system was severely hampered if only two surgeons in a centre were taking part.
2. Access to potentially eligible patients. In some centres, urgent inpatients were transferred several days before surgery, which provided sufficient time to gain the patient's consent and organise the surgery. In other centres, patients were not transferred until late on the day before surgery and the time frame for recruitment was invariably too short.
3. Referral system. Some centres operated a generic referral system for all patients (i.e. patients were placed in a pool) while in other centres there was a mixture of generic and named referrals, but the vast majority were named referrals. Surgeons were reluctant to 'share' patients referred to them whom they had met in clinic.
4. Targets. The need to meet referral-to-treatment targets and other local performance targets.
5. Insufficient information in the referral letter to determine eligibility. The EuroSCORE is made up of several components and frequently the information provided on referral was inadequate to allow the score to be calculated accurately.

Outside the UK, the main barriers that hampered the set-up were (1) obtaining approved translations of essential documents, (2) insurance/indemnity issues and (3) the limited per-patient funding available.

Actions taken and proposals to increase recruitment

Many initiatives were explored to overcome these barriers to recruitment, but these were largely unsuccessful. In August 2010 it was agreed that the study design should be changed from expertise-based randomisation to within-surgeon randomisation. However, several OPCABG experts were unwilling to operate ONCABG on high-risk patients so it was subsequently decided to allow both methods of randomisation within a centre.

Other changes to the trial design were also considered:

- (a) Widening the inclusion criteria. There was no support for this.
- (b) Changes to the primary outcome. A proposal to extend the composite 30-day outcome to include (1) reoperation for bleeding, (2) low cardiac output, (3) new onset of atrial arrhythmia and (4) replacing new-onset renal failure with the less severe acute kidney injury (AKI). It was estimated that the increased incidence of this revised composite outcome would have reduced the target sample size to 1094 patients.
- (c) Seeking Research Ethics Committee (REC) approval to randomise eligible patients prior to consent. This was not pursued owing to (1) ethical concerns, (2) the potential for bias and the opportunity for the surgeon to influence the patient's decision to participate or not and (3) potential for imbalance between the groups if the consent rates differed between those allocated to an ONCABG or OPCABG expert.

A recovery plan which included the proposed extended composite primary end point was considered by the National Institute for Health Research-Efficacy and Mechanism Evaluation (NIHR-EME) Board in February 2011. The proposal was not accepted and the trial was closed.

Withdrawals

Eight of the 106 randomised patients were excluded from the analysis population, six withdrew prior to surgery and two died prior to surgery.

Protocol deviations

Four patients randomised to OPCABG received ONCABG and there were no crossovers from ONCABG to OPCABG.

Patient follow-up

Follow-up data 4–8 weeks after surgery were obtained for all patients.

Baseline data and operative characteristics

The median EuroSCORE was 6 [interquartile range (IQR) 5–8], the median age 77.1 years (IQR 71.9–80.6) and 23% of patients were female. Approximately half (45%) of procedures were classified as urgent.

Fewer patients in the OPCABG group than in the ONCABG group had three or four grafts (63% vs. 79%). There were no deaths during surgery.

Primary outcome

In both groups, 6 out of 49 (12%) patients experienced the composite primary outcome. The estimated treatment effect, adjusted for age, sex, operative priority and surgeon, was odds ratio (OR) 1.07 (95% CI 0.27 to 4.14; $p = 0.93$). The most commonly occurring component was MI (which occurred in six patients).

Secondary outcomes

Quality-of-life data were similar in the two groups. On average, patients in the OPCABG group scored slightly higher than in the ONCABG group on the EQ-5D visual analogue scale and on the CROQ, albeit with no statistically significant differences [EQ-5D mean difference (MD) = 4.92, (95% CI –0.94 to 10.8; $p = 0.11$); CROQ core total MD = 1.10, (95% CI –0.97 to 3.17; $p = 0.30$)].

On average, resource use was greater for patients randomised to ONCABG. They spent longer in surgery (median 3.4 vs. 3.2 hours), were ventilated for longer (median 7.1 vs. 5.7 hours), spent longer in cardiac intensive care unit (CICU) (median 27.7 vs. 26.0 hours) and stayed longer in hospital (median 8 vs. 7 days) than patients randomised to OPCABG.

Adverse events and postoperative complications

There were 74 expected AEs, eight of which were classified as serious. There were fewer events in patients who received OPCABG [32 (1 serious) vs. 42 events (7 serious)]. There were also fewer unexpected AEs in the OPCABG group [24 (12 serious) vs. 44 events (24 serious)]. The most common complications were atrial fibrillation (AF), superficial wound infections and respiratory infections. There were four deaths (two in each group), three of which occurred more than 30 days after surgery.

Discussion

Main findings: study conduct

The main findings are that expertise-based randomisation is challenging to implement. For a range of logistical reasons, the trial failed to recruit to time and target and was closed prematurely.

Some of the challenges faced were due to the context and nature of the service provision in the UK. Cardiac surgery is a tertiary service. As a consequence, patients are referred from a large geographical area and a significant proportion of referrals are urgent inpatients. The information provided at referral was often limited, making the assessment of eligibility difficult. Elective patients were often unwilling to take part because they wished to stay with the surgeon they met at their first appointment. The availability of an expert surgeon to carry out the operation within a time scale that does not breach local and national targets for treatment, and the willingness or otherwise of surgeons to work together and 'share' their patients, are potential barriers to recruitment into any trial using expertise-based randomisation.

Main findings: study results

The CRISP trial did not find statistically significant differences between the OPCABG and ONCABG groups owing to the limited power. However, the question that the trial set out to address remains important.

The Cochrane review, published in 2012, acknowledged that mainly patients with low risk of postoperative complications were enrolled in the trials reviewed.

The two largest trials to compare ONCABG and OPCABG, the Randomised On/Off Bypass (ROOBY) and CABG off- or on-pump revascularisation (CORONARY) trials, have been published since the CRISP trial began. The ROOBY trial has been severely criticised because it recruited predominantly low-risk patients and many of the OPCABG surgeons were inexperienced. The CORONARY trial, the largest trial to date, had more experienced surgeons and recruited a higher proportion of higher-risk patients, although < 20% of participants had a EuroSCORE of > 5.

The Cochrane meta-analysis was updated to include the results from the CORONARY and CRISP trials. The RRs were death 1.18 (95% CI 0.98 to 1.40), MI 0.96 (95% CI 0.82 to 1.12), stroke 0.80 (95% CI 0.61 to 1.06) and renal complication 0.92 (95% CI 0.70 to 1.21). Data from three trials in high-risk patients (total $n = 534$) were also combined with the CRISP results. This analysis suggested a lower risk of death with OPCABG in the early postoperative period (RR 0.46, 95% CI 0.20 to 1.04; $p = 0.06$) and a comparable risk to 3 years (RR 0.90, 95% CI 0.32 to 2.58; $p = 0.85$). The risk of a MI was also reduced in the early postoperative period (RR 0.59, 95% CI 0.33 to 1.06; $p = 0.077$).

Strengths and limitations

Despite the failure of CRISP to recruit to target, the options to improve recruitment were thoroughly tested. We believe that expertise-based randomisation is the only way to evaluate established surgical procedures when there are strongly held preferences but collective equipoise; however, it may not be feasible in a tertiary referral setting.

The final study size is a clear weakness although the trial methodology was strong; the value of the trial data is their contribution to meta-analyses.

Lessons for the future

If we were setting up CRISP now, there are many things that we would do differently. First, we would design the trial in two phases, with a feasibility phase followed by a main trial phase. This design is being used in other surgical areas of difficult-to-do trials.

Second, we would include a qualitative research element in order to gain a full understanding of the barriers to recruitment and the extent of the equipoise. The strength of the bond formed between surgeon and patient at that first consultation would also be explored through interviews with patients.

Third, we would focus recruitment equally towards UK and overseas centres from the beginning of the trial. Many of the barriers to recruitment experienced in the UK may not be such a problem overseas. Fewer than 5% of patients recruited to the CORONARY trial were from the UK and the biggest contributors were India and China (1307 and 781 patients, respectively).

Future research

The answer to the question whether OPCABG offers an additional benefit over ONCABG in a high-risk population is unclear. The trial evidence in high-risk patients suggests the outcomes are similar although the collective evidence across all trials suggests the risk of death is higher with OPCABG. The views of members of the surgical community are polarised. A qualitative evaluation of the reasons behind the views held by the advocates of the two techniques is an area for future research.

One explanation for the polarisation is the belief that 'it's in the surgeon's hands'. If the surgeons are true 'experts', then one may anticipate no difference in outcomes between the two methods. An individual patient data meta-analysis of the trial data, classifying patients according to the characteristics/experience of the surgeon, could test this hypothesis.

Conclusion

We believe there is still a role for expertise-based randomisation to evaluate established treatments when there are strong practitioner preferences and both treatments are used. The CRISP trial was not successful but there are valuable lessons to be learnt for the future from the CRISP experience.

Trial registration

Current Controlled Trials ISRCTN29161170.

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