Coronary Artery Bypass Grafting Surgery Off- or On-pump Revascularisation Study (CORONARY): kidney substudy analytic protocol of an international randomised controlled trial

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ABSTRACT

Introduction: CORONARY is a large international randomised controlled trial comparing coronary artery bypass graft (CABG) surgery done with and without a bypass pump. Compared with on-pump, off-pump surgery may prevent acute kidney injury (AKI) in the short term and may better preserve kidney function 1 year following surgery. Secondary analyses may also clarify whether effects are similar in patients with and without pre-operative chronic kidney disease and whether AKI avoidance mediates preserved 1-year kidney function.

Methods and analysis: With respect to the study schedule, the last of 4752 patients from 79 sites in 19 countries were randomised in November 2011 to cardiac surgery performed with an on-pump or off-pump procedure. The authors will use regression models to compare the groups in the outcome of peri-operative AKI (per cent change in serum creatinine, ≥50% increase in serum creatinine) and 1-year kidney function (per cent change in estimated glomerular filtration rate (eGFR), ≥20% eGFR loss 1 year after surgery). The authors will use interaction terms in regression models to determine if there is a differential impact of the intervention in those with and without pre-existing chronic kidney disease. The authors will use regression-based tests to determine the proportion of the total effect of surgery type (off-pump vs on-pump CABG) on 1-year eGFR that is mediated by peri-operative AKI.

Ethics and dissemination: In the year 2009, the authors were competitively awarded a grant from the Canadian Institutes of Health Research to answer these kidney questions in CORONARY. Ethics approval was obtained for additional renal data collection in centres that agreed to study participation (>90% of participating centres). This collection began for patients enrolled after 1 January 2010. Remaining 1-year renal outcome data will be collected throughout 2012. Results will be reported in 2013.

Clinical trial registration number: NCT 00463294.
CORONARY kidney substudy protocol

We are conducting the CABG Off- or On-Pump Revascularisation Study (acronym CORONARY). The methods of this large, international randomised controlled trial are described elsewhere. In brief, after obtaining written informed consent, adult patients undergoing isolated CABG surgery (with a median sternotomy) are allocated to have the procedure done with or without a bypass pump. Allocation is done by a voice-activated telephone randomisation service. This trial is funded by the Canadian Institutes of Health Research. With respect to the study schedule, the last of 4752 patients from 79 sites in 19 countries were randomised in November 2011. The primary 30-day composite outcome is total mortality, stroke, non-fatual myocardial infarction or receipt of dialysis for severe AKI. The 30-day results will be analysed and reported in March 2012. One-year outcome data will continue to be collected throughout 2012 and will be reported in 2013. In addition to the primary outcome, CORONARY is uniquely positioned to answer important kidney-specific questions. In the year 2009, we were competitively awarded another grant from the Canadian Institutes of Health Research to collect additional renal information within CORONARY to address these questions. Ethics approval was obtained for additional renal data collection in centres that agreed to study participation (>90% of participating centres). This collection began for patients enrolled after 1 January 2010. Remaining 1-year renal outcome data will be collected throughout 2012. Results will be reported in 2013.

The kidney questions detailed in the grant are presented below and are followed by pre-specified analytic plans.

Primary questions

1. In patients undergoing CABG surgery, does use of an off-pump compared with an on-pump procedure (i) reduce the risk of AKI during the hospital stay and (ii) result in better kidney function 1 year after surgery?

Secondary questions

2. Does the presence of pre-operative CKD modify the impact of surgery type (off-pump, on-pump) on kidney outcomes?

3. If an off-pump compared with an on-pump procedure results in better kidney function 1 year after surgery is the effect mediated by avoiding peri-operative AKI?

CORONARY data collection

The pre-operative serum creatinine value (within 7 days prior to randomisation) has been recorded since the start of the trial, along with the peak value during the hospital stay. We define pre-operative CKD as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m², using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (which requires knowledge of whether a patient is of black race; <0.1% of CORONARY patients). In centres that agreed to additional renal data collection, we started recording all serum creatinine measurements during the hospital stay for patients enrolled after 1 January 2010 (not just the peak value) and a serum creatinine 1 year after surgery.

ANALYTIC PLAN

To refine the analytic plan in December 2011, we reviewed all CORONARY data without knowledge of
patient allocation. Table 1 presents AKI according to modern staging systems. 11-12 Table 2 presents changes in kidney function 1 year after surgery. The analytic plan was finalised without any knowledge of CORONARY outcomes by allocation group.

**Patient selection**
For CORONARY kidney substudy analyses, all randomised patients will be included except as follows: (1) patients receiving chronic haemodialysis prior to randomisation (as these patients cannot develop AKI—to date 1.3% of randomised patients), (2) patients with a baseline eGFR <15 ml/min/1.73 m² prior to randomisation (ie, patients with end-stage renal disease (ESRD)13; to date an additional 0.2% of patients), (3) patients missing a pre-randomisation serum creatinine value as we cannot reliably define AKI without knowledge of the baseline value (<1% of patients) and (4) patients who never undergo CABG surgery as they will not have the opportunity to have any post-operative serum creatinine measurements (<1% of randomised patients).

**Intervention group assignment**
Patients are randomised to on-pump or off-pump CABG, with randomisation stratified by centre. The intention-to-treat principle will guide all analyses, irrespective of whether there is a deviation from the randomly allocated therapy. Currently, the cross-over rate is 4% from on-pump to off-pump and 10% from off-pump to on-pump surgery.

**AKI during hospital stay**

**Peri-operative per cent change in serum creatinine**
We will use a logistic regression model to compare the groups in the outcome of per cent change in serum creatinine ((peak post-operative serum creatinine—pre-randomisation serum creatinine)/pre-randomisation serum creatinine), stratified by centre and adjusting for the following covariates: age (per year), sex, left ventricular function categories (≥50%, 35%–49%, 20%–34%, <20%), diabetes, pre-randomisation ACE inhibitor or angiotensin receptor blocker use, pre-randomisation statin use, pre-randomisation diuretic use, urgent versus elective surgery and pre-randomisation eGFR category (>60 ml/min/1.73 m², ≤60 ml/min/1.73 m²). We will include a missing data indicator value for each covariate (at present, there is <1% missing for each variable).14 In patients who underwent surgery but have a missing post-operative peak serum creatinine value (<4% patients), we will carry the pre-randomisation serum creatinine forward as the post-operative value (which should provide a more conservative estimate of the intervention effect than the alternative of removing such patients). We will test model assumptions (detailed in online appendix) and interpret a p value ≤0.05 as statistically significant. We will report the result as the average difference in per cent change in serum creatinine between the surgical groups with 95% CI. Visually the unadjusted results will be graphed as box-plots. A sample of ~4700 patients will have over 80% power to detect a 5% or greater difference in the mean per cent change in serum creatinine between the two groups (α 0.05, independent samples t test; adequate power to detect a small effect in relation to expected SD of 60).

**Categorised AKI**
We will use a logistic regression model to compare the groups in the outcome of ≥50% increase in serum creatinine, stratified by centre and adjusting for previously defined covariates.11 15 16 We will test model assumptions (detailed in online appendix) and estimate the adjusted RR of AKI with 95% CI (bootstrap method

| Table 1 | Per cent of CORONARY patients to date who met a definition of acute kidney injury according to modern staging systems |
|---|---|---|
| | All patients (n = 3089) | Patients with a pre-operative eGFR >60 ml/min/1.73 m² (n = 2372) | Patients with a pre-operative eGFR ≤60 ml/min/1.73 m² (n = 717) |
| Evidence of an absolute increase in SCr value ≥27 μmol/L or an increase of ≥150% from the baseline SCr value (AKIN stage 1 or more) | 28.9% | 25.3% | 41.1% |
| Evidence of an increase in SCr value ≥150% (≥1.5-fold) from baseline (RIFLE risk category) | 18.7% | 17.0% | 24.4% |
| Evidence of an increase in SCr value ≥200% (≥twofold) from baseline (RIFLE injury category, AKIN stage 2) | 6.9% | 5.6% | 11.4% |
| Evidence of an increase in SCr value ≥300% (≥threefold) from baseline or a baseline SCr ≥354 μmol/L with an increase ≥44 μmol/L from baseline. *Any patient who received acute dialysis is categorised in this category (RIFLE failure category, AKIN stage 3)* | 2.2% | 1.6% | 4.2% |
| Receipt of acute dialysis | 1.2% | 0.6% | 3.1% |

*Acute Kidney Injury Network (AKIN) and Risk, Injury, Failure, Loss and End-stage Renal Disease (RIFLE) classification systems. The categories are not mutually exclusive (ie, patients who meet the criteria for RIFLE injury also meet the criteria for RIFLE risk). eGFR, estimated glomerular filtration rate; SCr, serum creatinine.*
detailed in online appendix). We will have over 90% power to detect a 20% or more RR reduction should it exist (two-tailed \( \alpha = 0.05 \), \( \chi^2 \) test). Of note, many factors including haemodilution add ‘noise’ to post-operative serum creatinine measurements. When the value is markedly elevated, we are confident that the reason is due to AKI. It is conceivable that an intervention effect will be observed for categorised AKI but not per cent change in creatinine. If the p value is greater for per cent change than categorised AKI, we will interpret a p value \( \leq 0.025 \) for categorised AKI as statistically significant. Because categorised AKI is easy to interpret, if it meets criteria for significance, we will primarily focus on this outcome.

Supporting analyses
We will perform six analyses defining AKI in other ways. We will interpret a p value \( \leq 0.05 \) as significant provided there is concordance with the primary results.

- Absolute change in serum creatinine from the pre-randomisation value.
- \( \geq 100\% \) increase in serum creatinine (Risk, Injury, Failure, Loss and End-stage Renal Disease (RIFLE) injury category, AKIN (Acute Kidney Injury Network) stage 2).\(^{11,12} \)
- \( \geq 27\,\mu\text{mol/l} \) or \( \geq 50\% \) increase in serum creatinine (AKIN stage 1 or more).\(^{12} \)
- Composite of AKI or death during the hospital stay (death rate \( \sim 2\% \) at 30 days; 90% of patients who die have post-operative serum creatinine recorded; death rate within 2 days of surgery is \( <0.5\% \)).
- Evidence of a rise in serum creatinine in first 48 h after surgery (for patients enrolled after 1 January 2010).\(^{18} \)
- AKI that also considers later post-operative rises in serum creatinine in relation to earlier post-operative measurements (supplements the primary analysis which only considers peak post-operative measurement during hospital stay in relation to pre-randomisation value).\(^{18} \)

**Kidney function 1 year after surgery**

One-year per cent change in eGFR

Similar to the previously described AKI analysis, we will use a linear regression model to compare the primary results.

- Absolute change in serum creatinine from the pre-randomisation value.
- \( \geq 25\% \) reduction in eGFR
- \( \geq 5\,\text{ml/min/1.73 m}^2 \) reduction in eGFR
- \( \geq 10\,\text{ml/min/1.73 m}^2 \) reduction in eGFR
- Categorised change in kidney function

**Categorised change in kidney function**

Similar to the previously described AKI analysis, we will use a logistic regression model to compare the groups on the outcome of \( \geq 20\% \) eGFR decrease 1 year after surgery (ie, loss of over a fifth of kidney function). Anyone who develops ESRD in follow-up, or receives acute dialysis and dies before a serum creatinine measurement can be obtained, will be counted as having met this definition. We will have between 75% and 89% power to detect a difference of 4% or more between the two surgical groups (\( \alpha = 0.05 \), independent samples t test, adequate power to detect a small to moderate effect in relation to expected SD of 25).

**Supporting analyses**

We will perform two analyses examining 1-year kidney function in other ways. We will interpret a p value \( \leq 0.05 \) as significant provided there is concordance with the primary results.

- Absolute change in serum creatinine from the pre-randomisation value.
- Rank-based assessment accounting for potential competing event of death (detailed in online appendix).

**Subgroup analyses: presence of pre-operative CKD**

We will use interaction terms in the previously described linear and logistic regression models to determine if...
there is a differential impact of the intervention in those with and without CKD. We will interpret a p value ≤0.05 as statistically significant. Despite the size of CORONARY, there will only be adequate statistical power for very large subgroup effects.

Mediation analysis: impact of AKI on longer term kidney function

A mediating variable is one that explains all or part of the association between a predictor and a response. In CORONARY, mediation will occur if on-pump versus off-pump CABG surgery influences the development of AKI, which influences 1-year kidney function. Regression-based tests for mediation have been well developed and are widely used. Figure 1 presents our analytic framework. We will test for a significant mediation effect (methods detailed in online appendix). We will report the proportion of the total effect of surgery type (off-pump vs on-pump CABG) on per cent change in 1-year eGFR that is mediated by peri-operative per cent change in serum creatinine. As well, we will consider mediation with AKI defined as a categorical variable (methods detailed in online appendix).

CONCLUSIONS

The sample in CORONARY almost exceeds the combined number of patients enrolled across 70 randomised controlled trials, which tested strategies to prevent or treat AKI in cardiac surgery. It will be the largest AKI prevention trial conducted to date. International recruitment across 19 countries will provide generalisable estimates of the treatment effect. In this report, we have judiciously pre-specified the main questions and analytic protocol that will be used to test relevant kidney hypotheses in CORONARY. We have done so to minimise the chance of spurious post-hoc assertions of effect, so that the kidney results from this large international trial are robust and believable.

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Competing interests

None.

Ethics approval

Ethics approval was provided by all participating trial centres.

Provenance and peer review

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Data sharing statement

No additional data are available.

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