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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.

ARTICLE SUMMARY

Article focus

- 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 AKI in the short term and may better preserve kidney function 1 year after 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.

Key messages

- Presented is this pre-specified CORONARY kidney substudy analytic protocol.
- Data collection and analysis will be completed in 2013.
- Understanding the degree to which avoiding AKI preserves longer term kidney function has broader implications for the acceptability of side effects and costs of interventions which prevent AKI.

Strengths and limitations of this study

- This will be largest AKI prevention trial conducted to date.
- It will be one of the first trials to consider the impact of a peri-operative intervention on longer term kidney function.
- International recruitment across 19 countries will provide generalisable estimates of the treatment effect.

BACKGROUND

Coronary artery bypass grafting (CABG) surgery is an effective way of improving

symptoms and prolonging life in patients with severe coronary artery disease.[1] Globally, 1.25 million cardiac surgeries are performed annually.[2] A frequent and serious complication of CABG surgery is acute kidney injury (AKI), which is a sudden deterioration in kidney function. Peri-operative AKI is independently associated with increased short- and long-term mortality, a greater length of hospital stay and higher economic costs.[3]

CABG surgery is usually performed with the use of cardiopulmonary bypass ('on-pump'). This requires cannulation of the heart and aorta, cross clamping of the ascending aorta and cardioplegic arrest. In this setting, AKI is multifactorial: the bypass circuit changes blood concentration and pulsatility and introduces a blood/circuit interface, which stimulates a generalised inflammatory response including increased catecholamine and free haemoglobin levels.[4] Furthermore, aorta cannulation and cross clamping may lead to platelet or atheromatous embolic phenomena.

CABG surgery performed on a beating heart without the use of cardiopulmonary bypass ('off-pump') was developed to avoid post-operative complications from the pump. A systematic review published in 2010 evaluated AKI across 22 randomised trials comparing off-pump with on-pump surgery (total 4819 patients).[5] Off-pump CABG resulted in a 40% RR reduction in AKI (variably defined in the primary trials). The results did not demonstrate statistical heterogeneity. However, as concluded by the review authors, 'different definitions of AKI used in the individual trials and methodological concerns preclude definitive conclusions about the treatment effect'.

A limitation of most AKI prevention trials is a failure to consider any sustained effect of the intervention on longer term kidney function. It is possible that off-pump compared with on-pump surgery better preserves 1-year kidney function, but to our knowledge, this has not been previously evaluated. This effect may be mediated through the AKI itself (ie, avoiding AKI preserves kidney function at 1 year[6 7]) or may be mediated through other pathways (ie, off-pump bypass improves cardiac function which preserves 1-year kidney function). Understanding the degree to which avoiding AKI preserves longer term kidney function has broader implications for the acceptability of side effects and costs of interventions which prevent AKI. Finally, patients with pre-operative chronic kidney disease (CKD) are at high risk of AKI and are a subgroup where preservation of renal function is of key interest.[8]

CABG Off- or On-Pump Revascularisation Study

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.[9] 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-fatal 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 m^2, 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).[10] 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 m^2 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 linear 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 m^2, ≤60 ml/min/1.73 m^2). 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 will 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 m^2 (n=2372)	Patients with a pre-operative eGFR ≤60 ml/min/1.73 m^2 (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.

Table 2 One-year change in eGFR compared with the pre-operative value, expressed as categories

	All patients (n=1241)	Patients with a pre-operative eGFR >60 ml/min/1.73 m^2 (n=910)	Patients with a pre-operative eGFR ≤60 ml/min/1.73 m^2 (n=331)
≥15% reduction in eGFR	23%	24%	21%
≥20% reduction in eGFR	18%	19%	15%
≥25% reduction in eGFR	12%	12%	11%
≥50% reduction in eGFR	3%	2%	5%
≥5 ml/min/1.73 m^2 reduction in eGFR	38%	43%	24%
≥10 ml/min/1.73 m^2 reduction in eGFR	25%	29%	15%

Anyone who developed end-stage renal disease in follow-up was counted as meeting the reduction in eGFR definition as was anyone who received acute dialysis who subsequently died before their 1-year serum creatinine measurement.
eGFR, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

detailed in online appendix). We will have over 90% power to detect a 20% or more RR reduction should it exist (two-tailed α 0.05, χ^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 ≤0.025 for categorised AKI as statistically significant.[17] 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 ≤0.05 as significant provided there is concordance with the primary results.

- Absolute change in serum creatinine from the pre-randomisation value.
- ≥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]
- ≥27 μmol/l or ≥50% increase in serum creatinine (AKIN stage 1 or more).[12]
- Composite of AKI or death during the hospital stay (death rate ~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 groups in the outcome of per cent change in eGFR 1 year after surgery ((post-operative eGFR measured 1 year after surgery—pre-randomisation eGFR)/pre-randomisation eGFR), stratified by centre and adjusting for covariates described for AKI. In patients with missing 1-year values (~5% for reasons of death, target <10% for reasons of missing data), we will substitute the pre-randomisation eGFR value. We will impute an eGFR value of 5 ml/min/1.73 m^2 for any patient who developed ESRD anytime in follow-up (<0.1%) or who died after receiving acute dialysis (~0.6% patients). With at least 1800 patients, we will have over 80% power to detect a difference of 4% or more between the two surgical groups (α 0.05, independent samples t test, adequate power to detect a small to moderate effect in relation to expected SD of 25).

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 ≥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 25%–30% RR reduction should it exist (two-tailed α 0.05, χ^2 test). As with AKI, it is conceivable that an intervention effect will be observed in the categorised but not continuous outcome. In this scenario, we will interpret statistical significance as described for AKI.

Supporting analyses

We will perform two analyses examining 1-year kidney function in other ways. We will interpret a p value ≤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

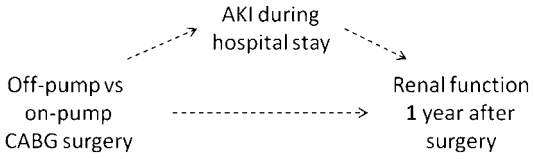

Figure 1 Directed acyclic graph of the causal pathway between coronary artery bypass grafting (CABG) surgery type (off-pump vs on-pump), mediating variable acute kidney injury (AKI) and dependent variable renal function 1 year after surgery. The dashed arrows indicate that the causal relationship is unknown but will be investigated.

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.[19] In CORONARY, mediation will occur if on-pump versus off-pump CABG surgery influences the development of AKI, which influences 1-year kidney function.[20] Regression-based tests for mediation have been well developed and are widely used.[21 22] 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.[23] 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.

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Data sharing statement No additional data are available.

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Appendix: CORONARY Kidney Substudy Analytic Protocol

Testing the assumptions of the linear regression model

We will test the assumptions of the linear regression model using the following steps: 1) visual assessment of a normal probability plot of residuals to assess whether residuals are normally distributed; 2) visual assessment of the plot of residuals versus predicted values to assess model fit and homoscedasticity of residuals; 3) the Durbin-Watson statistic to test for autocorrelation of residuals when data are ordered by randomization date (significant autocorrelation is detected if the test p-value is <0.05;[1]; 4) Cook's D statistics to detect outlying observations (where we will investigate a Cook's D $>|2|$ as influential.[2] If the residuals are non-normal or heteroscedastic, rather than a linear regression model we will use a non-parametric analysis of covariance with covariates to test whether the median response values are equal between the two groups. Since the study accrual period is only four years we expect no significant effect of time on the responses. If there are influential observations we will exclude them in sensitivity analysis, comparing the output to our main result.

Testing the assumptions of the logistic regression model

We will test the logistic regression model assumptions using the following steps:1) visual assessment of the plot of residuals versus predicted values to assess model fit and residual trends ; 2) for each observation we will compute the generalized difference of fits (GDFFITS) (a measure of how influential they are; if this measure is $\geq c*(k/(n-d))^{1/2}$ then the observation will be considered influential, where c is an arbitrary constant, k is the number of regression parameters, n is the number of observations (patients) and d is the number of observations that have been deleted;[3]; 3) a Hosmer-Lemeshow test to assess the goodness of fit of the logistic regression model (where a Hosmer-Lemeshow test p-value <0.05 indicates a poor fit [4]). If the logistic regression model does not provide a good fit, we will derive the odds ratio from the Mantel-Haenszel method, stratified by centre and pre-operative CKD.[5]

Bootstrapping method to derive the 95% confidence interval for the relative risk

The bootstrapping method involves the following steps: 1) we will draw a random sample of 4700 patients with replacement after the selection of each patient from the original sample of 4700 patients, 2) for each bootstrap sample, we will compute the adjusted relative risk, 3) we will repeat this process 2,000 times, with the 2.5^{th} and 97.5^{th} percentiles of the resulting bootstrap relative risk distribution corresponding with the 95% confidence interval for the adjusted relative risk.

Rank based assessment accounting for competing event of death

We appreciate if there is a differential impact of the intervention on 1-year mortality across the surgical groups this may introduce informatively missing 1-year eGFR values. To consider this issue we will perform a rank based procedure as follows: patients who die before 12 months will be ranked from lowest (indicating the poorest outcome) to the highest on the basis of survival time after surgery before death. Similarly, surviving patients will next be ranked from lowest to highest on the basis of survival time from surgery to the onset of ESRD (for patients who transition from acute dialysis to chronic dialysis care, this will be defined by 90 days after receipt of the first acute dialysis treatment). Finally patients who survive 12 months will be ranked on the basis of unfavourable to favourable 1-year percent change in eGFR. For patients who did not die or develop ESRD but have a missing 1-year serum creatinine measurement, we

will right-censor 1- year after surgery and impute a value of zero percent change in eGFR. We will compare ranks between the treatment groups using a log-rank test and calculate hazard ratios and 95% confidence intervals with the use of Cox proportional-hazards regression.[6] We will report the rate of missing 1-year eGFR values for both surgical groups for patients who did not die before 12 months.

Test of mediation: AKI as a percent change in serum creatinine

Methods to test for a significant mediation effect in the setting where the mediating and response variables can be modeled using linear regression include Baron and Kenny's causal steps , Sobel first-order test , PRODCLIN, percentile bootstrap, and bias corrected bootstrap.[7-9] We will use the PRODCLIN percentile bootstrap method to estimate the percentage of the total effect of surgery type (off-pump vs. on-pump CABG) on percent change in eGFR at 1- year (eGFR measured at 1- year compared to pre-operative eGFR) that is mediated by peri-operative percent change in serum creatinine [(peak post-operative serum creatinine – pre-randomization serum creatinine)/pre-randomization serum creatinine].[10]

Let X denote the binary variable indicating surgery type where X=1 for off-pump surgery and 0 for on-pump surgery (on-pump surgery is the referent surgery type). Let M denote percent change in serum creatinine. The linear regression model relating M to X is

$$E(M|X;\alpha_0, \alpha) = \alpha_0 + \alpha X \text{ . (Model 1)}$$

Then α represents the average difference in percent change in peri-operative serum creatinine comparing patients receiving off-pump surgery to those receiving on-pump surgery. Let Y denote percent change in eGFR [(post-operative eGFR measured 1-year after surgery - pre-randomization eGFR)/pre-randomization eGFR]. The linear regression model relating Y to X and M is

$$E(Y|X, M; \tau_0, \tau^*, \beta) = \tau_0^* + \tau^* X + \beta M \text{ . (Model 2)}$$

Then τ^* represents the direct effect of surgery type on percent change in eGFR (i.e. the effect that is not mediated by peri-operative percent change in serum creatinine), and β represents the effect of the percent change in peri-operative serum creatinine on percent change in eGFR at 1- year, controlling for surgery type. Note that the model relating X to Y is

$$E(Y|X; \tau_0, \tau^*, \beta) = \tau_0 + \tau X \text{ , (Model 3)}$$

where τ represents the total effect of surgery type on percent change in 1-year eGFR.

To detect mediation using the PRODCLIN method, we will perform the following steps:

1) Fit the data to obtain an estimate of α from (Model 1), $\hat{\alpha}$. Let $\hat{\sigma}_\alpha$ denote the standard error of $\hat{\alpha}$.
2) Fit the data to obtain an estimate of β from (Model 2), $\hat{\beta}$. Let $\hat{\sigma}_\beta$ denote the standard error of $\hat{\beta}$.
3) The product of the estimated coefficients $\hat{\alpha}$ and $\hat{\beta}$ is the indirect effect of X on Y. This product is not asymptotically normally distributed therefore a method to create confidence intervals based on the distribution of $\alpha\beta$ will be used. To create a confidence interval for $\hat{\alpha}\hat{\beta}$, we will undertake the following steps:
    a. Calculate $z_\alpha = \hat{\alpha}/\hat{\sigma}_\alpha$ and $z_\beta = \hat{\beta}/\hat{\sigma}_\beta$.
    b. Obtain critical values from the PRODCLIN Fortran program (http://www.public.asu.edu/~davidpm/ripl/Prodclin/) using z_α and z_β and the type I error rate equal to 0.05.

c. Let $\delta_{\substack{lower \\ upper}} = \dfrac{critical\ value - \dfrac{\hat{\alpha}\hat{\beta}}{\hat{\sigma}_{\alpha}\hat{\sigma}_{\beta}}}{\sqrt{\dfrac{\hat{\alpha}^2}{\hat{\sigma}_{\alpha}^2} + \dfrac{\hat{\beta}^2}{\hat{\sigma}_{\beta}^2} + 1}}$.

d. The limits $= \hat{\alpha}\hat{\beta} \mp \delta_{\substack{lower \\ upper}} \times \hat{\sigma}_{\alpha\beta}$, where $\hat{\sigma}_{\alpha\beta} = \sqrt{\hat{\alpha}^2\hat{\sigma}_{\beta}^2 + \hat{\beta}^2\hat{\sigma}_{\alpha}^2}$, are the lower and upper confidence limits respectively of the indirect effect of surgery type on 1-year percent change in eGFR. If the confidence interval does not contain zero, then the indirect effect is significant and we will conclude that some or all of the effect of surgery type on 1-year eGFR is mediated by the percent change in peri-operative serum creatinine caused by surgery type.[9]

If the indirect effect is significantly different from zero, the proportion of the total effect of surgery type on 1-year percent change in eGFR that is mediated through percent change in peri-operative serum creatinine, given by $\dfrac{\hat{\alpha}\hat{\beta}}{\hat{\tau}}$, will be reported. To do this, we will use (Model 3) to fit the data in order to obtain an estimate of τ, $\hat{\tau}$. We will report the bootstrap confidence interval for this measure. To do this, and expected 2,000 bootstrap samples of size n will be taken from the original sample of size n with replacement, and for each bootstrap sample, we will calculate the value. We then use bootstrap estimates corresponding to the ω/2 and the 1 - ω/2 percentiles of the bootstrap distribution to create a 100(1 – ω)% confidence interval, where ω is the type I error rate.

We will use previously described techniques to impute the peri-operative and 1-year serum creatinine value in cases where it is missing (expect this to be done in a minimal number of cases). Similarly, covariates that have been previously described will be used in the three linear regression models (steps (1) and (2)) to improve statistical efficiency.

The Sobel mediation method is similar to, but more conservative than, the PRODCLIN mediation method.[9] If a trial is adequately powered to detect a significant indirect effect using the Sobel mediation procedure, we will then assume there is adequate power to detect a significant effect using the PRODCLIN method. Presented in the table below are empirical power calculations for the Sobel mediation method for different true values of α and β from (Model 1) and (Model 2) respectively.

Power calculations for Sobel mediation tests

		β		
		-0.5	**-1**	**-1.5**
α	**-1**	10%	6%	7%
	-3	26%	30%	31%
	-5	58%	59%	59%
	-7	87%	87%	88%
	-9	97%	99%	99%

Results presented for given α and β from (Model 1) and (Model 2) respectively, for τ^{*}=3 from (Model 2), standard deviation of M|X = 50, standard deviation of Y|X,M = 50, and type I error rate=0.05. Number of subjects per simulated dataset is 2,000 and the number of datasets simulated per α, β combination is 300. In this table, if α=-3 then the percent change in peri-operative serum creatinine is 3 units lower than in the on-pump surgery group. If

β=-1, then a one unit increase in percent change in post-operative serum creatinine is associated with a 1% decrease in eGFR at 1-year, adjusted for surgery type.

In the event that the linear regression model assumptions do not hold for (Model 1), (Model 2) or (Model 3), we will use non-parametric methods as described below for binary variables to investigate mediation.

In the event that a significant subgroup by pre-operative eGFR categories ($\leq$60 mL/min per 1.73m^2 vs. >60 mL/min per 1.73m^2) effect is detected in prior analyses, we will conduct two mediation analyses, one for each subgroup. We note that power to detect significant mediation will be compromised if there is a significant subgroup effect.

Test of mediation: categorized AKI

Let X denote surgery type as before. Let M indicate post-operative AKI defined by a 50% increase in serum creatinine or more. Let Y indicate a 1-year decrement in eGFR of at least 20% compared to the pre-operative value. We define a direct effect as the effect of X on Y that is not mediated by M, and define an indirect effect as the effect of X on Y that is mediated by M.

Definition of values used to compute direct effects, indirect effects and total effects when X, M and Y are binary.

	X	**M**	**Y**	**P(Y=1|x, m) = g_{xm}**	**P(M=1|x) = h_x**
n_1	0	0	0	$n_2/(n_1+n_2) = g_{00}$	$(n_3+n_4)/(n_1+n_2+n_3+n_4) = h_0$
n_2	0	0	1		
n_3	0	1	0	$n_4/(n_3+n_4) = g_{01}$	
n_4	0	1	1		
n_5	1	0	0	$n_6/(n_5+n_6) = g_{10}$	$(n_7+n_8)/(n_5+n_6+n_7+n_8) = h_1$
n_6	1	0	1		
n_7	1	1	0	$n_8/(n_7+n_8) = g_{11}$	
n_8	1	1	1		

The direct effect (DE), the indirect effect (IE), and the total effect (TE) are given by:

$DE = (g_{10} - g_{00})(1 - h_0) + (g_{11} - g_{01})\, h_1$

$IE = (h_1 - h_0)(g_{01} - g_{00})$

$TE = g_{11}h_1 + g_{10}(1-h_1) - [g_{01}h_0 + g_{00}(1-h_0)]$

The mediated effect (ME) is given by

$$ME = (1-(DE/TE))*100\%.$$

The mediated effect is the percentage of the total effect that is owed to mediation [11]. We will obtain a confidence interval for the mediated effect using the percentile bootstrap method. We will take 2,000 bootstrap samples of size n from the original sample of size n with replacement, and for each bootstrap sample, the value ME is calculated. We will use bootstrap estimates corresponding to the $\omega/2$ and the $1 - \omega/2$ percentiles of the bootstrap distribution to create a $100(1 - \omega)\%$ confidence interval, where ω is the type I error rate.[9] We will report the confidence interval and we will conclude that significant mediation is detected if the confidence interval does not contain zero.

Appendix References

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