Postoperative 20% Albumin Vs Standard Care and Acute Kidney Injury After High-risk Cardiac Surgery (ALBICS): Study Protocol for a Randomised Trial

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Abstract

Background

Acute kidney injury (AKI) is a common complication of cardiac surgery. Factors such as cardiopulmonary bypass, aortic cross-clamping and surgical stress may precipitate renal hypoperfusion and ischaemia, inflammation, and oxidative stress are associated with development of AKI. Albumin's pharmacological properties and widespread availability have the potential to mitigate these factors. However, the effect of albumin on cardiac surgery associated AKI is unknown.

Objective

To evaluate the impact of postoperative 20% albumin infusion on kidney function after high-risk cardiac surgery.

Methods

We designed an open label, multicentre, randomised controlled trial – the ALBICS study (ALBumin Infusion and acute kidney injury following Cardiac Surgery). A total of 590 patients undergoing high-risk cardiac surgery (combined procedure or estimated glomerular filtration rate (eGFR) <60mL/min/1.73m^2) will be enrolled into the study and randomly allocated to receive a postoperative 20% albumin infusion or standard care in a 1:1 ratio, stratified by centre and baseline renal function. The study fluid will be administered upon arrival in intensive care for 16 hours. Patients will be followed up until 28 days after surgery or until discharge from the hospital. The primary outcome is the proportion of patients who develop AKI in both groups. Secondary outcomes to be measured are proportions of AKI stage II and III, 28-day mortality, mechanical ventilation time and length of stay in intensive care and hospital.

Conclusion

This trial aims to determine if a postoperative infusion of concentrated albumin reduces the risk of AKI following high-risk cardiac surgery.

Trial registration

Australian New Zealand Clinical Trials Registry, ACTRN12619001355167O3. Registered 03 October 2019 – retrospectively registered, https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=378383.

Background

Acute kidney injury is a well-recognised complication of cardiac surgery (CSA-AKI). A large retrospective cohort study of 25,086 patients reported CSA-AKI in 30% of patients[1]. This study also demonstrated odds ratios of in-hospital mortality equal to 3.17 in Acute Kidney Injury Network (AKIN) stage 1 and 43.77 in

AKIN stage 3. Given that over one million patients undergo cardiac surgery each year, CSA-AKI presents a significant burden of disease[2].

Pathophysiology and risk factors

Current understanding of the pathophysiological mechanisms surrounding CSA-AKI are limited. There is unlikely to be a single mechanism responsible for AKI in these patients but instead a myriad of injurious pathways that take place in the perioperative period. Many of these pathways relate to renal perfusion, inflammation and oxidative stress (Figure 1).

Cardiopulmonary bypass (CPB) is often administered with low flow with low mean arterial pressure. These haemodynamics are associated with postoperative renal injury, likely via a reduction in renal blood flow and glomerular filtration[3]. Non-pulsatile flow may also result in an imbalance between cortical and medullary perfusion, however, there is insufficient evidence to support this claim[4]. Haemodilution is an inevitable consequence of CPB and has been identified as an independent predictor of CSA-AKI[5-7]. The renal medulla and corticomedullary junction are particularly vulnerable to these changes given their relative hypoxia in comparison to other tissues[8,9]. Prolonged hypoperfusion precipitates ischaemic changes such as inflammatory cell infiltration, cell contraction and necrosis[10]. Other operative risk factors include aortic cross-clamp time, blood transfusion, inotrope requirements, and the complexity of the procedure performed[11,12].

Cardiac surgery results in increased levels of pro-inflammatory cytokines, notably interleukin (IL)-6 and tumour necrosis factor (TNF)-α[13]. High plasma concentrations of these cytokines are associated with increased risk of AKI after cardiac surgery[14]. Inflammation is the direct result of surgical stress and CPB, with higher levels of pro-inflammatory cytokines reported in patients undergoing on-pump cardiac surgery compared to off-pump surgery[15].

Cardiopulmonary bypass also leads to oxidative stress. Postoperative improvement of perfusion places patients at risk of ischaemia-reperfusion-injury. The resultant production of reactive oxygen species upregulates pro-inflammatory transcription factors, notably nuclear factor kappa-B[16]. Subsequent activation of macrophages, neutrophils and lymphocytes lead to renal parenchymal infiltration and development of AKI[17,18]. Many components of the CPB circuit may also damage erythrocytes. The ensuing haemolysis and increase in free haemoglobin precipitate reactive oxygen species production via the Fenton reaction, and are correlated with CSA-AKI[19,20]. Increases in free haemoglobin and haem also lead to nitric oxide consumption, reducing its availability for use in other tissues[21]. Neurohormonal activation can occur during cardiac surgery and compounds the effects of oxidative stress[18]. Subsequent constriction of the renal arteries, in addition to systemic vasoconstriction, leads to a reduction in renal perfusion.

Hypoalbuminaemia and cardiac surgery

Hypoalbuminaemia is common after cardiac surgery. A large observational study (n=2818) found that 94% of patients with normal preoperative serum albumin levels developed hypoalbuminaemia at 24 hours after cardiac surgery, where the risk of AKI approximately doubled with each 5g/l reduction[22]. Inflammation leads to suppression of albumin mRNA transcription[23,24]. Further, transcapillary escape rates of albumin increase by as much as 100% after cardiac surgery[25]. This effect has been attributed to blood loss, transfusion of large volumes of fluid, and vasodilation[26,27]. Albumin may also be sequestered in non-exchangeable parts of the body in the acutely ill[28].

A systematic review of one randomised controlled trial (RCT) and four observational studies totalling 2798 patients, determined low serum albumin as a predictor of CSA-AKI, and suggested that it may also be associated with increased mechanical ventilation requirements, mortality, and length of stay in hospital and intensive care (ICU)[29]. Notably, the RCT found that preoperative administration of 20% albumin decreased the risk of AKI after off-pump cardiac surgery in patients with preoperative serum albumin level <40g/l[30].

In separate meta-analyses of 90 cohort studies and 9 RCTs totalling 291,433 and 535 acutely ill patients, Vincent et al. found that a 10g/l reduction in serum albumin correlated with an increased odds of mortality and morbidity of 116% and 52% after cardiac surgery[31]. The analysis of randomised trials also suggests that albumin supplementation to maintain serum levels greater than 30g/l decreases the rate of complications. These results contend that hypoalbuminaemia is common after cardiac surgery and its correction may prevent AKI.

Nephroprotective properties of albumin

Fluid balance optimisation

Fluid overload is an independent risk factor for AKI in critically ill patients[32,33], where overload of as little as 5-10% is associated with organ dysfunction[34]. Further, congestion of the renal veins is correlated with AKI after cardiac surgery[35]. Subsequent neurohormonal activation and sodium retention may precipitate a cycle in which increases in venous pressure raise intravascular volume to further increase venous pressure[36]. A rise in venous pressure and subsequent renal interstitial oedema impair glomerular filtration[37] and may reduce cortical oxygen pressures[38].

Fluid overload may occur following cardiac surgery due to transfusion of large volumes of fluid, an increasingly recognised issue in critically ill patients. One study suggests an average patient receives 4.5L of intravenous fluid in the 24 hours after cardiac surgery[39]. Exacerbated by capillary leakage, transfused

fluids diffuse into the extracellular compartments. This effect is likely more pronounced in patients with low serum albumin due to reduced oncotic pressure.

The ALBIOS study was a randomised, open-label, multicentre trial which included 1818 patients from 100 ICUs[40]. Participants were randomised to receive either 20% albumin with crystalloid, or crystalloid alone. Albumin administration was titrated to maintain serum albumin levels greater than 30g/l for up to 28 days. Albumin administration resulted in lower daily ($p<0.001$) and cumulative net fluid balance (median 347ml vs 1220ml, $p=0.004$). The HAS FLAIR trial found similar results comparing 20% albumin and crystalloid fluid bolus therapy over the first 24 hours after cardiac surgery (median 1100ml vs 1970ml, $p=0.001$, $n=100$)[41]. Additionally, the SWIPE trial found that in a sample of 321 ICU patients, half of whom had undergone cardiac surgery, 20-25% albumin preparations reduced fluid requirements in the first 48 hours compared to 4-5% albumin preparations (median 3429ml vs 4217ml, $p=0.06$)[42].

Protection of endothelial integrity

Injury to the endothelium contributes to the development of AKI. Endothelial damage increases leukocyte adherence, platelet aggregation, vasoconstriction and podocyte dysfunction[43]. One function of the endothelium is to prevent protein filtration into the interstitium. In the glomerulus, this barrier is maintained by a negatively charged gel called the glycocalyx. It acts as a molecular sieve, allowing for the filtration of water and preventing the passage of large molecules[44].

Loss of the glycocalyx is thought to relate to microthrombi, ischaemia-reperfusion-injury, oxidative stress and systemic inflammation; all of which may occur following CPB[10,44,45]. Subsequent exposure of endothelial cells to the blood causes aggregation of platelets and neutrophils, local inflammation and oedema[45]. Dysfunctional endothelium reduces the capacity for arteriolar dilation. Proteins, are lost into the Bowman's capsule where they are taken up by the podocytes, inducing apoptosis and effacement[44]. Damage to podocytes and accumulation of albumin in Bowman's capsule then potentiate parietal cell proliferation and glomerulosclerosis[44]. Animal models identify CPB as a cause for damage to the endothelial glycocalyx and impaired microvascular perfusion of the renal cortex[46]. Human studies suggest that degradation of the glycocalyx begins during cardiac surgery[47] and persists into the postoperative period[48,49].

Administration of albumin protects the glycocalyx. In animal models, administration of albumin resulted in reduced measures of glycocalyx dysfunction[50,51]. Albumin was also observed to prevent endothelial apoptosis, improve endothelial integrity, and reduce fluid extravasation. The mechanism for the protective properties of albumin in this context remains unclear.

Antioxidant activity

Albumin contributes to antioxidant activity in plasma. Over 70% of free radical neutralisation is attributable to albumin[52]. This property is predominantly due to its abundance and the existence of a thiol group in the cysteine-34 position of its molecular structure. Thiols are known for their reaction with, and 'trapping' of, reactive oxygen species. In healthy subjects, 70-80% of serum albumin is reduced at the cysteine-34 thiol, while an additional 25% may be oxidised further[53,54]. Albumin's secondary antioxidant mechanism acts via the binding of bile salts and metal ions. In their unbound form, these ions may generate free radicals[55].

A randomised trial involving 20 patients with lung injury found that concentrated albumin infusion caused a statistically significant increase in serum thiol concentrations ($r=0.983$, $p<0.01$) and antioxidant capacity ($r=0.876$, $p=0.01$)[56]. In another study, albumin was isolated from the serum of 125 diabetic patients and antioxidant capacity and thiol content measured[57]. Both variables were inversely associated with glomerular filtration rate, suggesting that oxidative stress associated with advanced renal disease leads to oxidisation of the cysteine-34 thiol and subsequent depletion of antioxidant capacity. It should be noted that the fraction of reduced albumin varies between commercially available preparations[58]. However, when using a preparation of albumin that was predominantly oxidised, Lang et al.[59] found that concentrated human albumin still protected bovine endothelial cells from oxidative damage and concluded that this effect must have been due to a property of albumin other than its thiol content.

Anti-inflammatory effects

Albumin has the ability to modulate the immune response. A small randomised trial found that, in patients with spontaneous bacterial peritonitis (SBP), 20% albumin administration significantly reduced levels of pro-inflammatory cytokines TNF-α and IL-6 in plasma and ascitic fluid ($p<0.01$)[60]. This result is especially significant given that SBP is associated with renal failure in one third of patients, likely due to high levels of cytokines that persist even after the resolution of infection[60]. These findings suggest that albumin may bind to cytokines, thereby decreasing their potential to do harm. However, the conclusions of this study are limited by the small sample size used and the lack of blinding.

In a rodent model of acute lung injury, 45 rats with shock were randomly allocated for resuscitation with Hartmann's solution, 5% albumin or 25% albumin[61]. Resuscitation with 25% albumin led to decreased neutrophil counts in bronchoalveolar fluid and lower degree of histopathological lung injury. This suggests that albumin alters neutrophil activity by reducing neutrophil sequestration. In a study of 63 pigs with shock, lower neutrophil activation was achieved after resuscitation with 25% albumin compared to crystalloid and 5% albumin[62]. Cantin et al. also found that albumin modulated the immune response in rodents, this time by decreasing levels of glutathione which subsequently protected against TNF-α mediated activation of nuclear factor kappa-B[63]. However, the translation of these results into humans is unclear.

Clinical trials of albumin and cardiac surgery

In the first and only clinical trial investigating albumin in this way, Lee et al. randomised 220 patients with undergoing off-pump cardiac surgery to receive either preoperative 20% albumin or saline[30]. This, double-blinded study included patients with preoperative serum albumin level less than 40g/l. The volume of fluid administered varied between 100-300ml and was titrated to each patient's preoperative serum albumin level. Albumin administration reduced the risk of AKI by Kidney Disease: Improving Global Outcomes (KDIGO)[64] (RR=0.533, p=0.048) and Acute Kidney Injury Network (AKIN) criteria (RR=0.557, p=0.031). Results regarding severe AKI or AKI requiring dialysis were not statistically significant. The low event rates for these variables suggest the sample size was insufficient; however, it may also be true that albumin only exhibits protection in mild AKI.

There is insufficient scientific literature to determine the utility of exogenous albumin to prevent CSA-AKI. More clinical trials are needed in this area.

Objectives {7}

We hypothesise that an infusion of 20% albumin will reduce the proportion of patients who develop postoperative AKI after high-risk cardiac surgery, when compared to standard care.

The objective of this study is to evaluate the impact of postoperative 20% albumin infusion on kidney function after high-risk cardiac surgery.

Trial design {8}

The ALBICS (ALBumin Infusion and acute kidney injury following Cardiac Surgery) study is a multicentre, parallel-group, open-label, prospective, randomised controlled, superiority trial.

Methods

Participants, interventions and outcomes

Study setting {9}

Patients will be recruited at the following Australian hospitals: Monash Medical Centre, Cabrini Hospital, University Hospital Geelong, Prince of Wales Hospital and Prince of Wales Private Hospital.

Eligibility criteria {10}

To be included in the study, patients must meet all of the following inclusion criteria:

- aged 18 years or older;
- have undergone cardiac surgery;
- at least one of the following:

    1. estimated glomerular filtration rate (eGFR) <60mL/min/1.73m^2, or
    2. have had a combined valve and coronary procedure, or
    3. two or more valve procedures, or
    4. surgery involving the thoracic aorta.

Patients meeting any of the following exclusion criteria will be excluded from the study:

- eGFR <15mL/min/1.73m^2,
- serum albumin <20g/l,
- dialysis dependence,
- kidney transplant,
- undergone off-pump cardiac surgery,
- requiring extra-corporeal life support or ventricular assist device immediately post-operative,
- Jehovah's Witness.

Who will take informed consent? {26a}

A study investigator will obtain informed consent from each participant prior to enrolment in this study. The investigator will discuss the risks and benefits of participation and will check that the patient comprehends the information provided. Consent will be voluntary and free from coercion.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable.

Interventions

Explanation for the choice of comparators {6b}

Patients will be randomly allocated to either the intervention group (albumin 20% and standard care) or the comparator group (standard care only). Standard care was chosen as an appropriate comparator given that the intervention is proposed as an adjunct to routine care.

Intervention description **{11a}**

Patients randomised to the intervention arm will receive an intravenous infusion of 20% albumin for 16 hours at 20ml/hour as soon as possible after ICU admission, where the time to initiation of infusion does not exceed 6 hours.

Patients randomised to the standard care arm will not receive any 20% albumin for the first 24 hours of ICU admission.

Relevant concomitant care permitted or prohibited during the trial {11d}

Both treatment groups will receive standard care as per the clinician in charge. This includes any background treatments considered routine care such as vasopressors, inotropes, ventilation and initiation of dialysis. Administration of 4% albumin will not be restricted.

Criteria for discontinuing or modifying allocated interventions {11b}

For those randomised to receive 20% albumin, the infusion may be ceased if the patient develops an allergic reaction or fluid overload (shortness of breath, increased oxygen requirements).

For those randomised to receive standard care, 20% albumin may be administered within the first 24 hours if it is deemed clinically indicated. These decisions will be at the discretion of the clinician in charge.

Strategies to improve adherence to interventions {11c}

The design for the ALBICS study will be presented to staff at each participating site, with input from intensive care specialists, cardiac surgeons, and cardiac anaesthetists. These meetings will improve consistency of protocol implementation. Other measures include presentations and visual information provided to clinical staff to reduce the risk of inadvertent protocol deviation.

Provisions for post-trial care {30}

All patients enrolled in this trial will receive standard postoperative surgical care beyond 24 hours. Patients will be followed as per the study protocol.

Outcomes {12}

The primary outcome is the proportion of patients that develop AKI within hospital stay up to Day 28 post-enrolment. AKI is defined by creatinine-based KDIGO criteria (Table 1)[64]. Patients after cardiac surgery often have polyuria in the first few hours after surgery and they are frequently given diuretic

therapy after day 1 postoperatively. For this reason, urine output may not a be a reliable measure of AKI. In addition, oliguria may contribute to overdiagnosis of CSA-AKI given that it is a physiological response to cardiac surgery and is not associated with adverse outcome[65,66].

Secondary and tertiary outcomes are described in Table 2. These outcomes were chosen as appropriate measures of acute deterioration or recovery, and the haemodynamic effects of albumin.

Table 1 KDIGO creatinine based criteria for diagnosis and staging of AKI

Stage	Serum creatinine
1	1.5–1.9 times baseline within 7 days; or ³ 26.5 µmol/l (³ 0.3 mg/dl) increase within 48 hours
2	2.0-2.9 times baseline within 7 days
3	³ 3.0 times baseline within 7 days; or increase in to ³ 353.6 µmol/l (³ 40 mg/dl); or initiation of renal replacement therapy

Table 2 Study outcomes

Primary outcome	AKI (any stage)
Secondary outcomes	AKI stage II and III Mortality ICU LOS (hours) Hospital LOS (days) Ventilation time (hours)
Tertiary outcomes	Peak SCr (µmol/l) Serum albumin at 24 hours (g/l) Serum Hb at ICU discharge (g/l) Inotrope and vasopressor therapy Net fluid balance at 48 hours (ml) Quantity of RBCs transfused over first 48 hours (ml) Initiation of CRRT

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; Hb, haemoglobin; ICU, intensive care unit; LOS, length of stay; RBC, red blood cell; SCr, serum creatinine.

Participant timeline {13}

Patients will be followed up until the 28th day post-enrolment or hospital discharge, whichever occurs first. Data collected will be restricted to the parameters that are necessary to define clinical characteristics and will be obtained from routine laboratory investigations and hospital records (Figure 2). This includes baseline demographics, outcome measures, physiological parameters, operative data, therapeutic interventions, death and other adverse events.

Sample size {14}

The sample size for the study was determined by *a priori* power analysis. The anticipated incidence of AKI in the comparator group was based upon a cohort of over 25,000 patients that reported AKI in 30% of patients undergoing cardiac surgery[1]. Based on this estimate, the inclusion of 590 patients will achieve 80% power to detect a 10% absolute risk reduction in the risk of AKI (2-sided p=0.05).

Recruitment {15}

Recruitment will take place at metropolitan teaching hospitals that see a large number of cardiac cases. This will allow sufficient enrolment to reach the target sample size in a timely manner.

Assignment of interventions

Sequence generation {16a}

A permuted block, computer generated, randomisation sequence with fixed block size, stratified by hospital and eGFR (<60mL/min/1.73m^2 or >60mL/min/1.73m^2) will be used to allocate participants in a 1:1 ratio.

Concealment mechanism {16b}

Patients will be allocated using REDCap (Research Electronic Data Capture), a computer-based software for data collection. REDCap will use the prepared randomisation schedule to determine the allocation of the participant in a traceable manner, such that the treatment group is not knowable prior to allocation and cannot be changed after it. While blinding clinicians to treatment allocation is desirable, it is not deemed feasible for this study. We minimise bias through allocation concealment and evaluation of objective laboratory-based data.

Implementation {16c}

The allocation sequence will be generated by a person not involved with enrolment or future analysis. Participants will be screened and randomised on admission to intensive care by a site investigator or member of research support staff.

Blinding {17a}

While blinding is a desirable feature of clinical trials, the study outcomes are distant from the intervention and the open-label design is unlikely to influence the outcome at 28 days.

Procedure for unblinding {17b}

Not applicable.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All study data will be collected by research staff at each site using an electronic case report form and stored in a password protected, traceable, database managed by Monash University. All parameters will defined in a data dictionary detailing the way in which data should be collected. The central coordinating investigators will ensure site visits for data monitoring, timely resolution of queries, and correction of errata during quality control checks.

Plans to promote participant retention and complete follow-up {18b}

The intervention is to be administered soon after ICU admission and will last a short duration of time, likely while participants are unconscious. Patients will be approached once conscious and practical to do so, to inform them of study progress and follow up required. Obtaining data from medical records and and laboratory data will ensure complete follow up.

Data management {19}

Study data was collected and managed using REDCap electronic data capture tool hosted and managed by Helix (Monash University)[67,68]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Confidentiality {27}

Wherever possible, identifying information will be removed. Only de-identified data will be entered into the case report form. Identifying documents such as consent forms will be kept in locked rooms that may only be accessed by authorised personnel.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable. This study evaluates data collected via routine laboratory investigation.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Normality of continuous variables will be assessed and log-transformed where appropriate. Equality of variance for normally distributed variables will be assessed using Levene's test. Between group comparisons will be performed using Chi-squared tests for equal proportion, Student's t-test for continuous variables with equal variance, Welch's t-test for continuous variables with unequal variance, and Mann-Whitney U test otherwise. Categorical variables will be described as frequency with proportions (%). Continuous variables will be expressed as mean ± standard deviation if normally distributed, and median with interquartile range if not normally distributed. Analysis will be performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Methods for additional analyses {20b}

A subgroup analysis will be performed in patients with and without baseline renal insufficiency (eGFR $<60 mL/min/1.73m^2$ or $\geq 60 mL/min/1.73m^2$).

Interim analyses {21b}

An interim analysis is not planned.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Data will be analysed using an intention-to-treat methodology. A per-protocol sensitivity analysis will also be conducted. Ongoing site education would reduce the risk of protocol deviation. We will adjust for missing data using multiple imputation.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The trial steering committee is composed of investigators from the departments of cardiothoracic surgery and intensive care. The chair of the steering committee, through the School of Clincial Sciences at Monash Health, will be coordinating this study.

Composition of the data monitoring committee, its role and reporting structure {21a}

Albumin administration is considered part of routine postoperative care after cardiac surgery. In addition, the open-label design will allow the assignment of adverse events to the intervention. Serious adverse events will be reviewed regularly by the study steering committee and reported to the ethics committee.

Adverse event reporting and harms {22}

Adverse events will be collected in accordance with the Monash Health Human Research Ethics Committee guidelines. Serious adverse reactions will be reported to the institutional research support services at each site. Significant safety issues will be reported to the Monash Health Human Research Ethics Committee.

Frequency and plans for auditing trial conduct {23}

After each site is activated and has enrolled five patients, site monitoring of the consenting process, protocol adherence, and data collection will be conducted. At the end of this study, all sites will be monitored for protocol adherence and completion of data collection.

Plans for communicating important protocol amendments to relevant parties {25}

Protocol ammendments will be promptly distributed to all relevant parties via the appropriate channels; for example by email or formal ethics review.

Dissemination plans {31a}

The study will be published in the name of the individual investigators and in the group name “ALBICS study investigators”. Full credit will be given to all collaborating investigators, research staff and institutions. All authors will comply with the internationally agreed upon requirements for authorship and will approve the manuscript before submission.

The final results will be presented at one or more major scientific meetings and will be published in a peer-reviewed scientific journal that discusses care of critically ill patients. We will ensure that results are available to study participants and for translation to intensive care with concurrent recommendations for change in practice based on the study findings.

Availability of data and materials {29}

The datasets for the completed study will be available according to Monash University data sharing protocols. The authors have no contractual agreements to disclose that would limit such access.

Plans to give access to the full protocol, participant level-data and statistical code {31c]

The full protocol, participant-level dataset, and statistical code will be available in accordance with Monash University data sharing protocols.

Trial status

Recruitment began on 08 July 2019. As at October 2020, 25 patients have been enrolled in the ALBICS study. The COVID-19 pandemic has had a significant impact on study progress, having halted recruitment at all participating sites. We expect the trial to reach completion in 2023. Working protocol version 2.9, 16 September 2019.

Abbreviations

AKI	acute kidney injury
AKIN	Acute Kidney Injury Network

CPB	cardiopulmonary bypass
CSA-AKI	cardiac surgery associated-acute kidney injury
eGFR	estimated glomerular filtration rate
ICU	intensive care unit
IL	interleukin
KDIGO	Kidney Disease: Improving Global Outcomes
mRNA	messenger ribonucleic acid
REDCap	Research Electronic Data Capture
RCT	randomised controlled trial
SBP	spontaneous bacterial peritonitis
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TNF	tumour necrosis factor

Declarations

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- Cabrini Hospital: Vineet Sarode, Shannon Simpson
- Prince of Wales Hospital (public and private): Yahya Shehabi, David Bihari, David Collins

Author’s contributions {31b}

Authors MB, PB, AP, WA and YS contributed to the conception and design of this study. YS is the Coordinating Principal Investigator. AP, VS, MR and YS are the Site Principal Investigators at Monash Health, Cabrini Health, Barwon Health and Prince of Wales Hospital. All authors are involved with trial coordination. All authors read and approved the final manuscript.

Funding {4}

This study will be internally funded by the intensive care or cardiothoracic department at each site.

Ethics approval and consent to participate {24}

Ethics approval was granted by the Monash Health Human Research Ethics Committee (Review reference: HREC/51818/MonH-2019-174088(v3)) and the Monash University Human Research Ethics Committee (Review reference: 2019-20388-31894). Ethics approval and local site governance was obtained at all participating sites before study commencement.

Consent for publication {32}

Model consent forms are availalable upon request.

Competing interests {28}

The authors declare that they have no competing interests.

Conclusions

Acute kidney injury after cardiac surgery is common. Cardiopulmonary bypass appears to be an important factor and may precipitate AKI through various mechanisms related to renal hypoperfusion, inflammation and oxidative stress. Albumin's oncotic and pharmacological properties demonstrate its potential benefit for the prevention of CSA-AKI. A large, multicentre randomised trial is needed to determine this definitively. The ALBICS study is designed to answer this question.

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Figures

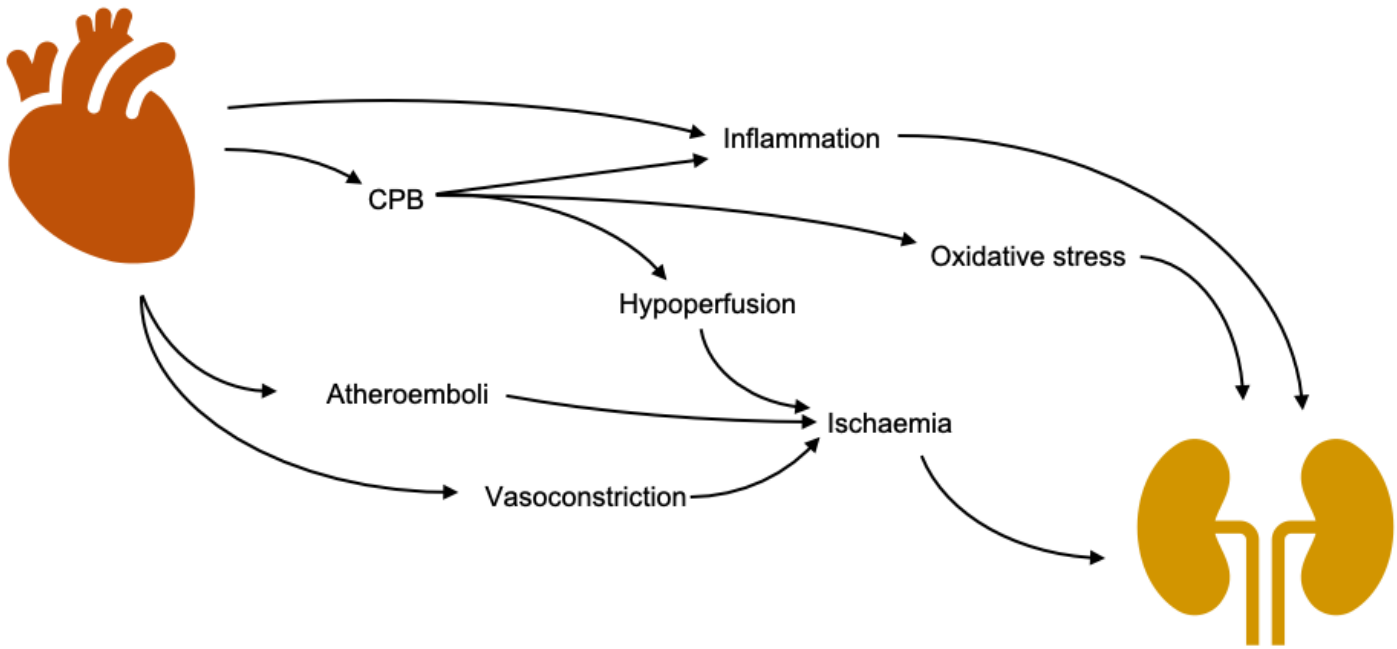

Figure 1

Pathophysiology of CSA-AKI

STUDY PERIOD									
	Enrolment	Allocation	Post-allocation						Day 28 or discharge
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_4	*etc.*	*ICU discharge*	t_x
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Cardiac surgery	X								
Allocation		X							
INTERVENTIONS:									
20% albumin			16 hours ↔						
Routine care			24 hours ↔						
ASSESSMENTS:									
Demographics, LVEF, medications, Hct, eGFR, APACHE III & risk of death, operative data	X								
Serum Hb	X							X	
Serum albumin	X		X	X	X	X	etc.		X
SCr	X		X	X	X	X	etc.		
Duration of ventilation, initiation of IV frusemide or non-loop diuretics, CRRT, Reoperation, ICU readmission			X	X	X	X	etc.		
Total and type of fluid input/output	During surgery		48 hours ↔						
Inotrope and vasopressors	During surgery		X	X	X	X	etc.		
ICU mortality, ICU discharge date/time								X	
Hospital discharge date/time, hospital mortality									X

Figure 2

Data collection timeline (SPIRIT figure) CRRT, continuous renal replacement therapy; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; Hct, haematocrit; ICU, intensive care unit; LVEF, left ventricular ejection fraction; SCr, serum creatinine.