Can J Anesth/J Can Anesth (2021) 68:1197–1213
https://doi.org/10.1007/s12630-021-01991-7

REVIEW ARTICLE/BRIEF REVIEW

Albumin in adult cardiac surgery: a narrative review
L'albumine en chirurgie cardiaque adulte : un compte rendu narratif

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Received: 8 January 2021 / Revised: 3 March 2021 / Accepted: 4 March 2021 / Published online: 21 April 2021

Abstract

Purpose *Intravascular fluids are a necessary and universal component of cardiac surgical patient care. Both crystalloids and colloids are used to maintain or restore circulating plasma volume and ensure adequate organ perfusion. In Canada, human albumin solution (5% or 25% concentration) is a colloid commonly used for this purpose. In this narrative review, we discuss albumin supply in Canada, explore the perceived advantages of albumin, and describe the clinical literature supporting and refuting albumin use over other fluids in the adult cardiac surgical population.*

Source *We conducted a targeted search of PubMed, Embase, Medline, Web of Science, ProQuest Dissertations and Theses Global, the Cochrane Central Register of Controlled trials, and the Cochrane Database of Systematic Reviews. Search terms included albumin, colloid, cardiac surgery, bleeding, hemorrhage, transfusion, and cardiopulmonary bypass.*

Principal findings *Albumin is produced from fractionated human plasma and imported into Canada from international suppliers at a cost of approximately $21 million CAD per annum. While it is widely used in cardiac surgical patients across the country, it is approximately 30-times more expensive than equivalent doses of balanced crystalloid solutions, with wide inter-institutional variability in use and no clear association with improved outcomes. There is a general lack of high-quality evidence for the superiority of albumin over crystalloids in this patient population, and conflicting evidence regarding safety.*

Conclusions *In cardiac surgical patients, albumin is widely utilized despite a lack of high- quality evidence supporting its efficacy or safety. A well-designed randomized controlled trial is needed to clarify the role of albumin in cardiac surgical patients.*

Résumé

Objectif *Les liquides intravasculaires sont une composante nécessaire et universelle des soins aux patients de chirurgie cardiaque. Les cristalloïdes et les colloïdes sont utilisés pour maintenir ou restaurer le volume plasmatique en circulation et assurer une perfusion adéquate des organes. Au Canada, les solutions d'albumine humaine (concentration de 5 % ou 25 %) constituent un colloïde couramment utilisé à cette fin. Dans*

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ce compte rendu narratif, nous discutons de l'approvisionnement en albumine au Canada, explorons les avantages perçus de l'albumine et décrivons la littérature clinique soutenant ou réfutant l'utilisation de l'albumine par rapport à d'autres solutions pour la population chirurgicale cardiaque adulte.

Sources *Nous avons effectué une recherche ciblée dans les bases de données PubMed, Embase, Medline, Web of Science, ProQuest Dissertations and Theses Global, le Cochrane Central Register of Controlled trials et la Cochrane Database of Systematic Reviews. Les termes de recherche (en anglais) incluaient albumine, colloid, cardiac surgery, bleeding, hemorrhage, transfusion, et cardiopulmonary bypass (soit albumine, colloïde, chirurgie cardiaque, saignement, hémorragie, transfusion et circulation extracorporelle).*

Constatations principales *L'albumine est fabriquée à partir de plasma humain fractionné et importée au Canada à partir de fournisseurs internationaux au coût d'environ 21 millions CAD par année. Bien qu'elle soit largement utilisée chez les patients de chirurgie cardiaque à travers le pays, elle est environ 30 fois plus coûteuse que des doses équivalentes de solutions cristalloïdes équilibrées, avec une grande variabilité interinstitutionnelle quant à son utilisation et aucune association claire avec des devenirs améliorés. Il n'existe en général pas de données probantes de qualité élevée confirmant la supériorité de l'albumine par rapport aux cristalloïdes dans cette population de patients, et les données probantes quant à son innocuité sont contradictoires.*

Conclusion *Chez les patients de chirurgie cardiaque, l'albumine est largement utilisée en dépit d'un manque de données probantes de haute qualité soutenant son efficacité ou son innocuité. Une étude randomisée contrôlée bien conçue est nécessaire pour clarifier le rôle de l'albumine chez les patients de chirurgie cardiaque.*

Keywords Albumins · cardiac surgical procedures · cardiopulmonary bypass · crystalloid solutions · colloids · fluid therapy · blood transfusion

Cardiac surgical patients uniformly require intravascular fluid administration. Crystalloids, colloids, and allogeneic blood products are all commonly infused during routine patient care, both for priming of the cardiopulmonary bypass (CPB) circuit and maintenance of adequate intravascular volume in response to blood loss.[1] Colloids are synthetic or natural substances that exert an oncotic pressure facilitating intravascular fluid retention. They differ substantially from crystalloid solutions, which are electrolyte solutions of varying compositions and physiologic similarity to human plasma (Table 1). Synthetic colloids are not commonly used in Canada because of safety concerns, particularly relating to the hydroxyethyl starches.[2] Thus, intravenous albumin, which is a natural protein colloid purified from human plasma, is the colloid of choice at many Canadian cardiac surgical centres. Albumin is distributed by Canadian Blood Services and Héma-Québec as a sterile, pathogen-reduced blood product in a 5% (250 mL [12.5 g] or 500 mL [25 g]) solution and a 25% (100 mL [25 g]) solution. The 5% solution is thought to exert a colloid osmotic pressure similar to that of human plasma, while the 25% solution is typically used to treat oncotic deficits.

Albumin is a water-soluble, globular, negatively charged 65 kDa protein that is endogenously synthesized in the liver and catabolized in the endothelium, as well as degraded in muscle, skin, and other organs.[3] It represents approximately half of the total plasma protein content, and while approximately 60% of albumin is interstitial and is an important contributor to interstitial oncotic pressure, much of the debate surrounding albumin as a resuscitation fluid is centred on the 40% of total body albumin found intravascularly, which is thought to contribute to 80% of total plasma oncotic pressure.[3] Despite the focus on intravascular volume expansion, albumin has numerous other biologic roles, including binding of endogenous and exogenous ligands (drugs, bilirubin, ions, hormones), antioxidant properties, and nitric oxide modulation.[3]

Albumin was first crystallized in 1934, and subsequently introduced as an intravascular solution in numerous jurisdictions throughout the 1940's—being widely adopted throughout the decades as a resuscitation fluid in a variety of patient populations.[4] The crystalloid *vs* colloid debate of the last several decades[5] brought albumin into the spotlight in the critical care literature, and germinated more rigorous study of its potential advantages and drawbacks. This ongoing debate produced a number of large, randomized controlled trials (RCTs) of albumin use in critically ill patients that even today provide the highest quality evidence informing use in many other patient populations, where the evidence is often restricted to retrospective observational data or small prospective studies.[6–8]

There is little clarity regarding the role of albumin in cardiac surgical patients, with significant heterogeneity in where and how albumin is used in this population in Canada and elsewhere.[9,10] Given the well-known safety concerns associated with synthetic colloid alternatives to albumin, such as the hydroxyethyl starches,[11] the role of albumin in lieu of or to supplement crystalloids will be the main focus of this article. In this narrative review, our aims are fourfold: 1) to detail the supply and economic

Table 1 Reported characteristics of colloids (albumin) *vs* balanced crystalloids[13,14,115]

Characteristics	Balanced crystalloid solution (PLASMA-LYTE 148)*	Albumin (5% or 25% albumin)
Approximate cost	2 CAD per 1 L	62 CAD per dose[13] (25% 100 mL or 5% 500 mL)
Typical *in vitro* pH	4–6.5	6.4–7.4
Typical constituents	Sodium: 140 $mEq \cdot L^{-1}$ Potassium: 5 $mEq \cdot L^{-1}$ Chloride: 148 $mEq \cdot L^{-1}$ Magnesium: 3 $mEq \cdot L^{-1}$ Acetate: 27 $mEq \cdot L^{-1}$ Gluconate: 23 $mEq \cdot L^{-1}$	Sodium: 130–160 $mEq \cdot L^{-1}$ Chloride: 109–137 $mEq \cdot L^{-1}$
Oncotic pressure effects	Lower, with intravascular and interstitial fluid replacement effect but potential for protein dilution and greater peripheral edema	Higher, allowing for translocation of interstitial fluid into plasma volume. Less peripheral edema but potential for pulmonary edema in capillary leak states and excessive intravascular volume expansion with mobilization of fluid intravascularly
Plasma volume expanding effect	Variable depending on serum oncotic pressure	450 mL per 25-g dose
Perceived effect on fluid balance	Greater interstitial edema and higher cumulative fluid balance	Lower interstitial edema and lower cumulative fluid balance[123]
Perceived hemodynamic effect	Shorter lived increase in plasma volume	Sustained increase in plasma volume (likely less in critically ill patients)[123]

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environment of albumin use in Canada; 2) to explore the perceived advantages of albumin suggested by early clinical or preclinical data compared with other resuscitation fluids in the perioperative management of cardiac surgery patients; 3) to describe the clinical evidence relating to albumin use in cardiac surgical patients, which is largely informed by the more general surgical and critical care settings; and 4) to highlight the most important controversies drawn from the currently available evidence, including potential future areas of research.

Methods

This narrative review is based on a targeted search of the literature databases including PubMed, Embase, Medline, Web of Science, ProQuest Dissertations and Theses Global, the Cochrane Central Register of Controlled trials, and the Cochrane Database of Systematic Reviews, using search terms combining *albumin, colloid, cardiac surgery, bleeding, hemorrhage, transfusion,* and *cardiopulmonary bypass.* Searches of trial registries (ClinicalTrials.gov and WHO ICTRP) were also included. References cited in the retrieved literature were also examined for relevance. Articles were included if they described an association between albumin use in cardiac surgical patients and clinical outcomes. Non-English language articles and abstracts not subsequently published as articles were excluded. This review followed the SANRA reporting recommendations for high-quality narrative reviews.[12]

The context of albumin prescribing in Canada

As a blood product, albumin is relatively expensive, at approximately 62 CAD per dose (5% 500 mL or 25% 100 mL), compared with approximately 2 CAD per 1 L dose for crystalloids. Medical use of albumin solution is estimated to cost the Canadian healthcare system approximately 21 million CAD per annum,[A] 20% of which is related to cardiac surgical patients.[13] Currently, Canada lacks a plasma fractionation company, and is dependent on other developed nations where donors are paid (largely the United States) for its albumin supply (Table 2).

Canadian Blood Services officially recognizes albumin use for a narrow set of specific indications, including 1)

[A] *Roman R. In:* Cullum J (Ed.): Medical Services & Hospital Relations, Canadian Blood Services; 2021 (personal communication).

Table 2 Characteristics of common intravenous albumin solution products available in Canada[117,124–126]

Supply	Brand name	Dosage form and strength	Characteristics compared with human plasma	Components
Manufactured by Grifols Therapeutics LLC, based in North Carolina, United States Obtained from pooled human plasma using Cohn cold ethanol fractionation process Imported and distributed by Grifols Canada Ltd, Mississauga	Plasbumin®-5	5% sterile solution of albumin in aqueous diluent	Isotonic pH 6.4–7.4	Stabilizers include acetyltryptophan and sodium caprylate Sodium concentration approximately 145 $mEq{\cdot}L^{-1}$ Chloride concentration approximately 109.4 $mEq{\cdot}L^{-1}$ Buffered with sodium carbonate Aluminum content $\leq$ 200 $\mu g{\cdot}L^{-1}$ No preservatives
	Plasbumin®-25	25% sterile solution of albumin in aqueous diluent	Hyperoncotic pH 6.4–7.4	
Manufactured by CSL Behring AG in Switzerland and CSL Behring LLC in Illinois, USA Obtained from pooled human plasma by low temperature controlled fractionation via the Cohn process modified by Kistler Nitschmann Imported and distributed by CSL Behring Canada, Inc, in Ottawa	Alburex® 5	5% sterile solution of albumin in aqueous diluent	Mildly hypooncotic pH 6.4–7.4	Stabilizers include Sodium N-acetyltryptophanate and sodium caprylate Sodium concentration approximately 140 $mEq{\cdot}L^{-1}$ Chloride concentration approximately 123.6 $mEq{\cdot}L^{-1}$ May contain hydrochloric acid or sodium hydroxide as buffering agents Aluminum content $\leq$ 200 $\mu g{\cdot}L^{-1}$ No preservatives
	Alburex® 25	25% sterile solution of albumin in aqueous diluent	Hyperoncotic pH 6.4–7.4	

patients with liver disease and bacterial peritonitis, 2) large volume paracentesis in patients with cirrhosis, 3) hepatorenal syndrome type 1, 4) thermal injury involving $>$ 50% body surface area, and 5) therapeutic plasma exchange.[14] Notably, this list does not include the resuscitation of cardiac surgical patients. Nevertheless, albumin remains freely available for clinicians to prescribe at their discretion. The provincial Ministries of Health across Canada are required to pay for all albumin orders issued in Canadian hospitals, regardless of the cited indication for use or the quality of evidence supporting its use in a given patient population. Despite general encouragement at the local level and from externally published advisory groups encouraging "restrictive" albumin use, between 2003 and 2009 the amount of albumin issued to Canadian hospitals (excluding Québec) grew by 51.8% overall.[13]

Practice surveys confirm the popularity of albumin as a resuscitation fluid in North America in cardiac surgical patients, whereas in Europe, balanced crystalloid is preferred.[15,16] In a European practice survey, crystalloids or a combination of crystalloids with synthetic colloids (primarily gelatins) were used in 89% of perioperative cardiac surgical patients. Only 11% of European cardiac anesthesiologists considered using albumin in the operating room, and the majority did not change their practice for postoperative care in the intensive care unit (ICU).[17] However, in the United States, 37% of anesthesiologists and 39% of surgeons considered albumin their first choice fluid in the operating room when replacing intravascular volume for non-bleeding patients, favouring it even over crystalloids in many situations.[15] Given the significant associated costs, there have been noted initiatives to decrease albumin utilization at different centres in the United States.[17] Nevertheless, the economic benefits of albumin reduction and its impact on patient outcomes is based on only a few studies at present,[17] and currently there

are no high-quality, large RCTs or systematic reviews and meta-analyses available.[17–19]

There are few appealing substitutes to albumin that offer a colloid oncotic effect and have acceptable safety in cardiac surgical patients. While frozen plasma has in the past been suggested for volume expansion and prevention of coagulopathy, evidence suggests that this practice has little benefit while exposing the patient to allogeneic blood products and potential transfusion complications, particularly transfusion-related acute lung injury.[20–22] With an overall decline in recent years in the use of synthetic colloids (i.e., hydroxyethyl starches) because of their association with increased incidence of acute kidney injury (AKI), coagulopathy, and mortality in the critical care population, there are few viable synthetic colloid options remaining.[23–25] Perhaps unsurprisingly given the lack of alternatives, there has been a resultant resurgence in the use of human albumin solution to supplement crystalloids for resuscitation. Thus, despite a lack of compelling clinical evidence indicating superiority over balanced crystalloids, albumin remains a frequently utilized option in the armamentarium of many perioperative clinicians.[26–30]

The perceived advantages of albumin influencing its use in cardiac surgical patients: preclinical and preliminary clinical evidence

Intravenous fluid therapy is a key component of perioperative cardiac surgical care. Both crystalloids and colloids are commonly used for priming the CPB circuit, volume expansion on CPB, management of intra- and postoperative hypotension, and volume restoration in the bleeding patient prior to or in addition to the provision of allogeneic blood products. Individualized hemodynamic-guided fluid therapy and blood product transfusion, with judicious vasopressor and inotrope use, is a crucial component of perioperative management in cardiac surgical patients to maintain end-organ perfusion, avoid complications of excessive fluid volumes, and improve patient outcomes.[1,31–33]

Cardiac surgical patients tend to receive large volumes of intravenous fluids, particularly in the first 24 postoperative hours, with marked heterogeneity in clinical practice and little consensus on the optimal fluid to be used.[34,35] The principles guiding fluid management in cardiac surgery differ from other types of major surgery. The fluid kinetics are more complex and involve a delicate balance of multiple perioperative factors.[31] These include the patient's age, body weight, intraprocedural CPB (circuit, priming volume, fluid composition), cardioplegia solution, thermoregulation, and the use of vasoactive drugs. Low cardiac output and renal dysfunction are common and frequently multifactorial in their etiology.[36,37] Surgical factors such as the procedure specifics, surgical urgency, and complexity of the case also contribute.[31] The inflammatory changes and direct tissue injury associated with both CPB, ischemia-reperfusion injury, and the surgery itself result in endothelial glycocalyx dysfunction, and altered hydrostatic and oncotic pressure gradients, which lead to increased vascular permeability and transcapillary fluid shifts.[36,37]

While the superiority of intravenous albumin over balanced crystalloids as a volume expander in cardiac surgery patients has not been established, its use is primarily guided by the belief that it is more effective than crystalloids in preventing interstitial edema through its oncotic effect, and in maintaining microcirculatory perfusion and endothelial glycocalyx integrity.[15,38,39] Relating to its colloid oncotic effect, albumin is thought to produce a more sustained intravascular volume expansion compared with crystalloids for a given volume, ostensibly preventing generalized fluid overload and minimizing interstitial edema—with resultant beneficial end-organ effects. This potential volume-sparing effect of colloids is perceived as advantageous in preventing fluid overload complications such as pulmonary edema and right ventricular impairment; nevertheless, it is variably supported by the published literature.[39–41] Additionally, albumin may also function as an antioxidant to reduce inflammation,[42] may play a role in preserving platelet number and function,[43] and through its action as a nitric oxide scavenger may decrease nitric oxide mediated vasodilation.[44] These effects may be of particular benefit during and after CPB.

Avoiding fluid overload is one of the central tenets of the perioperative care of cardiac surgical patients. Both hypovolemia and hypervolemia are associated with end-organ dysfunction, and the associated morbidity has been described as a "parabolic-U-shape" curve.[45] In non-cardiac surgery, a positive fluid balance during the first three to seven days in the ICU is associated with increased in-hospital mortality.[46,47] In many cardiac surgery patients, the presence of concomitant cardiopulmonary and renal dysfunction does not allow "excessive" volume administration to treat hypotension. While "excessive" is not well defined, a retrospective study of 1,358 cardiac surgical patients showed a more than three-fold increase in 90-day mortality after 4 L of intraoperative fluid.[48] A progressively positive cumulative fluid balance may also be associated with increased renal adverse events, including new requirement for postoperative dialysis.[49]

Given the association of excess fluid with adverse outcomes, albumin has become popular as a colloid "volume-sparing" bridge to restore peripheral perfusion and to wean vasopressors, although this is not a

standardized practice.[39] Notably, the addition of albumin to balanced crystalloid resuscitation to minimize the total fluid balance has not been definitely associated with improved patient outcomes such as major morbidity or mortality. Four to five percent human albumin solution is generally iso-oncotic and isotonic with plasma, and is thought to lead to an intravascular volume expansion similar to the infused volume, whereas hyperoncotic 20–25% albumin solutions are purported to result in an intravascular volume increase four times higher than the infused volume.[14] This expansion effect may last for up to 24 hr, although in sicker patients with more severe or persistent endotheliopathy the magnitude and duration of this effect may be unpredictable.[50] It has been shown that the actual ratio of intravascular to administered volume of colloids in critically ill patients may be closer to 1:1.2, which is significantly less than previously believed.[51,52] This magnitude of oncotic effect may in part be modulated by impairments in the integrity of the endothelial glycocalyx associated with cardiac surgery and CPB, leading to increased vascular permeability, decreased intravascular colloid retention, and worsened microvascular perfusion.[53–55]

Distinct from the use of albumin as a perioperative resuscitation fluid, albumin may also be used to prime the CPB circuit along with crystalloids. In North America, approximately 30% of perfusionists use a mixture of 25% albumin and crystalloids for this purpose.[15] Several studies have suggested that the use of albumin in the CPB priming solution is beneficial for maintaining colloid oncotic pressure.[56–59] In a 2004 meta-analysis incorporating 21 studies with a total of 1,346 patients, the addition of albumin into the priming fluid was found to be associated with a reduced absolute drop in platelet count while on CPB, better preserved intravascular colloid oncotic pressure, and decreased postoperative weight gain and on-bypass fluid balance.[57] Nevertheless, the limited available data show no difference in clinically important, "hard" patient outcomes.[60] In recent years, methods to reduce the priming volume (e.g., autologous priming, mini-circuits) have gained popularity given the evidence that they reduce perioperative blood transfusions, potentially reducing the perceived advantages of including albumin in the priming solution.[61,62]

Clinical evidence for the use of albumin in cardiac surgical patients

Most of the evidence comparing albumin with crystalloids stems from critical care studies that recruited from mixed medical and trauma populations, thus limiting generalizability to the cardiac surgical patient population. This is related to significant underlying physiologic differences in the cardiac surgical population, as well as different patterns of albumin use in current cardiac surgical care compared with administration protocols in prior large critical care trials.[7,8,52]

In 1998, a Cochrane meta-analysis was published showing a significantly increased risk of harm to critically ill patients administered albumin.[63] Of the initial 32 RCTS eligible for inclusion, 14 included surgical patients, and of those, only two had cardiac surgical patients as the primary population of interest. From the 30 RCTs reporting mortality data and involving a total of 1,419 patients, the overall pooled relative risk of death associated with albumin administration was 1.68 (95% confidence interval [CI], 1.26 to 2.23). This had a marked influence on clinical practice at the time, and the use of albumin fell out of favour, with usage decreasing by approximately 50% over six months in some jurisdictions.[64]

The safety of albumin remained a contested topic in subsequent years, and in 2004 the Saline versus Albumin Fluid Evaluation (SAFE) study, one of the largest albumin studies to date, was published.[52] The SAFE study found no benefit on morbidity or mortality of 4% albumin compared with normal saline when used for fluid resuscitation for the initial 28 days from ICU admission. The population included a heterogeneous group of 6,997 ICU patients, from which cardiac surgical patients were notably excluded. Nevertheless, a subgroup analysis of patients with "severe sepsis" (35% of whom had septic shock) showed a potential benefit of 4% albumin, with an adjusted odds ratio (OR) for death of 0.71 (95% CI, 0.52 to 0.97; $P = 0.03$). Patients who were randomized to the albumin group also received more red blood cell transfusions within the first 48 hr of the study (mean [standard deviation (SD)], 106.5 [321.4] mL *vs* 61.1 [235.2] mL; $P < 0.001$). The reasons for this are unclear but may have involved greater hemodilution or coagulopathy associated with albumin, leading to increased bleeding and transfusion.[65]

Subsequent studies, such as the 2014 Albumin Italian Outcome Sepsis (ALBIOS) trial, compared 20% albumin with crystalloid with crystalloid alone in 1,818 patients with septic shock, but found no mortality benefit at 28 days.[6] In the ALBIOS study, only 7% of patients in both groups were elective surgical patients, with nearly 60% comprising medical ICU admissions. Consistent with clinical practice at the time, a large proportion of patients in both groups also received synthetic colloids.[66,67] The 2013 Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial, which was a multinational RCT of 2,857 patients, also found no difference in 28-day mortality with the use of albumin.[7] Nevertheless, both the ALBIOS and CRISTAL trials did show some benefit in hemodynamic variables for those

patients who had received colloid, including faster weaning of vasopressors and decreased overall vasopressor use, a reduced net fluid balance, and higher sustained mean arterial pressure during the first seven days of ICU admission. A recent synthesis of the evidence from a large systematic review and meta-analysis of 55 RCTs involving over 27,000 ICU patients suggested that colloids, including albumin, improved hemodynamic variables such as mean arterial pressure and cardiac index at lower volumes compared with crystalloids, although this did not translate into improved outcomes.[68]

The most recent (2018) Cochrane review examining the relative utility of colloids over crystalloids for fluid resuscitation in the critically ill included 69 studies and 30,020 patients. Albumin or frozen plasma ($n = 22$ studies), as well as starches, dextrans, and gelatins, were compared with crystalloids. The review concluded with "moderate certainty" that the use of colloids in critically ill patients, including albumin or frozen plasma, is unlikely to improve mortality, and that its effects on transfusion requirements are "uncertain."[69] Of note, this 2018 Cochrane review specifically excluded studies of elective surgical patients, including elective cardiac surgical patients. In a similar vein, the latest Surviving Sepsis guidelines issued only a weak recommendation for the use of albumin in patients requiring large volumes of crystalloid resuscitation in septic shock because of a low quality of evidence.[70,71]

Data outside of the critical care setting in cardiac surgery is limited to small, generally retrospective studies that have yielded conflicting results. Various retrospective reviews have suggested that there is no major outcome difference between the use of colloids or crystalloids in cardiac surgical patients, although there are large cost savings with more restricted albumin use.[17,18,72] Fink *et al.* showed that transitioning from a clinical practice with albumin freely available to a balanced crystalloid-based regimen in postoperative cardiac surgical patients at a quaternary centre resulted in significant cost savings (30,549.20 USD over three months) without significantly impacting patient outcomes.[17] A large retrospective database study of 19,578 patients who underwent coronary artery bypass grafting surgery indicated lower all-cause mortality with albumin use compared with nonprotein colloids (OR, 0.80; 95% CI, 0.67 to 0.96).[73] In a second, more recent retrospective propensity score matched analysis of 1,095 patients undergoing on-pump cardiac surgery from a United States administrative database including 59 hospitals, patients receiving 5% albumin in the operating room and on postoperative day one had significantly decreased in-hospital mortality (OR, 0.5; 95% CI, 0.4 to 0.9) than those who received crystalloid, as well as lower all-cause 30-day readmission in the albumin group (OR, 0.7; 95% CI, 0.5 to 0.9).[44] These large effect sizes are unexpected and appear biologically implausible, and hence may be indicative of residual confounding relating to the underlying indication for which albumin was given, reinforcing the concept that a high-quality prospective study in the cardiac surgery setting is needed.

Based on other retrospective studies, it is possible that albumin use in cardiac surgical patients could be harmful overall. In a retrospective cohort study of 2,594 patients undergoing cardiac surgery at a single Australian centre, Matebele *et al.* observed an association between perioperative exposure to 4% albumin and increased ICU and hospital length of stay, adjusted healthcare costs, and morbidity, including a higher incidence of "redo" operations for bleeding or tamponade, as well as greater red blood cell transfusion ($P < 0.01$). Nevertheless, patients who received albumin had a higher severity of illness (as measured by ANZROD and EuroSCORE-1) and were more likely to have had greater severity of postoperative bleeding with an unclear temporal relationship to albumin exposure. There was no difference in adjusted mortality between those who did or did not receive albumin (adjusted OR, 1.24; 95% CI, 0.56 to 2.79; $P = 0.6$).[74]

More recent prospective studies in cardiac surgical patients have reported improved clinical outcomes, although sample sizes have generally been small, and a risk of publication bias prevails. The 20% Human Albumin Solution Fluid Bolus Administration Therapy in Patients After Cardiac Surgery (HAS-FLAIR) study was a single-centre, open-label pilot which included 100 consecutive cardiac surgical patients requiring volume resuscitation or improvement in cardiac index in the first 24 postoperative hours.[39] The first 50 patients requiring fluid bolus therapy were assigned to crystalloid, and the subsequent 50 patients received up to two treatments of 100 mL of 25% albumin, followed by crystalloid if required. HAS-FLAIR showed volume- and vasopressor-sparing benefits of albumin use in cardiac surgery, including a faster time to cessation of norepinephrine administration and a less positive median [interquartile range] fluid balance (albumin group, 1,100 mL [650–1,960] *vs* crystalloid group, 1,970 mL [1430–2550]; $P = 0.0$.[39] However, this was a small, non-randomized study, and was not designed to detect differences in clinically important outcomes such as morbidity or mortality. Recent studies in cardiac surgical patients are highlighted and detailed further in Table 3.

The Albumin in Cardiac Surgery (ALBICS) trial (NCT02560519), which is anticipated to be published soon, is comparing 4% albumin with Ringer's acetate solution for both CPB prime and volume replacement in cardiac surgery. The primary outcome of this trial is the number of patients with at least one major adverse event during the first postoperative 90 days, including all-cause

Table 3 Select studies examining albumin utilization in cardiac surgical patients

Study	Design	Size and population details	Primary exposure
Sedrakyan *et al.* 2003 [73]	Retrospective cohort constructed from an administrative database comprising the discharge records of 182 US hospitals from 1997 to 1998	19,578 patients undergoing coronary artery bypass grafting	Receipt of albumin compared with patients receiving nonprotein colloids (HES, gelatins, and others)
Frenette *et al.* 2014 [112]	Retrospective cohort study from a single Canadian centre composed of patients undergoing cardiac surgery with cardiopulmonary bypass from 2008 to 2010	984 patients undergoing either coronary artery bypass and/or valve surgery; patients with significant renal disease were excluded	Albumin administration from surgery until 36 hr postoperatively
Lee *et al.* 2016 [80]	Single-centre, parallel-arm, double-blind RCT at an academic hospital in Seoul, Korea	220 patients with preoperative serum albumin levels < 40 g/L undergoing elective off-pump coronary artery bypass grafting	Before skin incision, patients were administered 100, 200, or 300 mL of 20% human albumin solution according to the preoperative serum albumin level with an equal volume of saline. Patients in the control group were only administered normal saline
Ryhammer *et al.* 2017 [113]	Retrospective analysis of prospectively collected registry data from 3 Danish hospitals, including adult (> 15 yr) patients undergoing cardiac surgery from 2007 to 2014	17,742 patients > 15 yr undergoing standard cardiac surgical procedures with and without cardiopulmonary bypass, regardless of surgical urgency. Patients who died within the first 48 hr were excluded	Perioperative use of albumin, HES, and crystalloids was compared
McIlroy *et al.* 2017 [114]	Prospective, open-label, four-period sequential study at a single centre in Melbourne, Australia recruiting adult patients from 2014 to 2015	1,298 adult patients undergoing cardiac surgery and not requiring preoperative renal replacement therapy	This study compared a "chloride-rich" fluid management strategy (0.9% saline and 4% albumin) with a "chloride-limited" strategy (buffered salt solution and 20% albumin). These strategies were implemented from the start of anesthesia until discharge from the ICU
Kingeter *et al.* 2018 [44]	Retrospective cohort assembled from an administrative database including 59 US hospitals from 2001 to 2013	6,188 adult patients undergoing cardiac surgery with cardiopulmonary bypass. Patients undergoing valve, coronary bypass, or two or more procedures who survived at least 24 hr were eligible (except patients undergoing bypass after percutaneous intervention)	Any volume of 5% albumin on the day of or on the day following surgery. Patients were excluded if they received hypertonic saline or a colloid other than 5% albumin or plasma protein fraction
Fink *et al.* 2018 [17]	Retrospective interrupted time series analysis of administrative data from CVICU patients between January and March 2015 and 2016	192 patients after cardiac surgery (patients undergoing heart transplant and implantation of mechanical circulatory support were excluded)	An "albumin-limited" primarily lactated Ringer's based fluid management strategy was implemented in 84 patients and compared with a retrospective cohort of 108 patients where fluid management was albumin-based
Wigmore *et al.* 2019 [39]	Sequential-period, open-label prospective study in a single centre in Melbourne, Australia	100 consecutive patients admitted to the ICU and prescribed fluid bolus therapy according to well-defined hemodynamic criteria by the attending physician	During the control period, fluid bolus therapy was administered as either 0.9% saline or Hartmann's solution, with volumes of up to 1 L before any colloid could be given. After a wash-out period, fluid bolus therapy consisted of 100 mL of 20% albumin for the first two required boluses, after which the attending physician could administer the fluid of their choice
Matebele *et al.* 2020 [74]	Retrospective cohort study from a single centre in Brisbane, Australia, including patients undergoing cardiac surgery from 2016 to 2018	2,594 patients > 16 yr undergoing cardiac surgery with cardiopulmonary bypass (patients undergoing transplant, thoracic, or mechanical circulatory support were excluded)	Patients who received any amount of 4% albumin were compared with patients who received none. The study centre did not use any HES

Table 3 continued

Study	Outcome
Sedrakyan *et al.* 2003 [73]	In-hospital and all-cause death
Frenette *et al.* 2014 [112]	AKI defined by RIFLE risk and AKIN stage 1 within 96 hr after surgery
Lee *et al.* 2016 [80]	AKI as defined by AKIN criteria (stage 1 or greater) within 48 hr of surgery
Ryhammer *et al.* 2017 [113]	Primary outcome: 30-day mortality. Other outcomes: 6-month mortality, new postoperative renal replacement therapy, and new cardiac ischemic events
McIlroy *et al.* 2017 [114]	Peak change in serum creatinine and the proportion of patients meeting KDIGO stage 2 or 3 criteria within the first 5 postoperative days
Kingeter *et al.* 2018 [44]	Primary outcome: all-cause in-hospital mortality during the index admission during which cardiac surgery was performed
Fink *et al.* 2018 [17]	Fluid management practices in CVICU patients before *vs* after implementation of discrete fluid management strategies
Wigmore *et al.* 2019 [39]	24-hr fluid balance after cardiac surgery
Matebele *et al.* 2020 [74]	In-hospital mortality

Study	Major findings	Comment
Sedrakyan *et al.* 2003 [73]	The use of albumin was not associated with specific patient characteristics and was utilized in 41.3% of cases. In multivariable regression, albumin use was associated with lower odds of mortality compared with nonprotein colloids (OR, 0.80; 95% CI, 0.67 to 0.96)	Given the robust literature showing harm in critically ill patients with HES use, the findings are not surprising. Nevertheless, the magnitude of the findings may be related to residual confounding. While the authors adjusted for age, sex, insurance status, hospital volume, ED admission, comorbidities and surgical type, the potential for residual confounding remains. Patients who received no colloids or both albumin and synthetic colloids were excluded
Frenette *et al.* 2014 [112]	In a propensity score analysis, albumin was associated with increased AKI (RIFLE risk: 12% *vs* 5%; $P = 0.03$) and AKIN stage 1 (28% *vs* 13%; $P = 0.002$)	This study highlighted a dose-response relationship between higher volumes of albumin administered and subsequent AKI risk. To address potential bias related to the indication for albumin use, a propensity score analysis was conducted. A significant proportion of individuals also received HES
Lee *et al.* 2016 [80]	The incidence of postoperative AKI was lower in the albumin group than the control group (13.7% *vs* 25.7%; $P = 0.048$). There were no differences between groups in AKIN stage 2 AKI, renal replacement therapy, or 30-day mortality	Patients received significant volumes of HES in the operating room as well as in the ICU postoperatively. The control (albumin-free) group received twice as much 25% albumin in the ICU postoperatively as the albumin group: control, (median [IQR], 170 mL [85–180] *vs* albumin group, 85 mL [34–180]; $P < 0.001$. Therefore, the impact of albumin on renal outcomes may be confounded. Additionally, the use of saline in the control arm is problematic because of the known association with adverse renal outcomes
Ryhammer *et al.* 2017 [113]	In adjusted regression analysis, albumin compared with crystalloids was associated with a significantly increased risk of 30-day and 6-month mortality, new renal replacement therapy, and 6-month cardiac ischemic events	HES remained widely used in this cohort of patients. There is a strong possibility of residual confounding, particularly given that no association was found between HES use and renal or mortality outcomes but strong associations were observed with albumin use. This is generally contradicted by large multicentre studies

Table 3 continued

Study	Major findings	Comment
McIlroy *et al.* 2017 [114]	There was no association between a chloride-rich fluid management strategy and worse renal outcomes compared with the chloride-limited strategy	While no difference in the prespecified clinical outcomes was observed, patients in the chloride-rich group had a significantly increased odds of serum chloride concentration > 110 $mmol \cdot L^{-1}$ (OR, 7.30; 95% CI, 5.01 to 10.64) and a pH < 7.3 (OR, 2.40; 95% CI, 1.89 to 3.05). Given the small absolute difference in risk for clinical outcomes observed in other trials assessing similar questions, overall the study was likely underpowered to detect a difference.[122]
Kingeter *et al.* 2018 [44]	In a propensity score analysis comparing 1,095 patients who received albumin plus crystalloids to 1,095 patients who received crystalloids alone, albumin use was associated with decreased mortality (OR, 0.5; 95% CI, 0.3 to 0.9; $P = 0.02$)	Albumin use was not associated with differences in major morbidity, or AKI severity. While the confidence intervals were wide, the magnitude of the effect size for mortality was large and does not seem biologically plausible, suggesting residual confounding as acknowledged by the authors
Fink *et al.* 2018 [17]	When an "albumin-limited" fluid strategy was implemented, albumin use decreased significantly. Restriction of albumin use was largely responsible for a net-cost savings of 30,549.20 USD over 3 months. There were no differences between the groups in 30-day mortality or hospital length of stay.	This small study reported significant cost savings related to albumin restriction, with no major impact on patient outcomes. The time to weaning of vasopressors and time to extubation was similar between groups, despite a more positive fluid balance in the "albumin-limited" group.
Wigmore *et al.* 2019 [39]	The albumin group had a significantly less positive median [IQR] fluid balance in the first 24 hr than the crystalloid group (1,100 [650–1,960] mL *vs* 1,970 [1,430–2,550] mL; $P = 0.001$). Additionally, the median [IQR] time to cessation of norepinephrine was shorter in the albumin group (17 [5–18] hr *vs* 28 [20–48] hr; $P = 0.002$). Median [IQR] ICU length of stay was shorter in the albumin group (1.1 [0.9–2.1] days *vs* 1.9 [1.1–3.0] days, $P = 0.048$), as was hospital length of stay (10.0 [7.3–13.5] days *vs* 13.5 [8.3–17.7] days; $P = 0.018$). No impact on renal replacement therapy or mortality was observed	This was a small study assessing the effect of small-volume hyperoncotic albumin administration for a defined indication. While the authors observed a significant effect of albumin on a number of outcomes, these results are striking in magnitude compared with the much more modest effect estimates similar interventions have produced in large RCTs.[6] Patients in the control group had a higher APACHE III score, and more patients in the control group appear to have undergone combined and potentially more complicated procedures. Because of the small study numbers in each group and potential for residual confounding despite adjustment, some degree of caution when interpreting results is warranted
Matebele *et al.* 2020 [74]	Albumin use was not associated with in-hospital mortality (adjusted OR, 1.24; 95% CI, 0.56 to 2.79; $P = 0.6$]. Nevertheless, albumin use was associated with surgical re-exploration, red blood cell transfusion, hospital length of stay, and higher ICU and hospital costs	Patients receiving albumin had higher illness severity and experienced a greater proportion of complications. Given the systematically different populations receiving albumin in this and similar prior studies, the authors concluded that an RCT trial should be conducted to assess the efficacy and safety of albumin in cardiac surgical patients

AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; CVICU = cardiovascular intensive care unit; HES = hydroxyethyl starch; ICU = intensive care unit; KDIGO = Kidney Disease: Improving Global Outcomes; OR = odds ratio; RCT = randomized controlled trial; RIFLE = Risk, Injury, Failure, Loss, and End-stage renal disease.

death, acute myocardial injury, acute heart failure or low output syndrome, resternotomy, stroke, major arrhythmia, major bleeding, infection compromising post-procedural rehabilitation, or AKI. The trial has completed its recruitment target of approximately 1,400 patients from a single academic centre in Finland and closed to recruitment in 2020, and will hopefully shed further light on the role of albumin in the perioperative care of this complex patient group.[75]

Current controversies

Exogenous albumin for the correction of hypoalbuminemia

Hypoalbuminemia, regardless of underlying pathophysiologic etiology, is an independent predictor of morbidity and poor long-term survival in cardiac surgical patients, major non-cardiac surgical patients, the critically ill, and many other chronic disease states.[76–78] Prior meta-analyses of cohort studies examining hypoalbuminemia as a predictor of outcomes in the critically ill have found that for each 10 $g{\cdot}L^{-1}$ decrease in serum albumin concentration, there is an accompanying 137% increase in the odds of death, an 89% increase in morbidity, and a 71% increase in length of hospital stay.[77] Despite this, the administration of exogenous albumin to correct hypoalbuminemia does not appear to improve outcomes in the critical care population, as was shown in numerous large randomized studies.[4,6,8,66,79] It is unclear if this is different in cardiac surgical patients. One small, parallel-arm RCT showed that pre-emptive administration of 20% albumin to hypoalbuminemic patients immediately before off-pump coronary artery bypass surgery was associated with a reduced incidence of postoperative AKI (defined using AKI Network [AKIN] criteria) compared with the crystalloid control group (25.7% in the control group *vs* 13.7% in the treatment group; $P = 0.048$).[80] As a study in off-pump cardiac surgical patients, CPB was minimized as a risk factor. Nevertheless, the crystalloid used in the control group was 0.9% saline, which may be a risk factor for AKI in cardiac surgery patients.[81] Additionally, the control group actually received more albumin within 24 hr of CPB than the treatment group did after the surgical insult, which makes the true association of albumin (particularly the timing of administration) with outcomes less clear.[80]

The role of albumin in the preservation and maintenance of the endothelial glycocalyx

The endothelial glycocalyx is a protein and carbohydrate-rich inner vascular lining that plays a key role in vascular permeability, microvascular tone, prevention of microvascular thrombosis, and cellular adhesion.[82] Disturbances of the endovascular glycocalyx precipitated by surgery and CPB are thought to be associated with microcirculatory dysfunction and end-organ complications.[53] Significant glycocalyx disturbances, with a resultant potential effect on clinical outcomes, have been documented in various critically ill patient populations.[82] There is limited clinical evidence comparing different types of fluids and their effect on the glycocalyx.[82,83] Glycocalyx dysfunction is multifactorial in cardiac surgery—resulting from direct tissue injury, systemic inflammation, ischemia-reperfusion injury, oxidative stress, and hypervolemia—and it may persist for days following the original surgery.[53] The transcapillary extravascular leak rate of albumin increases within three hours of cardiac surgery, likely because of disruption of the endothelial glycocalyx.[31,54,55,84] Therefore, the relative effect of crystalloids and colloids on volume expansion may be determined by the degree of underlying glycocalyx dysfunction. Especially in critically ill cardiac surgical patients, altered glycocalyx permeability may actually result in worsening interstitial edema with colloid administration[85] and is unlikely to improve existing interstitial edema.[86,87] Preclinical evidence has suggested that albumin not only causes less damage to the glycocalyx but also contributes to its restoration and allows for more favourable microcirculatory perfusion compared with crystalloids.[88–92] Nevertheless, these favourable preliminary findings have generally not been replicated in larger clinical studies and/or translated into major advantages in patient outcomes, particularly in cardiac surgical patients.[87]

Bradykinin-mediated albumin-induced hypotension

Hypotension associated with rapid infusion of albumin products has been recognized since the 1970s.[93] This is postulated to be caused by a bradykinin-mediated mechanism, secondary to pre-kallikrein activator (PKA) in the albumin solution. Although believed to be associated with older-generation albumin products containing higher levels of PKA, paradoxical hypotension has been reported with the use of newer-generation 4% albumin for resuscitation in postoperative cardiac surgical patients.[94] Such hypotension may be exacerbated in patients taking angiotensin-converting enzyme inhibitors.[94] Angiotensin-converting enzyme inhibitors block the conversion of angiotensin-I to angiotensin-II (a potent vasoconstrictor) and block the breakdown of bradykinin (a potent vasodilator).[95] Based on the above evidence, consideration may be given to the avoidance or minimization of albumin in patients exposed to renin-angiotensin system inhibitors preoperatively. Nevertheless, this would be rendered difficult given their widespread use in patients presenting for cardiac surgery.[96]

The association of albumin with hemodilution and coagulopathy

There is some evidence that use of intravenous albumin in cardiac surgery causes greater hemodilution and increased coagulopathy compared with crystalloids, potentially resulting in increased bleeding and blood product

transfusion.[97–99] Albumin may trigger and exacerbate coagulopathy through several mechanisms. Firstly, it may lead to greater hemodilution compared with other fluids, resulting in increased coagulopathic bleeding and need for blood product transfusion.[97–99] However, the coagulopathy associated with albumin is likely less severe than that produced by synthetic colloids.[100,101] Other suggested mechanisms whereby albumin may contribute to coagulopathy include fibrinolysis; inhibition of platelet aggregation through induction of nitric oxide; binding of arachidonic acid, prostacyclin (PGI_2), and platelet-activation factor; and a heparin-like activity due to its capacity to bind antithrombin, thereby producing an anti-Xa effect.[4,102–104]

Albumin is known to reduce fibrinogen and coagulation protein levels and prolong laboratory coagulation profiles in patients who undergo plasma exchange.[105] A substudy of the SAFE trial confirmed that 4% albumin is associated with a prolonged activated partial thromboplastin time.[106] Paar *et al*. examined the *in vitro* effect of "low" (mean [SD] 19.3 [7.7] $g{\cdot}L^{-1}$), "physiologic" (45.2 [7.8] $g{\cdot}L^{-1}$), and "high" (67.5 [18.1] $g{\cdot}L^{-1}$) albumin levels on coagulation assays in samples from 25 healthy volunteers.[104] Using thromboelastometry, platelet function assays, and thrombin generation assays, these authors reported increased primary hemostasis, increased platelet aggregation, and enhanced clot formation in groups with lower albumin levels than in groups with higher albumin levels. Thrombin generation was not significantly affected. This is in keeping with findings from other viscoelastic testing studies looking at the anticoagulant effects of hemodilution with albumin in clinical (plasma exchange) and experimental settings.[105,107]

The evidence regarding whether these prolongations of laboratory parameters translate into important bleeding is mixed depending on the clinical context. In a study by Rasmussen *et al*. in patients undergoing major non-cardiac surgery, albumin was shown to impair platelet activation and to negatively affect clot amplitude and strength, but without any significant difference in the amount of bleeding or need for blood products.[108] In a study of patients undergoing plasma exchange, thromboelastographic assessment showed a reduction in clot formation and clot firmness without an increase in bleeding complications.[109] In contrast, Shirozu *et al.* found that preoperative plasma exchange with 5% albumin in patients undergoing living related renal transplantation resulted in similar thromboelastographic derangements but was associated with increased surgical bleeding and prolonged ICU length of stay.[110]

The association of albumin with perioperative renal injury

The nephrotoxic effects of synthetic colloids have been well documented.[111] However, the effects of albumin specifically on renal function are less clear, particularly in cardiac surgery. A recent RCT of 220 hypoalbuminemic cardiac surgical patients undergoing off-pump cardiac bypass grafting found a significantly decreased incidence of AKI within 48 hr in those who underwent albumin replacement perioperatively, although there were some noted sources of bias within the study (Table 3).[80]

Conversely, in a retrospective single-centre cohort study of 984 on-pump cardiac surgical patients, Frenette *et al.* found that use of intravenous albumin was associated with a dose-dependent increased risk of AKI.[112] This finding persisted after propensity score matching of 141 patients who had received either 5% or 25% albumin with 141 patients who had not received albumin. In this propensity-matched analysis, albumin use was associated with an increased risk of AKI (Risk, Injury, Failure, Loss, and End-stage renal disease [RIFLE] definition) (12% *vs* 5%; $P = 0.03$) and AKIN stage 1 events (28% *vs* 13%; $P = 0.002$).[112] Similarly, in a prospective observational study including 17,742 consecutive patients undergoing cardiac surgery across three centres in Denmark, albumin use compared with crystalloids was associated with adjusted ORs of 2.45 for 30-day mortality (95% CI, 1.21 to 4.96) and 4.84 for new postoperative dialysis (95% CI, 1.91 to 12.2), and adjusted hazard ratios of 1.81 for six-month mortality (95% CI, 1.15 to 2.85) and 1.43 for six-month ischemic events (95% CI, 1.00 to 1.05).[113] This signal for an association of albumin use with adverse renal outcomes was not seen in the recent Limiting IV Chloride to Reduce AKI After Cardiac Surgery (LICRA) trial, which was an open-label, prospective study including 1,136 patients undergoing cardiac surgery at a single centre in Australia.[114] In this study, there was no significant increase in Kidney Disease: Improving Global Outcomes (KDIGO)-defined stage 2 or 3 AKI across the phases of the perioperative fluid protocol, where both 4% and 20% albumin were used as part of a chloride-limiting strategy.[114] Although there was no significant difference in the incidence of AKI, 20% albumin was associated with a significantly lower incidence of hyperchloremia (Table 3).

The tonicity of the albumin solution may also be an important determinant of AKI. Higher concentration albumin solutions contain less chloride than many crystalloid solutions and lower tonicity albumin solutions. There is also significant variability in the chloride concentration of the different commercially available 5% albumin solutions, most of which are hyperchloremic (Table 2).[115] This is clinically relevant as there is

substantial evidence that supraphysiologic concentrations of chloride result in increased AKI, need for renal replacement therapy, and mortality in surgical and critical care patients.[116–119] In a 2018 trial which randomized 7,942 critically ill patients to either balanced crystalloids or isotonic saline, a greater number of patients in the isotonic saline group had plasma chloride concentrations > 110 mmol·L^{-1} (35.6% *vs* 24.5%, $P < 0.001$) and bicarbonate concentrations < 20 mmol·L^{-1} (42.1% *vs* 35.2%; $P < 0.001$). Correspondingly, the isotonic saline group had a small absolute increase in the risk of death, new renal replacement therapy, or persistent renal dysfunction which may be attributable to hyperchloremic metabolic acidosis, among other factors.[120]

The mechanism by which hyperchloremia and its related acidosis is associated with adverse outcomes is likely multifactorial.[120] Hyperchloremia increases the "strong ion difference," calculated by adding the plasma sodium, potassium, magnesium and other common positive ion concentrations and subtracting the negative ion concentrations, typically chloride, lactate, and urea.[121] The strong ion difference is a major determinant of H^+ concentration.[122] A decrease in the strong ion difference due to an increase in negative ions such as chloride is associated with metabolic acidosis. Additionally, excess chloride has important effects on renal blood flow and glomerular filtration rate, potentially inducing renal-specific vasoconstriction and reducing glomerular filtration.[122] Future RCTs assessing the use of albumin in cardiac surgical patients must carefully account for the variable chloride concentrations found in different albumin formulations, given the independent effect of hyperchloremia on adverse outcomes in the critically ill.[120]

Conclusion

There is a clear lack of high-quality data to conclusively support the efficacy and safety of albumin over balanced crystalloids for acute volume resuscitation in cardiac surgical patients.[26–30,72] This has facilitated ongoing routine administration of albumin without clear evidence of benefit and without a clear understanding of potential harm, particularly in high-risk patient subpopulations undergoing cardiac surgery (such as those with underlying renal dysfunction or heart failure). The associated healthcare expenditures associated with routine albumin administration in the absence of well-defined evidence for its superiority over other fluids are not insignificant.

Results of the ALBICS trial are anticipated soon, and will make an important contribution to the literature.[75] Nevertheless, it is likely that this trial will generate as many questions as it answers. ALBICS aims to compare 4% albumin solution with balanced crystalloid, with a primary composite endpoint composed of a broad array of events such as mortality, renal injury, heart failure, stroke, arrythmia, and infection. Based on the current literature, there is limited biological plausibility of albumin having a strong effect on outcomes such as stroke or arrythmia, and ALBICS has relatively low power to detect a difference in more biologically plausible outcomes such as renal injury and days alive outside of ICU. The ALBICS trial had a patient recruitment target of approximately 1,400 patients. Conversely, other trials aiming to detect differences in mortality and renal outcomes in critically ill populations recruited approximately 8,000 patients for adequate power.[120] Notably, ALBICS excluded high-risk patients in which clinicians might be significantly more likely to employ albumin, such as patients with very low left ventricular ejection fraction, those with end-stage renal disease, congenital patients, and patients requiring preoperative mechanical ventilation, inotropic support, or mechanical circulatory support. Additionally, the ALBICS trial will not clarify the role of 25% albumin in cardiac surgical patients.

Many questions remain unanswered. Given that the role of RCTs is to provide compelling evidence to change clinical practice, a future trial must include intervention and control arms that reflect how albumin-inclusive resuscitation and albumin-free resuscitation is actually conducted across Canadian cardiac surgical centres, while controlling for differences across albumin formulations (such as chloride content) that could influence outcomes.[117] Such a trial would ideally involve at least ten centres across the country to ensure generalizability. As albumin may be preferentially used in higher-risk cardiac surgical patients, such as those with right or left ventricular dysfunction, pre-existing renal disease, and those undergoing complex procedures, such patients should be considered and perhaps even prioritized for study inclusion. Additionally, given the large cost differential between albumin and crystalloids, a well-designed randomized trial showing non-inferiority of balanced crystalloid resuscitation to resuscitation incorporating albumin should provide a compelling rationale to curtail albumin utilization. There is a clear need for well-designed RCTs and higher quality evidence to clarify the role of albumin in cardiac surgical patients, and to better inform clinical practice.

Author contributions All authors supported manuscript conception, content, and writing, and review of the final paper.

Disclosures None.

Funding statement Keyvan Karkouti, MD, MSc is in part supported by a merit award from the Department of Anesthesia and

Pain Medicine, University of Toronto; and has received research support, honoraria, or consultancy for speaking engagements from Octapharma, Instrumentation Laboratory, and Bayer. Jeannie Callum, MD has received research support from CSL Behring, Octapharma, and Canadian Blood Services.

Editorial responsibility This submission was handled by Dr. Stephan K.W. Schwarz, Editor-in-Chief, *Canadian Journal of Anesthesia/Journal canadien d'anesthésie.*

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