Cardiac surgery-Associated acute kidney injury - A narrative review

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Abstract

Cardiac Surgery-Associated Acute Kidney Injury (CSA-AKI) is a serious complication seen in approximately 20-30% of cardiac surgery patients. The underlying pathophysiology is complex, often involving both patient- and procedure related risk factors. In contrast to AKI occurring after other types of major surgery, the use of cardiopulmonary bypass comprises both additional advantages and challenges, including non-pulsatile flow, targeted blood flow and pressure as well as the ability to manipulate central venous pressure (congestion). With an increasing focus on the impact of CSA-AKI on both short and long-term mortality, early identification and management of high-risk patients for CSA-AKI has evolved. The present narrative review gives an up-to-date summary on definition, diagnosis, underlying pathophysiology, monitoring and implications of CSA-AKI, including potential preventive interventions. The review will provide the reader with an in-depth understanding of how to identify, support and provide a more personalized and tailored perioperative management to avoid development of CSA-AKI.

Keywords:

acute kidney injury; cardiac surgery; cardiac surgery-associated acute kidney injury; cardiopulmonary bypass; renal replacement therapy

Introduction

Cardiac surgery has evolved considerably and nowadays more than 2 million procedures are performed worldwide each year.[1] The techniques are getting more advanced, and the patient group, who can be offered surgical treatment, has been extended, including older, and more comorbid patients. Consequently, there is an increasing need of thorough perioperative risk assessment in order to minimize the complication rate and improve outcome.

Acute kidney injury (AKI) is one of the more common and serious complications after cardiac surgery. Cardiac surgery-associated AKI (CSA-AKI), even at mild severity, is associated with increased short- and long-term mortality.[2,3] Furthermore, AKI entails a large socioeconomic impact due to the high costs for treatment, prolonged length of hospital stay, and the cost for derived diseases following AKI, including transition to chronic kidney disease (CKD).[4] The reported incidence of CSA-AKI varies highly according to different sources, ranging between 5% to 40%.[5,6] Two meta-analyses from 2016 reported a pooled CSA-AKI incidence of 22%.[7,8]

An AKI incident may cause irreversible loss of nephrons and shorten the lifespan of the kidneys, either through intermediate conditions such as acute kidney disease and disorders (AKD) or directly through development of progressive CKD.[9] Indeed, a recent systematic review, including cardiac surgery patients, found an almost five-fold risk for developing CKD in patients having AKI perioperatively.[10] Nevertheless, we do not have sufficient knowledge on preventive interventions or management to avoid CSA-AKI, neither on any effective treatment prevent progression to a chronic state.

The aim of this review is to provide an up-to-date summary on definition, diagnosis, underlying pathophysiology, monitoring and implications of CSA-AKI, including potential preventive interventions. The review will give an in-depth understanding of how to identify, support and provide

a more personalized and tailored perioperative management to avoid development of CSA-AKI. Finally, we will make suggestions for where there is currently not enough attention or in which areas new research may contribute.

Definition and diagnostic criteria

Variation on reported occurrence of CSA-AKI is partly related to absence of a standardized AKI definition. In 2004, Risk, Injury, Failure, Loss, End Stage Kidney Disease (RIFLE) criteria were established based on serum creatinine levels (SCr) or urinary output (UO), as well as need for renal replacement therapy (RRT).[11] Based on reports indicating that even minor changes in SCr will impact outcome, the Acute Kidney Injury Network (AKIN) modified in 2007 the RIFLE criteria with new definitions for AKI diagnosis.[12,13]

In 2012, Kidney Disease: Improving Global Outcomes (KDIGO) group suggested an updated AKI definition, combining RIFLE and AKIN criteria – the KDIGO definition[14], which has since been found more sensitive and more predictive for in-hospital mortality.[9,15] Accordingly, consensus is now to use the KDIGO definitions (Table 1). If kidney function is reduced, in terms of a glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2 for more than 3 months, the condition is defined as chronic kidney disease (CKD). However, if structural damage persists or if kidney function is not restored following the AKI incident this may lead to an intermediate condition referred to as AKD, which is defined as either AKI beyond the first seven days or development of reduced GFR < 60 ml/min/1.73 m^2 or decreased GFR by more than 35% within three months (Table 1).

SCr, UO or need for RRT remain standard criteria for the AKI definition. All of these markers have several disadvantages. SCr levels can vary interindividually and are dependent on other factors like diet and muscle mass.[16] SCr does not increase until GFR is reduced to 50%, and since AKI predominantly affects the tubules in the kidney, SCr will not increase until advanced parenchymal

injury has occurred.[17,18] In cardiac surgery cardiopulmonary bypass (CPB) is used in the majority. An increase in SCr may be concealed due to haemodilution, primarily caused by the CPB priming volume. Consequently, SCr levels measured shortly after CPB are often unchanged or even decreased.[19]

Urine output in patients undergoing cardiac surgery is influenced by several factors including; extensive use of diuretics, hypovolemia, blood loss, fluid shifts, and renal vasoconstriction during CPB, all affecting UO, which makes this criterion less reliable for diagnosing CSA-AKI.[20–23] Finally, indications for initiating RRT in intensive care are variable including fluid overload, persisting acidosis, etc.

Table 1 – Current definitions for AKI, AKD and CKD[9,14,24,25]

	AKI	AKD	CKD
Duration	≤7 days	<3 months	>3 months
Functional criteria	***Stage 1*** Increase in SCr by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 h from the onset of the disease or after cardiac surgery, OR increase in SCr of 1.5–1.9-fold from baseline level, OR Urine output <0.5 ml/kg/h for 6–12 h ***Stage 2*** Increase in SCr of 2.0–2.9-fold of from baseline, OR urine output <0.5 ml/kg/h for ≥12 h ***Stage 3*** Increase in SCr of 3.0-fold of the baseline level, OR increase in SCr to ≥4.0 mg/dl (≥353.6 µmol/l), OR initiation of renal replacement therapy, OR urine output <0.3 ml/kg/h for ≥24 h or anuria for ≥12 h	AKI OR GFR<60 ml/min/1.73m^2 OR decrease in GFR by ≥35% over baseline OR increase in sCr by >50% over baseline	GFR<60ml/min/ 1.73m^2
Structural criteria	Not defined	Elevated markers of kidney damage i.e., albuminuria	Elevated markers of kidney damage i.e., albuminuria

AKI, acute kidney injury; AKD, acute kidney disease; CKD, chronic kidney disease; GFR, glomerular filtration rate; SCr, serum creatinine level.

Pathophysiology

The underlying pathophysiology of CSA-AKI is complex and multifactorial; however, several key factors have been identified to contribute particularly to AKI in cardiac surgery patients. Important risk factors include hemodynamic alterations during CPB, low oxygen delivery (DO_2), anaemia, bleeding and transfusion of blood, as well as activation of inflammatory cascades (Figure 1).

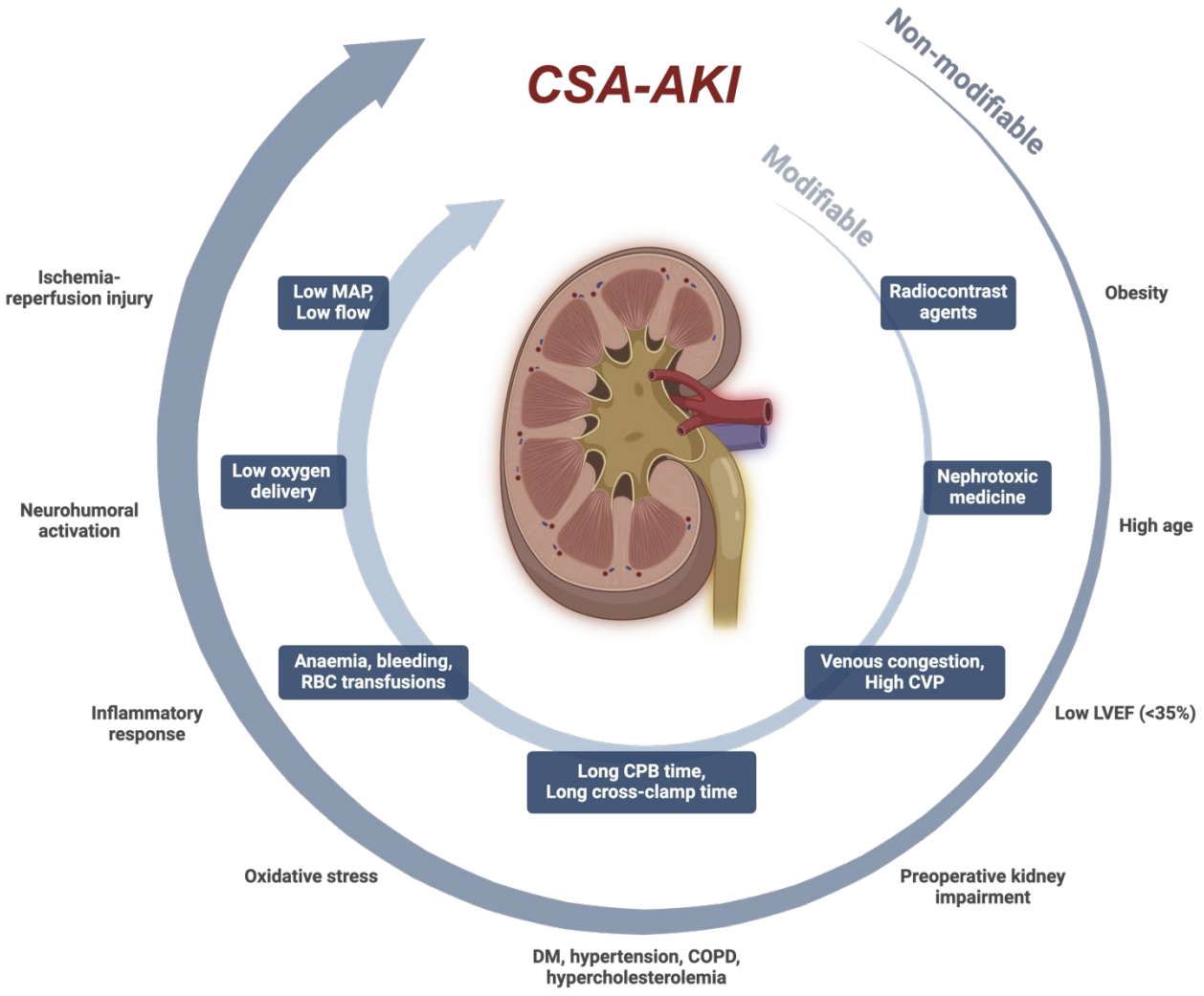

Figure 1. Established risk factors for cardiac surgery-associated acute kidney injury (CSA-AKI). COPD; chronic obstructive pulmonary disease, CPB; cardiopulmonary bypass, CVP; central venous pressure, DM: diabetes mellitus, LVEF; left ventricle ejection fraction, MAP; mean arterial pressure, RBC; red blood cell.

Pressure, flow and congestion

A key difference between cardiac surgery and other major surgery is the use of CPB, which changes the anaesthesiologists' hemodynamic focus from blood pressure to flow-based perfusion. The CPB is usually set at an indexed perfusion flow based on body surface area in order to maintain sufficient organ perfusion. However, the target for mean arterial blood pressure during CPB is less clear. Model simulations based on several clinical- and experimental data suggest that renal autoregulation may be inoperative during CPB.[26] This could, theoretically, encourage avoidance of low blood pressures during CPB. Consequently, the use of vasoconstrictors to increase arterial blood pressure may prove renoprotective. On the other hand, vasoconstrictors, such as norepinephrine stimulate α-adrenergic receptors, which potentially increase intra-organ vascular resistance to an extent that renal perfusion pressure would decrease as a result of the treatment.[27] A randomized trial, in cardiac surgery patients with several known risk factors for AKI, evaluated two targets for mean arterial pressure during CPB (79 mmHg vs 60 mmHg) and found no difference on renal outcome (postoperative serum creatinine, initiation of dialysis or AKI development) between groups.[28] Similar findings were confirmed in a more recent randomized trial evaluating even lower targets of mean arterial pressure during CPB (47 mmHg vs 61 mmHg).[29] In the latter study, a Cr-EDTA measurement after four months revealed no difference between interventions, however, patients having an episode of AKI within 48 hours after surgery all had a > 10% reduction in GFR at four months postoperatively.[29]

The results indicate that arterial blood pressure during CPB *per se* is not of major importance for development of kidney injury in the presence of sufficient flow during CPB. However, the average blood pressure during CPB does not preclude shorter episodes of hypotension, and this effect was not examined. One study found that patients developing postoperative renal failure requiring RRT had lower CPB perfusion flow, and longer periods with perfusion pressures < 60 mmHg compared with patients without renal failure.[30] These findings could not be confirmed in other larger studies,

including a recent multicentre retrospective study: where neither the duration of a perfusion flow < 1.6 L/min/m^2, nor the duration of mean arterial pressure < 50 mmHg was associated with AKI following cardiac surgery.[31]

Traditionally, most studies have focused on improving renal perfusion primarily by ensuring higher mean arterial pressure. However, only little attention has been given to the venous pressure and its relation with kidney perfusion. Nevertheless, it is imperative to identify venous congestion in this context, since the perfusion pressure relies on the difference between pressure in the renal artery and venous system. Cardiac surgery patients are often congested due to either pre-existing systolic or diastolic heart dysfunction, positive pressure ventilation, venous cannula displacement, administration of blood products and intravenous fluids, including the priming volume for the CPB circuit. In a patient with congestive heart failure, the venous backward pressure will be distributed to the entire venous system and induce an increased "afterload" on the renal venous system equivalent to the extent of heart failure.[32] Moreover, experimental studies indicate that an increase in venous pressure causes a more pronounced decrease in renal blood flow compared to a corresponding decrease in arterial pressure.[33]

A dose-response relationship between increasing perioperative central venous pressure (CVP) and the risk of postoperative AKI in cardiac surgery patients has been found in several studies.[34,35] The deleterious effect of a high CVP is not solely due to an increased backward pressure, but also the associated neurohumoral response, including several vascular receptors, which in the congested hypotensive patient operate in opposite directions. The arterial baroreceptors, in the carotid arteries and the aortic arch, sense a low-pressure state through decreased stretching of the arterial wall resulting in an increased sympathetic neurohumoral drive. This leads to increased cardiac output, vasoconstriction and retention of sodium and water.[36,37] Conversely, the cardiopulmonary receptors, located in the cardiac chambers and venae cavae, works as volume receptors, and will give an opposite

response to an increased intravascular volume by reducing sympathetic activity and downregulate natriuretic peptide secretion.[38,39] Interestingly, in acute haemodynamic alterations, when the cardiopulmonary receptors reach a certain threshold, the volume-sensitive receptors will have priority over the pressure-sensitive baroreceptors, which means that in order to increase renal blood flow, it is of utmost importance to focus on reducing CVP to physiological levels.[40,41]

Oxygen consumption and oxygen delivery

The physiology behind adequate renal oxygenation is complicated. The kidneys receive one fifth of the cardiac output to maintain sufficient glomerular filtration, but consumes only five percent of the body's oxygen.[42] This is most likely caused by a substantial amount of arterio-venous shunting of oxygen in the renal vascular beds, which functions to maintain diffusion gradients for reabsorption of solutes.[43] It is also clear that there are large differences in how vulnerable the kidney is to changes in oxygen availability depending on anatomical location within the kidney. As oxygen diffuses through the vasa recta, the renal medulla gradually becomes more hypoxic with an oxygen partial pressure of 10-20 mmHg in the outer medulla in contrast with 50 mmHg in the renal cortex.[44] Unfortunately, most of the oxygen consumption relates to active reabsorption of primarily sodium in the thick ascending limb of the loop of Henle located in the outer medulla (Figure 2), and therefore this area is especially susceptible to hypoxic injury.[45] Several human studies demonstrate, that tubular damage mainly occurs in the outer medulla.[46,47] One study evaluated the oxygen supply/demand relationship in cardiac surgery patients on CPB using comprehensive detailed measurements.[48] They found that the systemic blood flow increased during CPB, but without a corresponding increase in renal blood flow, mainly caused by an increased renal vascular resistance.[48] The relative decrease in renal blood-flow together with haemodilution resulted in a drop in renal oxygen delivery by approximately 20% during CPB.[48] This mismatch in oxygen supply/demand led to increased renal oxygen extraction during and after CPB and an accompanying increase in tubular injury biomarkers.[48]

For this reason, the duration of CPB should be kept as short as possible. The risk of CSA-AKI related to the duration of CPB was not long ago confirmed in a systematic review.[49]

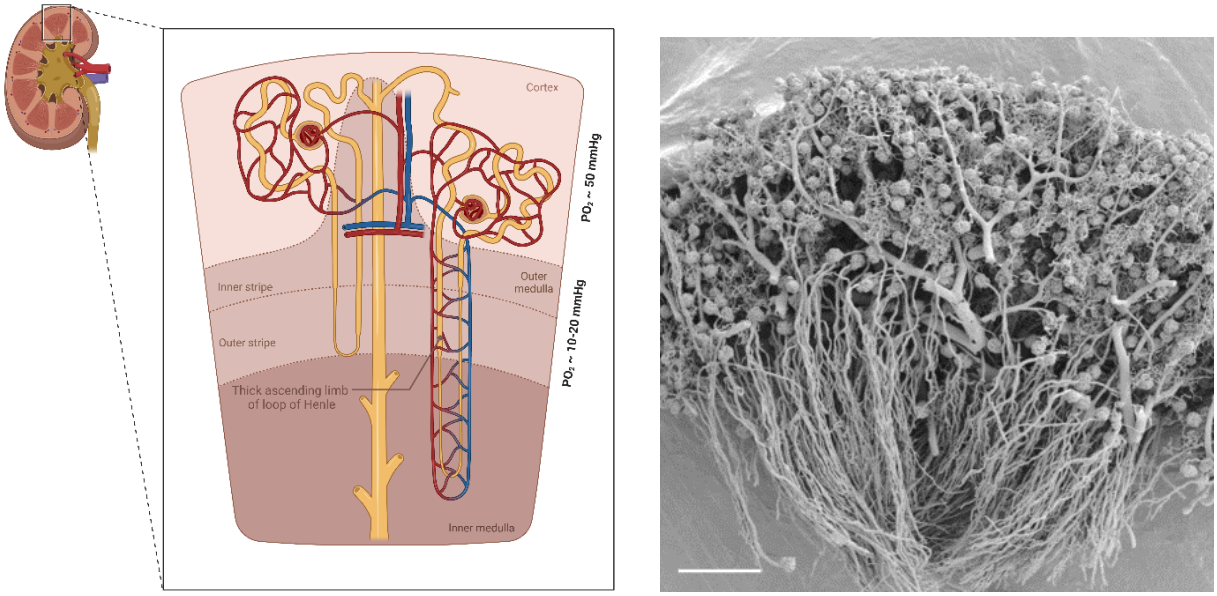

Figure 2. Illustration (left); an overview of the renal anatomy and relative hypoxia. Picture (right); resin cast of the renal vasculature of a rabbit, demonstrating the medullary vasa recta. Scale bar = 1 mm. Picture is kindly provided with permission from the corresponding author Evans, R. G. (published in: Mechanisms underlying the differential control of blood flow in the renal medulla and cortex. Journal of Hypertension, 2004; 22 (8): 1439).

In recent decades, there has been an increasing awareness on keeping the oxygen delivery above a critical threshold in order to mitigate the mismatch. This is easily available as real-time oxygen delivery (DO_2) can be calculated in the monitoring system of the heart- and lung machine. Several observational studies found an association between increased risk of CSA-AKI and intraoperative DO_2-levels ranging between 225 and 272 mL/min/m^2.[50–55] Furthermore, both duration and the integral of amount and time below a critical DO_2 level are associated with increased occurrence of CSA-AKI.[56,57] In addition to avoiding critical levels of DO_2, clinicians could also aim at keeping a high

DO_2 available throughout CPB. This hypothesis was tested in two recent randomized controlled trials, both demonstrating that goal-directed perfusion with DO_2 levels above 280 and 300 mL/min/m^2, respectively, reduced the incidence of CSA-AKI by more than 50%.[58,59] Of notice, however, the reduction was only significant for stage 1 AKI, and did not affect the more severe stages of kidney injury.[58,59]

Anaemia, bleeding, transfusion

Since haematocrit level is crucial in the DO_2 formula, it may be advantageous to maintain a relatively high haematocrit during cardiac surgery without compromising viscosity. A systematic review on preoperative anaemia in cardiac surgery found a threefold higher risk of CSA-AKI in anaemic patients.[60] Furthermore, the risk of CSA-AKI increases inversely with nadir haematocrit during CPB.[51,61] On the other hand, the benefit of a high haematocrit cannot be achieved by transfusion of red blood cells. Several studies have shown a dose-response relationship between red blood cell transfusions and risk of CSA-AKI, even after adjusting for pre- and perioperative hematocrit.[62–66] For this reason, it is necessary to have a safe transfusion trigger counterbalancing the potential risks and benefits for transfusions. A recent systematic review evaluated blood transfusion triggers in cardiac surgery and confirmed that a restrictive transfusion-trigger was non-inferior to a liberal in terms of any outcome investigated, including renal failure.[67] This analysis included the two most recent and influential studies – the TRICS-III trial and the TITRe 2 trial, which both used a restrictive threshold of haemoglobin <7.5 g/dl (<4.7mmol/L).[68,69] The safety of a restrictive approach regarding renal outcomes was further confirmed in a sub-study from the TRICS-III trial evaluating patients with pre-existing kidney disease.[70] Since some of the more significant perioperative risk factors for CSA-AKI are prone to multicollinearity, it is difficult to tease out the impact of one risk factor from the others. For instance, both short- and long-term outcome after cardiac surgery is associated with pre-operative anaemia and kidney function, as well as transfusion of blood products.[71,72] Several studies have tried

to separate some of these risk-factors and have described an additive risk of having both anaemia, transfusions and/or major bleeding during cardiac surgery.[73–75]

Ideally, all cardiac surgery patients should be timely assessed in order to correct anaemia, but in reality, this is not feasible in most institutions. Although the evidence for iron or erythropoietin to correct preoperative anaemia is low, an increased haemoglobin level has the potential to improve outcome after cardiac surgery.[76,77] A recent retrospective propensity matched study found that correction of anaemia with ferric carboxymaltose and/or erythropoietin at the pre-admission examination significantly reduced the need of red blood cells and units transfused.[78]

Inflammation and oxidative stress

Even though not fully understood, inflammation has a decisive importance in the pathophysiology of CSA-AKI. The use of CPB increases a wide range of pro- and anti-inflammatory cytokine signalling molecules such as the interleukin-6 and 10 (IL-6, IL-10), Interferon γ (IFN-γ) and stem cell growth factor β (SCGF-β), all associated with a higher frequency of CSA-AKI.[79,80] Oxidative stress mediators have been linked to renal injury in several studies.[81,82] When erythrocytes pass through the extracorporeal circuit and are exposed to shear-stress, this causes haemolysis and plasma-free haemoglobin release, which ultimately can produce free-iron related nephrotoxic reactive oxygen species (ROS).[83–85] Conversely, the harmful effect of oxidative stress on kidney injury can be reduced in the presence of a sufficient level of antioxidants.[86] When the patient is weaned from the CPB, ischaemia-reperfusion injury may occur. Even though this phenomenon is not fully understood, it initiates deleterious cascades of inflammation, programmed cell death, all of which promotes development of AKI.[87–89] Central to this phenomenon is mitochondrial dysfunction, and this could be an important area for future research where focus should be on restoring normal oxidative phosphorylation in the mitochondria.

Risk assessment

Several risk factors have been identified for CSA-AKI, which can be divided into patient- and procedure-related factors. High age and comorbidities, such as preoperative kidney disease, diabetes mellitus, obesity, hypercholesterolemia, hypertension, reduced left ventricular ejection fraction <35%, chronic obstructive pulmonary disease, are among the most frequently reported patient related risk factors.[90,91] Furthermore, a variety of pre-existing cardiac conditions may enhance renal impairment (the cardio-renal syndrome), through intertwined pathophysiologic mechanisms, including neurohumoral regulation with activation of renin-angiotensin-aldosterone system (RAAS), sympathetic regulation and vasopressin secretion.[92]

Procedure-related risk factors include: type of surgery (CABG, valve and/or aortic surgery), emergent versus elective surgery, duration of CPB and cross-clamp times, all of which are risk factors associated with AKI development.[5]

The use of CPB may also be a risk factor in itself.[93] A systematic review with comparison of on-pump and off-pump CABG found a significantly reduced risk by off-pump surgery in relation to CSA-AKI.[94] However, two large randomized trials demonstrated conflicting results; with no difference in the ROOBY trial[95] but a reduced risk of CSA-AKI with off-pump surgery in the CORONARY trial, but without any difference in kidney function at 1-year's follow-up.[96]

Risk scoring systems

A number of clinical risk scores have emerged during the recent decade. Most common are the Leicester Score and Cleveland Clinic Score.[97] Both risk scores focus mainly on preoperative patient characteristics, where preoperative hypertension, eGFR < 60 ml/min/1.73 m^2, and peripheral vascular disease were the strongest predictors. Prediction was less precise in patients without preoperative reduced kidney function.[97] Overall, Leicester Score is better at predicting any AKI degree, whereas

the Cleveland Clinical Score better identifies more severe AKI.[98–100] Nevertheless, only a small part of the patients developing CSA-AKI will require RRT. Independent on the need for RRT, AKI is associated with worse outcome.[12]

Unmodifiable risk factors, like demographics, comorbidities, and procedure-related information (type or surgery, CBP use, cross-clamp time) are included in the majority of the AKI prediction models, limiting their preventive utility.

Numerous reports on the use of novel biomarkers for estimation of CSA-AKI risk have been published during the last decades. A short overview of a number of markers, reflecting structural changes in the kidneys, are described under "Novel biomarkers" below. The knowledge on the timing and appropriate interpretation of the results is still scarce, and technical possibilities for the routinely use of novel biomarkers worldwide is insufficient.

A recent study developed a risk prediction model for moderate to severe CSA-AKI, based on easily available perioperative metabolic parameters and electrolytes, with an excellent discriminatory ability (area under ROC curve ~0.9).[101] However, this model incorporated the absolute change in SCr, and therefore affected by the same pitfalls as described earlier, including the delayed increase. The main problem with AKI risk predictive models is that the great majority aim to predict RRT-AKI. In this setting the preoperative SCr or eGFR has major impact, mainly since patients with reduced renal function have a higher risk of requiring RRT postoperatively. However, when prediction incorporates AKI stages I and II, the preoperative SCr becomes a confounder, since patients with preoperative low values are at higher risk for a 50% increase in SCr, but not an increase requiring RRT.[102]

In recent years, several studies have applied machine learning in CSA-AKI predictive models, with excellent discriminative abilities and with an area under ROC curve up to 0.97.[103–107] Although these findings are both encouraging and impressive, to our knowledge, no studies have yet performed

comprehensive external validation, which is critical step when creating applicable predictive models. Despite promising results, risk scoring models for CSA-AKI are not widely adopted in daily practice. An individualised approach based on preoperative assessment and calculation of AKI risk, might be a future strategy with change of perioperative management, such as timing, perioperative medication and procedural technique, and thereby counteract CSA-AKI in high-risk patients. Recently, a dynamic model incorporating CPB-related factors has been proposed, but further validation is required.[108]

Novel biomarkers

Due to limitations of SCr and UO, many attempts have been made to find more sensitive biomarkers for AKI. Novel biomarkers have been identified to evaluate some of the underlying pathophysiologic processes in the nephrons, also in order to get a more precise location of injuries.[18]

Preoperative biomarkers

Urinary dickkopf-3 (DKK3), a renal tubular stress marker, was evaluated in cardiac surgery patients and in contrast-associated kidney damage in patients with chronic kidney disease. High levels of urinary-DKK3 normalised to creatinine in urine demonstrated a strong association both with development of AKI and subsequent loss of function. In contrast to perioperative injury markers, DKK3 concentrations reflect ongoing (preoperative) tubular cell stress, a condition that conveys increased risk of AKI and progression of kidney dysfunction as well as cardiovascular disease.[109,110] Along the same line, high levels of soluble urokinase-type plasminogen activator receptor (suPAR) in plasma has been associated with increased risk of AKI in cardiac surgery patients[111,112], and experimental evidence indicate that suPAR increases cellular energy demands and inflicts oxidative stress on tubular cells, particularly susceptible to ischaemia-reperfusion injury.[113] Whether these two preoperative biomarkers are mutually reflecting the same underlying pathogenesis remains to be

explored. It probably does not just reflect a generally increased inflammatory state, since there was no association with high-sensitivity C-reactive protein in the same study population.[112]

Perioperative markers

In contrast to the preoperative biomarkers, the majority of novel perioperative biomarkers are used to identify early kidney injury, before SCr and UO is affected. Cystatin C, a small molecule normally completely filtered in the glomeruli, is a functional biomarker, similarly to SCr for GFR assessment. Cystatin C is made by all nucleated cells, not just muscle as for sCr, and therefore demonstrates less variability and is considered as an alternative to creatinine measurements. Studies evaluating use of serum cystatin C for AKI diagnosis in cardiac surgery patients report earlier increase in Cystatin C and more accurate GFR estimation after 48 hours with Cystatin C calculated GFR compared to SCr based GFR assessment compared with iohexol clearance as reference.[114,115]

Tissue metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP7), released from the proximal tubule during cell cycle arrest, are stress biomarkers measured in urine, to predict CSA-AKI early on.[116] Patients developing KDIGO stage 2 and 3 had bimodal elevations occurring immediately after CPB and 6 hours after surgery, before SCr had increased above baseline.[117] Stage 1 AKI also had increased TIMP-2 and IGFBP7 levels postoperatively, but to a lesser degree.[117]

Kidney injury molecule-1 (KIM-1), a kidney damage biomarker, is a transmembrane glycoprotein released into urine after tubular damage. KIM-1 used in combination with other biomarkers has demonstrated acceptable sensitivity for AKI detection in cardiac surgery patients.[118]

Neutrophil gelatinase-associated lipocalin (NGAL) is a kidney damage marker peptide, released from the distal tubule. NGAL, is normally not present in plasma or urine. The role of NGAL in CSA-AKI

development, severity, and timing for RRT, is uncertain probably due to the overall inflammatory response in surgical patients.[25,119,120]

After the Acute Disease Quality Initiative (ADQI) consensus conference in 2020, recommendations were published on the use of novel biomarkers for AKI diagnosis and prevention.[25] They provide 11 recommendations of various strength. Of interest for this review, they recommend combining clinical assessment with validated biomarkers of AKI.[25] Overall, the negative predictive value of novel biomarkers is generally good, whereas the positive predictive value is often moderate to low.[25] However, use of novel biomarkers will enable preventive measures prior to manifest AKI as judged by SCr. In the PrevAKI trial, use of stress biomarkers TIMP-2 & IGFBP7 identified high risk patients for AKI within 4 hours after CPB and randomisation to protocolised vs standard care reduced the occurrence of AKI by 17%.[121]

Finally, the use of functional kidney markers like Cystatin C may also optimize drug dosing, since eGFR estimated by creatinine-cystatin C is more precise than eGFR evaluated by creatinine or cystatin C alone.[25]

Preventive interventions

Pharmacological concerns

The potential role of pharmacologic agents as either pre-emptive or harmful regarding CSA-AKI have been thoroughly discussed in the literature. A meta-analysis on risk and harms by discontinuation of ACE-inhibitors (ACEi) or angiotensin receptor blockers (ARBs) prior to either cardiac surgery or coronary angiography, demonstrated a reduced risk of AKI around 15% by discontinuation.[122] CSA-AKI, however, was only evaluated in a prospective cohort, demonstrating a trend towards increased functional AKI according to no exposure, paused the day of surgery or continued medication.[123] However, proper RCTs are needed since others have found a potential protection from RAAS inhibitors (RAASi).[124] RAASis hinder vasoconstriction caused by RAAS activation during CPB,

resulting in improved renal perfusion.[125] However, a recent larger systematic review found no significant impact of RAASi on AKI, including more than 75.000 cardiac surgery patients.[126]

Diuretics, like furosemide, are often prescribed in cardiac surgery patients. A large retrospective study found that preoperative use of any diuretics was associated with increased occurrence of CSA-AKI, but due to the observational design confounding by indication cannot be ruled out.[127] However, intra- and postoperative use of loop diuretic furosemide in cardiac surgery patients was associated with higher rates of renal impairment in a randomized study from 2000.[128] A recent systematic review found no significant effect of intraoperative use of furosemide on CSA-AKI incidence or need for RRT.[129] The mineralocorticoid receptor blocker spironolactone was evaluated in a RCT with 100 mg 12-24 hours before surgery, followed by 3 doses of 25 mg every day for the first two days, where spironolactone was associated with an increased occurrence of AKI.[130] The lack of benefit from both furosemide and spironolactone may relate to the many indications for diuretics. Favourable effects of diuretics due to hindering of renal congestion, suggest that the indication should be evaluated on a case-to-case basis.[131]

Sodium-glucose co-transporter type 2 inhibitor (SGLT2i) use has increased tremendously in recent years with indications not only for diabetes mellitus, but also heart failure and CKD independent of diabetes mellitus status. Conflicting data on their risk of producing AKI have been reported, but in a recent review providing an in depth understanding of SGLT2is role in both predisposing and preventive effect from AKI, there was overall unambiguous data demonstrating that SGLT2is are safe and do not predispose to AKI.[132] However, in the clinical situations with high risk of AKI, their role remains unaddressed. In 2015, FDA issued a warning on the risk of diabetic ketoacidosis - often euglycemic - after SGLT2i treatment with recommendations to withhold SGLT2is in the perioperative phase. In a recent review on cardiac surgical patients, ketoacidosis with an increased

anion gap was reported to occur mainly on postoperative day 1, but with a time range from immediately postoperatively and until postoperative day 3.[133] SGLT2is had been withheld from between 24-72 hours prior to surgery. Too few data exist on their association with CSA-AKI.

Independently of surgical procedures nonsteroidal anti-inflammatory drugs (NSAIDs) have renal complications, including AKI which relate to their inhibition of cyclooxygenase enzyme. NSAIDs cause renal vasoconstriction, in particular in patients with RAAS activation like heart failure and liver cirrhosis, due to dependency of local renal prostaglandins vasodilatory effect to preserve blood flow and GFR. NSAID may lead to ischaemic kidney injury, salt and water retention with hypertension and electrolyte disturbances. There are only observational studies on CSA-AKI, indicating NSAID should be withheld prior to surgery.[124] In contrast, a beneficial effect of preoperative low dose aspirin in cardiac surgery patients has been reported, although evidence is mainly from observational studies.[134]

Antibiotics, in particular aminoglycosides have adverse renal effects, but a single shot gentamycin perioperatively is generally considered safe. However, in a matched analysis in cardiac surgery patients, aminoglycosides were associated with increased risk of CSA-AKI[135] and aminoglycosides were in a separate study associated with significantly increased risk of need for RRT.[136]

Contrast media can induce AKI, and in a retrospective observational study, a coronary angiogram performed less than 7 days prior to cardiac surgery was associated with 2.5 times higher risk of experiencing CSA-AKI.[137] Similarly, restricting coronary angiograms at the day of surgery reduce occurrence of CSA-AKI.[138] As a consequence, the most recent practical guidelines from the American College of Cardiology/American Heart Association now suggests a minimum 24-hour delay from angiography to CABG in stable patients with CKD.[139] However, it is important to individually counterbalance the increased risk of AKI against the potential benefit of prompt revascularisation –

and if delay is not clinically feasible, clinicians should focus to minimise contrast volume and ensure adequate hydration.[139]

Fenoldopam is a vasodilator with a selective action on the dopamine receptor, inducing an increased renal blood flow. Due to this characteristic, it has been proposed as a renal protective strategy in cardiac surgery. A randomized controlled trial, however, did not show any advantage of fenoldopam in reducing RRT-AKI.[140] A recent meta-analysis confirmed this finding, also including non-RRT AKI.[141]

Remote ischemic preconditioning

The concept of remote ischemic preconditioning (RIPC) involves introducing a temporary occlusion of blood flow to a limb with a blood-pressure cuff, to induce the release of various signalling molecules, providing a natural defence with bioenergetic down-regulation and protection of the kidney during ischemic exposure.[142,143] A recent systematic review evaluated RIPC on postoperative AKI in 28 RCTs and found RIPC to significantly reduce the incidence of AKI after cardiac surgery[144] However, the studies included represented significant heterogeneity and subgroup analysis revealed that the beneficial effect of RIPC was only applicable using volatile anaesthetics or in non-high risk patients. Further research is needed in order to understand the mechanism of action and to identify which patient may benefit of treatment.

Guidelines and recommendations

The European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Cardiothoracic Anaesthesiology and Intensive Care (EACTAIC) and European Board of Cardiovascular Perfusion (EBCP) have made a joint set of guidelines for CPB in adult surgery including hemodynamic targets in order to minimize CSA-AKI.[145] Furthermore, the North America

based Society of Cardiovascular Anesthesiologists (SCA) have recently published a set of practical strategies for management of CSA-AKI.[146] However, recommendations are based only of low to moderate level evidence.[146] While both of these societies guidelines mainly focus on factors in relation to CPB management, the Kidney Disease: Improving Global Outcomes (KDIGO) published in 2012 a set of general recommendations for patients at high risk of developing AKI.[14] These recommendations describe overall supportive measures, often referred to as the "KDIGO bundle of care". The overall aim of these strategies is to maintain renal perfusion and oxygen delivery, and to avoid nephrotoxic agents. Consequently, volume optimization, blood pressure maintenance, avoidance of toxins, ACEi and ARBs treatment modification in the perioperative period, avoidance of hyperglycaemia are all included in the recommendations. Despite the "KDIGO bundle of care" recommendation in cardiac surgery patients[147], a multinational observational study reported low adherence and lack of additional attention in patients developing CSA-AKI.[148] This is particularly important, since the PrevAKI multicentre RCT demonstrated a significant 10% absolute reduction in moderate to severe AKI with adherence to the "KDIGO bundle of care", but overall development of AKI was not significantly reduced.[149]

Conclusion and perspectives

Despite advances in cardiac surgery management and a better understanding of the pathophysiology behind CSA-AKI, this complication remains frequent postoperatively. A better understanding of how basic renal physiology is affected by simple changes in hemodynamics during laminar flow is still highly warranted. A possible way forward is to develop large animal proof-of-concepts models or integrate kidney flow-pressure parameters and injury markers in existing animal models.

Recognizing that patients are heterogeneous, and that CSA-AKI has multifactorial causes, it appears important to differentiate interventions in relation to the individual patient's risk profile to obtain a

more personalised approach rather than providing general recommendations. Figure 3 gives an overview of potential measures to consider in order to reduce the occurrence of CSA-AKI. Future studies should focus not only on prevention of CSA-AKI, but also on long-term consequences and outcome to identify patients at risk for development of chronic kidney disease, who may benefit from medical interventions to slow down progression of loss of kidney function.

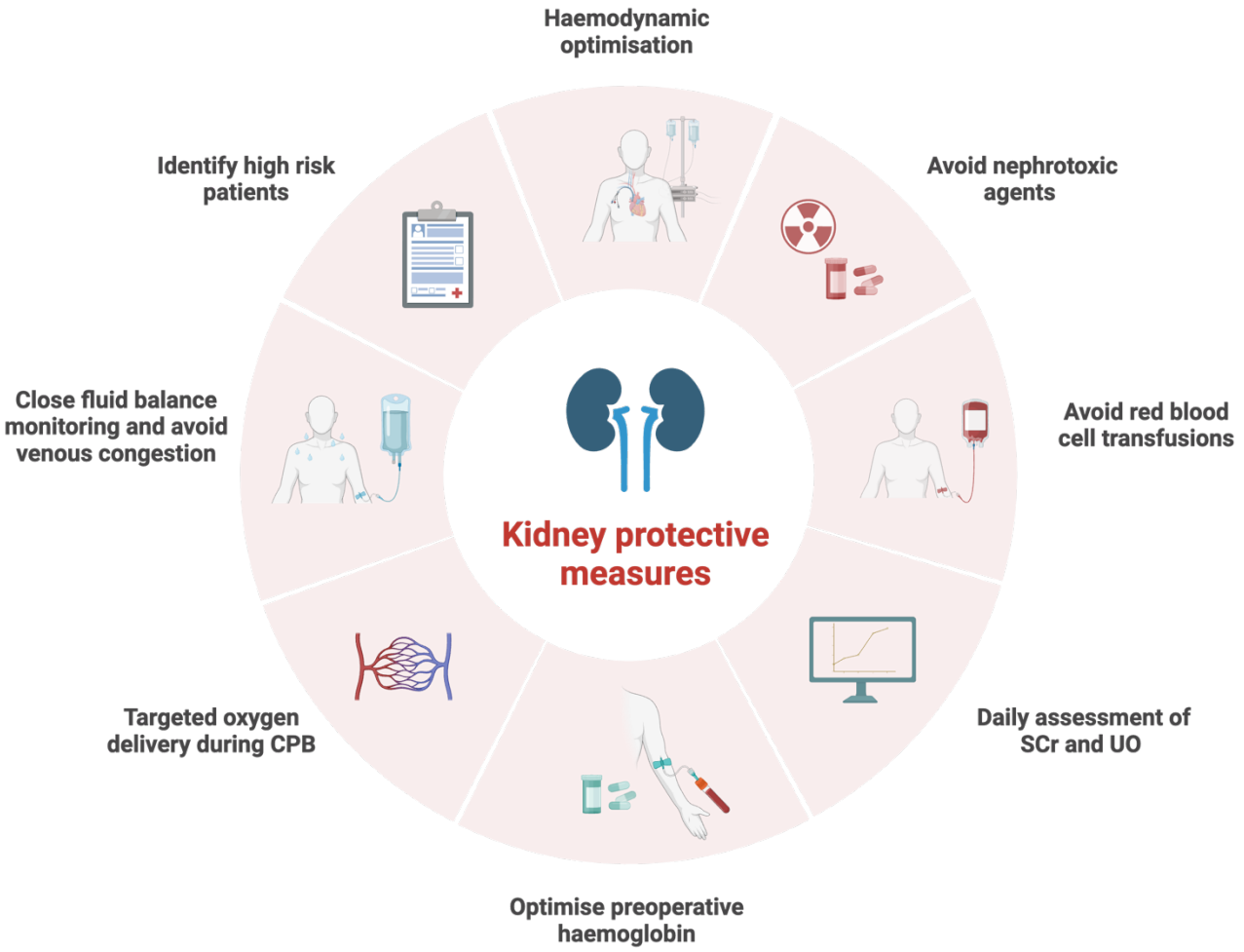

Figure 3. General initiatives to implement at cardiac surgery facilities to reduce the occurrence and progression of acute kidney injury. SCr; serum creatinine, UO; urine output

Declaration of conflicting interests

MR is a consultant for Livanova and Medtronic. MR is the inventor of an algorithm based on CPB data and aimed to predict postoperative AKI. The remaining authors have no competing interest to declare.

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Authors' contributions

SBR and YB performed the literature search and selected papers. SBR, YB and HBR wrote the original manuscript draft. MR and FDS critically revised the original draft and contributed to manuscript outlay. All authors have reviewed and approved the final manuscript submitted for publication and agree to be accountable for all aspects of the work.

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