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Review

New Insights Into Mechanisms of Acute Kidney Injury in Heart Disease

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ABSTRACT

Acute kidney injury is a frequent occurrence in patients with heart disease, and is associated with higher risk of adverse outcomes, including mortality. In the setting of decompensated heart failure, acute kidney injury can occur from hemodynamic and neurohormonal activation, venous congestion, and nephrotoxic medications. Certain medications, such as loop diuretics, renin angiotensin system blockers, and mineralocorticoid antagonists can seemingly cause acute kidney injury. However, this increase in creatinine level is not always associated with adverse outcomes and should be carefully differentiated so as to allow deliberate continuation of these cardio- and nephroprotective agents. In other settings such as cardiac surgery, acute kidney injury can occur from factors related to the cardiopulmonary bypass, renal hypoperfusion, or other perioperative factors. Last, patients with heart disease commonly undergo imaging procedures that

RÉSUMÉ

L'insuffisance rénale aiguë survient fréquemment chez les patients atteints de maladies cardiaques et est associée à un risque accru d'issues défavorables, y compris le décès. Dans un contexte d'insuffisance cardiaque décompensée, l'insuffisance rénale aiguë peut se produire à la suite d'une activation hémodynamique et neurohormonale, d'une congestion veineuse et de la prise de médicaments néphrotoxiques. Certains médicaments, comme les diurétiques de l'anse, les inhibiteurs du système rénine-angiotensine et les antagonistes des récepteurs des minéralocorticoïdes peuvent vraisemblablement causer une insuffisance rénale aiguë. Cependant, l'augmentation du taux de créatinine n'est pas toujours associée à une issue défavorable et sa cause doit être soigneusement différenciée de façon à permettre la poursuite délibérée du traitement par ces agents cardio- et néphroprotecteurs. Dans d'autres contextes, en chirurgie

The function of the heart and the kidneys has long been known to be intertwined. Several mechanisms have been advanced to explain their complex and bidirectional relationship. These mechanisms involve altered hemodynamics, electrolyte and acid-base imbalances, neurohumoral activation, and underlying gene variations. More than a century ago, Richard Bright described ventricular hypertrophy in the absence of valvular disease in patients with albuminuria.[1] Before the measurement of blood pressure had even been formalized, he speculated that changes in the quality of the blood in kidney disease might have a role to play in explaining this phenomenon. Fast forward to the present time, the term, "cardiorenal syndrome" (CRS) is now established in the literature and in clinical practice. This review article is intended to consolidate the pathophysiological mechanisms by which acute kidney injury (AKI) can occur in heart disease. The spectrum of AKI reviewed herein extends beyond CRS related primarily to heart failure and will also encompass AKI incurred during percutaneous and surgical procedures.

The Terminology of Kidney Dysfunction in Cardiac Disease

Definitions

The terminology for what used to be known as acute renal failure and chronic renal failure (or renal insufficiency) related to cardiac dysfunction has evolved in the past decade or so (see Table 1 for details). The term, acute renal failure, has been completely replaced by AKI, which now has established criteria.[2] Current definitions for AKI stipulate oliguria (urine output < 0.5 mL/kg/h) or an increase in serum creatinine of 26.5 μmol/L or more within 48 hours, or a 50% increase in 7 days. A slower and sustained increase in creatinine level over 3 months or longer is labelled as chronic kidney disease (CKD). Less well recognized is what lies between AKI and CKD, and has been more recently been termed, "acute kidney disease" (AKD). As per Kidney Disease: Improving Global Outcomes criteria,[1] AKD refers to when kidney dysfunction (defined as glomerular filtration rate [GFR] < 60 mL/min/1.73 m^2 or a 35% decline in GFR, or an

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require contrast administration. Contrast can indeed cause acute kidney injury, but these interventional procedures also can result in kidney injury from atheroembolic phenomena. This is well documented by the recent data reporting a higher risk of acute kidney injury from femoral compared with radial access. The advent of biomarkers of kidney injury present an opportunity for early detection, accurate differential diagnosis, as well as potentially designing innovative biomarker-enriched adaptive clinical trials.

cardiaque notamment, l'insuffisance rénale aiguë peut résulter de facteurs liés à la circulation extracorporelle ou à l'hypoperfusion rénale, ou d'autres facteurs périopératoires. Enfin, les patients atteints de maladies cardiaques subissent généralement des examens d'imagerie qui nécessitent l'administration de produits de contraste. Or, ces produits peuvent effectivement causer une insuffisance rénale aiguë, quoique les procédures interventionnelles puissent également entraîner une atteinte rénale par suite de phénomènes athéroemboliques. Ce fait est bien documenté par les données récentes indiquant un risque plus élevé d'insuffisance rénale aiguë lorsque la voie d'abord est fémorale plutôt que radiale. L'arrivée de biomarqueurs de l'insuffisance rénale ouvre la voie à un dépistage précoce, à un diagnostic différentiel précis ainsi qu'à la conception d'essais cliniques adaptatifs et novateurs mettant à profit le biomarquage.

increase in creatinine level of > 50%) has been present for < 3 months in duration. In a recent study that used routinely collected data from 1.1 million residents of Alberta, AKD without AKI was not uncommon, and was associated with greater long-term risks of CKD and mortality.[3]

The term, "cardiorenal syndrome," which was highlighted by Claudio Ronco with a new classification over a decade ago, was immediately found useful, and now has widespread acceptance.[4,5] The Acute Dialysis Quality Initiative set forward a detailed classification for CRS in 2010. More recently the American Heart Association issued a thorough scientific statement covering its pathophysiology, diagnosis, and management.[4,6] CRS has 5 subtypes (Table 1). Despite these classifications of CRS, there is significant overlap and the arrow of causation is not always clear because the relationship between heart dysfunction and kidney dysfunction is typically bidirectional. In this review, we focus specifically on the various mechanisms by which AKI occurs in cardiac disease (ie, CRS subtype 1 and AKI that is otherwise related to cardiac interventions or cardiac surgery).

Table 1. Terminology of kidney dysfunction, using the KDIGO and ADQI classification schemes

Terminology	Description
AKI	Oliguria for > 6 hours defined as < 0.5 mL/kg/h for 6-12 hours, or increase in creatinine by > 26.5 μmol/L in 48 hours, or increase in creatinine by > 50% in 7 days
AKD	AKI, or GFR < 60 mL/min/1.73 m^2, or decrease in GFR by > 35%, or increase in creatinine by > 50%, or markers of kidney damage for < 3 months
CKD	GFR < 60 mL/min/1.73 m^2 for > 3 months
CRS	
CRS 1, acute cardiorenal	Acute cardiac impairment leading to AKI
CRS 2, chronic cardiorenal	Chronic cardiac impairment leading to renal impairment
CRS 3, acute renocardiac	AKI leading to cardiac impairment
CRS 4, chronic renocardiac	CKD leading to cardiac impairment
CRS 5, secondary cardiorenal	Systemic disease leading to renal and cardiac impairment

ADQI, Acute Dialysis Quality Initiative; AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; CRS, cardiorenal syndromes; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

"Permissive hypercreatininemia" or worsening renal function

Worsening renal function (WRF) is the term frequently used in studies to describe renal dysfunction that occurs during hospitalization for acute decompensated heart failure (ADHF).[7] These studies define WRF as an absolute increase in creatinine of > 26.5 mmol/L, corresponding to the stage 1 AKI definition.[2] Observational data suggest a high incidence of WRF in the setting of ADHF, with several associated adverse clinical outcomes. As an example, WRF was observed in almost a third of patients in a chart review of 1004 consecutive patients from 11 different hospitals who presented with ADHF.[8] Cox regression model analysis identified a history of heart failure or diabetes, high admission creatinine level (> 1.5 mg/dL or 132.6 μmol/L) and systolic blood pressure (> 160 mm Hg) as risk factors for WRF. There was a higher adjusted relative risk (RR) for in-hospital deaths (RR, 7.5; 95% confidence interval [CI], 2.5-19.3), and length of hospitalization (RR, 3.2; 95% CI, 2.2-4.9).

The WRF terminology seems precise, but it does imply that actual kidney function is decreased, as opposed to just an increase in the serum creatinine level. An increase in serum creatinine level might not really signify a true worsening of kidney function because serum creatinine is an imperfect indicator of true kidney function, and more importantly, of kidney damage. Small changes in creatinine level have been epidemiologically linked to poor clinical outcomes, including long-term mortality. However, they could merely reflect an underlying sicker patient population, who already have a poor prognosis, and hence develop AKI as well as have lower rates of survival. Thus the occurrence of AKI might not be in the causal pathway. In support of this, a systematic review included placebo controlled trials of interventions, which showed a benefit in creatinine, and also reported longer-term clinical outcomes.[9] Despite almost halving the risk of creatinine level increase, the pooled risks for CKD and mortality associated with interventions did not differ from those with placebo.

Additionally, many biomarkers have been described in the past decade that are more sensitive indicators of kidney injury. Do these show a similar change with WRF? Surprisingly the answer is no. In the hypertension literature, the seminal

studies in the past decade have been **A**ction to **C**ontrol **C**ardi**o**vascular **R**isk in **D**iabetes (ACCORD) and **S**ystolic Blood **P**ressure **In**tervention **T**rial (SPRINT).[10,11] These trials did report a reduction in stroke and heart failure, cardiovascular outcomes, and mortality but did not report a similar benefit in kidney-related outcomes. Indeed, intensive blood pressure-lowering even resulted in an increase in new-onset CKD (defined as an absolute GFR < 60 mL/min/1.73 m^2, and/or a 30% decline).[11] Two elegant studies measured these biomarkers in a subset of patients from ACCORD and SPRINT.[12,13] They did not report an increase in markers of kidney injury in these patients who developed new onset "CKD" after intensification of blood pressure-lowering. These data suggest that even WRF might reflect hemodynamic changes more than true structural damage. This aspect specifically applies even more to drug-induced changes in kidney function, as discussed in detail in the section on *Role of Medications*. From a therapeutic aspect, this is an important consideration when an elevation in creatinine level occurs during treatment of heart failure, as discussed in a recent guidance document (Fig. 1).[14]

Biomarkers in AKI

Biomarkers are indeed useful in potentially differentiating changes in creatinine from hemodynamic factors vs true tubular damage as discussed previously. They are also useful in diagnosing AKI early, and many different biomarkers are in various stages of development, and some have been approved and are commercially available in select countries (Table 2).[15] One of the most well studied is neutrophil gelatinase-associated lipocalin, which is produced in the distal tubular epithelial cells, appears in the urine as early as 3 hours after kidney injury, and peaks at approximately 6-12 hours, depending on the severity of AKI.[15] Another biomarker is kidney injury molecule-1, which undergoes marked upregulation and insertion into the apical membrane of the proximal tubule after ischemia-reperfusion injury and persists in epithelial cells until recovery.[16] More promising are the cell cycle arrest biomarkers, which are expressed during times of cellular stress or injury such as during ischemic AKI. Tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein-7 have been validated as prediction tools for AKI, and have even been in a pilot study to triage patients at high risk of AKI after cardiac surgery.[17,18] Beyond their role in early diagnosis, differentiating "true" tubular damage, these biomarkers might also be useful for enrichment in clinical trial design.[19] See Table 2 for a summary of biomarkers being studied, and approved for use in AKI.

Mechanisms of AKI in Heart Failure

Hemodynamics and neurohormonal activation

The historical explanation for type 1 CRS is that, when cardiac output is reduced, the kidneys become less well-perfused and prerenal AKI is the consequence. However, this simplistic scenario fails to take into consideration the numerous physiological defenses that are overcome in heart failure. Although undoubtedly an important mechanism by which AKI can occur, in many cases, hypoperfusion is not the primary driver of AKI. The kidney has a remarkable ability to autoregulate arterial and glomerular arteriolar blood flow in the face of decreasing cardiac output. In particular, the GFR can be maintained by neurohormonal mechanisms that result in increased afferent glomerular arteriolar dilatation and efferent arteriolar vasoconstriction. In experimental models, it takes a significant degree of reduction in the cardiac index (to < 1.5 L/min/m^2) to cause an effect on GFR.[20] In normal circumstances, any increase in atrial pressure is accompanied by a decrease in vasopressin release, a decrease in the renal sympathetic tone, and an increase in atrial natriuretic peptide.[21-23] The net effect is to increase urinary sodium and water excretion and restore homeostasis, the so-called atrial-renal reflex. A complex overlay of neurohormonal system activation and inappropriate target response lead to the downstream consequences in decompensated heart failure as described in the section on *Hemodynamics and Neurohormonal Activation*.

Activation of the renin-angiotensin system (RAS) occurs early in biventricular failure due to increased renin secretion.[24] Among other effects, this increases aldosterone synthesis with resultant sodium and water retention which, in normal physiological conditions, does not persist beyond approximately 3 days. In congestive heart failure, an "aldosterone escape" is described and this results in ongoing sodium retention.[25] Sympathetic activation triggered by decreased cardiac output ultimately leads to catecholamine levels in the plasma being increased. Although this is accompanied by a paradoxical decrease in cardiac norepinephrine levels because of maximal turnover in the failing heart,[26] the consequences of increased systemic catecholamines are felt in the kidneys: alpha-receptor stimulation in the proximal tubule leads to increased sodium absorption and further RAS activation. Over time, the aforementioned atrial-renal reflex that leads to secretion of atrial natriuretic peptide has a reduced effect in potentiating sodium and water excretion in the kidneys. This stems from reduced sodium delivery at its site of action, the distal tubule, and/or potentially downregulation of its receptors.[25] Last, nonosmotic stimulation of the release of vasopressin results in water retention from the collecting ducts causing hyponatremia as well as enhanced urea reabsorption, resulting in elevation in serum urea levels. Thus, the imbalance between vasoconstriction/sodium retention and vasodilatation/natriuresis is the major mechanism at play.[23] These effects are not merely seen with low cardiac output states. Even in the high cardiac output state, arterial vasodilatation decreases the inhibitory effect of the atrial stretch receptors, allowing the same neurohormonal cascade to begin.[25]

Elevated renal venous pressure

As alluded to previously, although renal hypoperfusion resulting from decreased cardiac output is at the forefront of any cardiorenal pathophysiology discussion, the role of increased central venous pressure remains under-recognized and underappreciated. In high-volume resuscitation with septic shock and after abdominal surgery, increased abdominal pressure resulting in an "abdominal compartment syndrome" and consequent impairment of perfusion involving renal arteries and veins is being slowly recognized, with objective criteria, such as the difference between the mean arterial pressure (MAP) and the intra-abdominal pressure. Similarly,

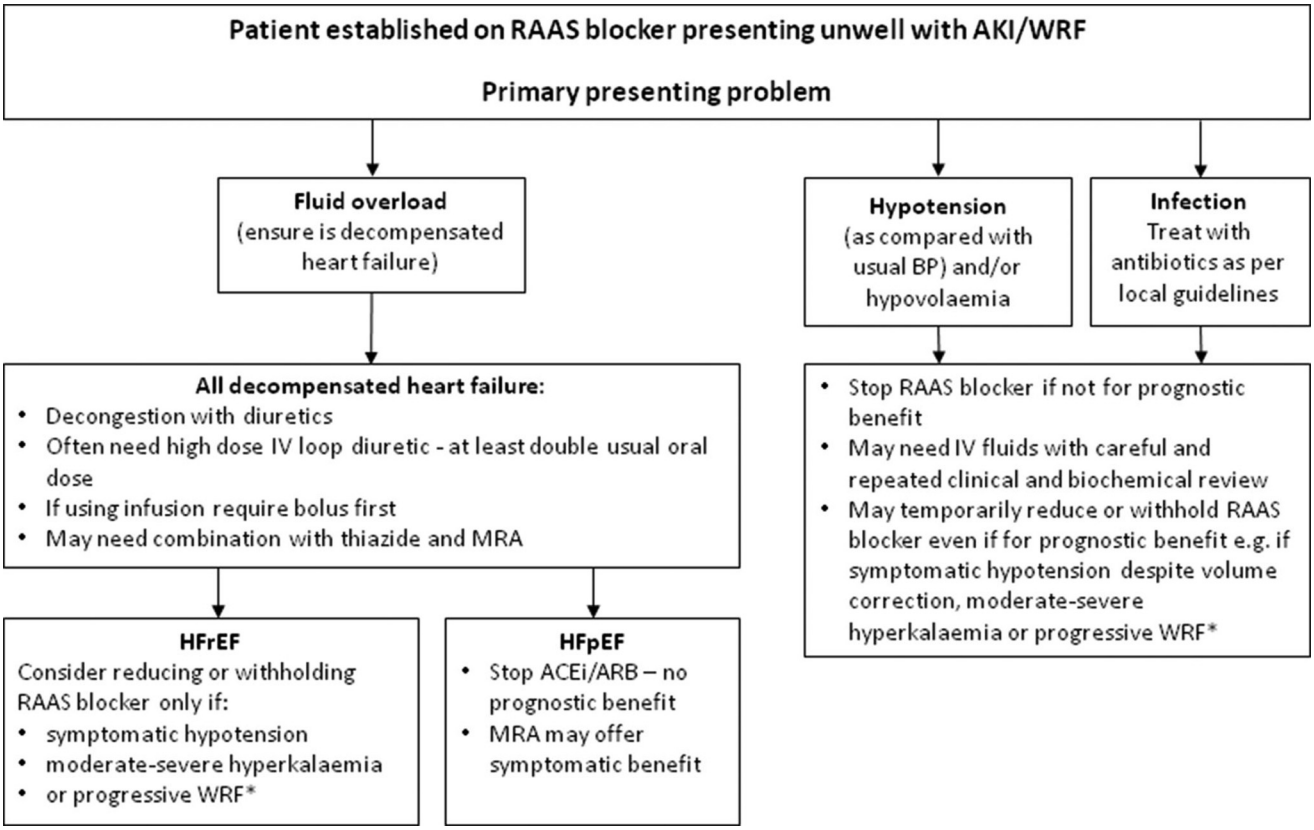

Figure 1. Management of patients with acute kidney injury (AKI) or worsening renal function (WRF) who are receiving renin-angiotensin-aldosterone system (RAAS) inhibitors. Clinical assessment of the individual patient is key. In all cases consider original indication for RAAS inhibitor. Major prognostic benefit: heart failure with reduced ejection fraction (HfrEF), post myocardial infarction, and left ventricular systolic dysfunction, chronic kidney disease (CKD), and albuminuria. No/little prognostic benefit: hypertension (other drug options available) and heart failure with preserved ejection fraction (HfpEF). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; IV, intravenous; MRA, mineralocorticoid receptor antagonist. Reproduced from Clark et al.[14] with permission from the BMJ Publishing Group Ltd.

in hepatorenal syndrome, along with the hemodynamic issues, tense ascites plays a similar role in contributing to AKI. In the setting of decreased cardiac output, the kidney maintains the GFR by local autoregulation, involving afferent arteriolar dilatation and efferent arteriolar vasoconstriction. Below a certain cardiac index (1.5 L/m^2/min) the afferent flow is critically reduced, allowing little input from additional efferent vasoconstriction.[27] In this scenario, venous congestion and renal venous pressure can play a larger role in the GFR homeostasis than otherwise would be anticipated according to the concurrent hemodynamic readings. Experimental data suggest that increased renal venous pressure raises interstitial pressure and consequently peritubular hydrostatic pressure as well, increasing sodium reabsorption, and resultant oliguria.[28] The increased renal venous pressure is hypothesized to extend all the way to a net reduction in GFR as well. Increased renal interstitial pressure might also activate inflammatory and fibrotic pathways in the kidney. In a post hoc analysis of the **E**valuation **S**tudy of **C**ongestive He**a**rt Failure and **P**ulmonary Artery Catheterization **E**ffectiveness (ESCAPE) trial, right atrial pressure was the only measure associated with kidney dysfunction, a finding confirmed in another study.[29,30] Another intriguing mechanism relates to the intra-abdominal pressure, similar to that seen in abdominal compartment syndrome. Ascitic fluid accumulation in heart failure can lead to an increase in intrathoracic pressure thus decreasing cardiac preload and the end diastolic volume, both of which would have a downstream effect on the GFR.[31] In a study of patients with ADHF, 60% were identified as having elevated intra-abdominal pressure, which was associated with a lower level of kidney function.[32] Overall, although these data seem sporadically scattered over 4 decades, they have resulted in a call to term this a "congestive kidney failure" state to increase awareness and research in this area.[33] Figure 2 shows a summary of the interplay between arterial underfilling, venous congestion, and the bidirectional nature of AKI in this setting.

Role of medications

Medications that are commonly used in patients with heart failure can indeed be nephrotoxic. As an example, prolonged courses of antibiotics such as vancomycin (especially when combined with piperacillin-tazobactam) and aminoglycosides when given for endocarditis or sternal osteomyelitis can cause tubular injury and AKI. Other medications that are commonly used in this population would include nonsteroidal anti-inflammatory drugs, which can cause AKI and CKD. When reasonable alternatives are available, stopping use of the offending agent and replacing them is a convenient option.

Table 2. Summary of biomarkers in AKI

	Characteristic	Applicability
NGAL	Present in neutrophil granules; released with tissue injury and freely filtered. Urine NGAL represents intrarenal production	Approved in Europe (Conformité Européene [CE]), Australia (Therapeutics Goods Administration), South Africa (South African National Accreditation System), and Canada (Health Canada)
Kidney injury molecule	Transmembrane glycoprotein induces on proximal tubular apical membrane with injury	Mixed results; few supporting data in heart failure
Nephrocheck (combination of insulin-like growth-factor binding protein 7 and tissue inhibitor of metalloproteinases)	Cell cycle arrest proteins expressed with cellular stress or injury	Several validity studies done; approved in United States and Europe
Interleukin 18	Proinflammatory cytokines, expresses in proximal tubules with injury	Promising data in kidney transplantation population; mixed results in the setting of heart failure
Liver-type fatty acid-binding protein	Part of lipid-binding protein superfamily, binds with fatty acids and elevated with ischemia reperfusion injury	Predictor of AKI after cardiac surgery; approved in Japan
N-acetyl-β-D-glucosaminidase	Lysosomal enzyme, found in proximal tubular cells and presence in urine reflects tubular injury	Promising data in chronic kidney disease; mixed results in the setting of heart failure
Procalcitonin	116-amino acid peptide, upregulated in many tissues during infections compared with chronic inflammatory states	High levels seen in infectious conditions and heart failure (with or without AKI)
Copeptin	The C-terminal segment of the arginine vasopressin prohormone, with high ex vivo stability that is easy to measure	Theoretically would be useful as an indirect measure of vasopressin activation in decompensated heart failure

AKI, acute kidney injury; NGAL, neutrophil gelatinase-associated lipocalin.

This is somewhat difficult when the case relates to drugs that are used in the management of heart failure, such as RAS blockers and diuretics. Stopping these drugs prematurely and inappropriately at the slightest bump in creatinine level might not allow the patients who need it the most to obtain much-needed benefit. Diuretics are the drugs most often held, but their putative role, beyond the setting in which misuse results in hypovolemia and a prerenal state, is unclear. Although a single-centre study reported an increased adverse neurohormonal activation with loop diuretics compared with extracorporeal fluid removal using ultrafiltration, these findings were mechanistically not very plausible, nor were they reproduced.[34] Although they have made it into the collective folklore of furosemide being nephrotoxic, this is an inaccurate understanding, and is not supported by findings from the **Car**diorenal **Res**cue Study in Acute Decompensated **H**eart **F**ailure (CARRESS-HF) trial.[35] Loop diuretics are most often prescribed, or their doses escalated in ADHF in the presence of congestion, the persistence of which has been reported with a fourfold higher risk of subsequent mortality. However, in an analysis of 599 patients with ADHF, the absence of congestion, even when accompanied by WRF, provided a prognosis similar to patients who did not have congestion or WRF, compared with the worse outcomes in those who had congestion, with, or without, WRF.[36] Thus, the use of loop diuretics to successfully manage congestion is prognostically more important than the occurrence of WRF in this setting. Similarly, in an analysis from the **R**andomized **Al**dactone **E**valuation **S**tudy (RALES), WRF was more common in those randomized to spironolactone (17%) and then in the placebo group (7%). However, the adjusted risk of death with WRF was only higher in the placebo group (hazard ratio [HR], 1.9) but not in those randomized to spironolactone (HR, 1.1; *P* value for interaction = 0.009).[37] Indeed, diuretic withdrawal has been associated with an increase in markers of kidney injury, disconnected from creatinine fluctuations.[38]

RAS blockers often suffer a similar fate. Clearly, sensible care dictates these should be withheld when there is hypotension, or AKI from clinically suspected hypoperfusion. However, withholding them for every creatinine fluctuation might potentially deprive a patient of a meaningful and useful therapy.[39,40] In the **S**tudies **o**f **L**eft **V**entricular **D**ysfunction (SOLVD) trial, WRF was associated with a higher mortality rate. In further analysis, this was only shown in the placebo group (HR, 1.4), but not in the enalapril group (HR, 1.0).[41] Additionally, intriguing observational data from Alberta supports continuing these agents in the setting of AKI. Doing so was associated with a lower mortality rate whereas stopping use of a RAS blocker prescribed before hospital admission was associated with increased mortality (HR, 1.23; 95% CI, 1.17-1.30).[42]

One of the most important therapeutic developments in recent years has been the advent of the sodium-glucose transporter inhibitors, which have been proven to have a cardio- and nephroprotective role far beyond mere glucose-lowering. Like RAS blockers, these agents also cause a small acute elevation in creatinine level, but in the long term reduce the risk of kidney failure, hospitalization for heart failure, and even all-cause mortality.[43-45] Hence, acute elevations in creatinine level are context-dependent, especially when induced by drugs with a protective effect, and should be differentiated from spontaneous AKI (Fig. 3).[46]

Because of the role of natriuretic peptides in AKI in this setting, one might presume that neprilysn inhibition might have an effect on kidney function. Neprilysn is a neural endopeptidase that increases the levels of natriuretic peptides as well as bradykinin and adrenomedullin. The **P**rospective Comparison of **ARNi** With **ACEi** to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure

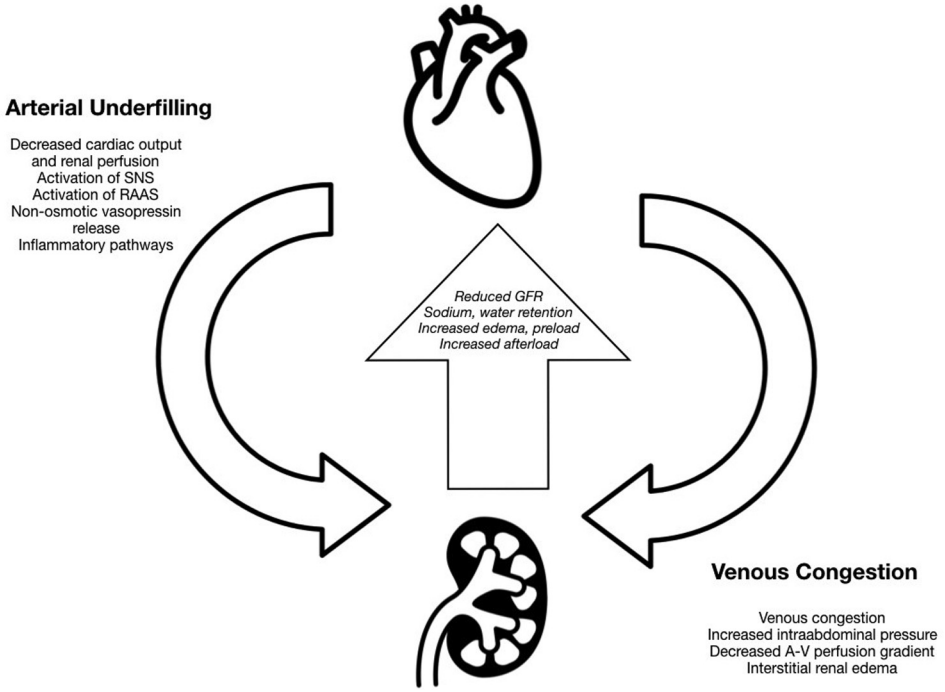

Figure 2. Schematic depicting the pathogenesis of acute kidney injury in decompensated heart failure, and the bidirectional mechanisms involved. A-V, arterio-venous; GFR, glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

(PARADIGM-HF), which reported a remarkable reduction in all-cause mortality, also reported secondary renal end points, which were not significant, although the composite kidney outcome was slightly less common with sacubitril/valsartan (2.2%) than enalapril (2.6%).[47] A subgroup analysis reported a potentially slower decline in kidney function (-1.3 mL/min/1.73 m^2/y with sacubitril/valsartan vs -1.8 mL/min/1.73 m^2/year with enalapril; $P < 0.001$) in patients with diabetes.[48] However, patients with either CKD (GFR $<$ 60 mL/min) or AKI were appropriately excluded in the PARADIGM-HF trial. According to the previous discussion about continuation of RAS blockers in AKI, it would be interesting to see the effect of sacubitril/valsartan in the cardiorenal setting. With respect to CKD, a subsequent trial in patients with CKD did not report any difference in kidney function, although sacubitril might have other hemodynamic effects that might affect GFR (natriuresis and blood pressure-lowering) that could mask any favourable long-term effects on CKD progression.[49] Sacubitril/valsartan does show a similar initial decrease in GFR akin to RAS blockers (likely from the valsartan component), but their putative long-term kidney effects still need rigourous testing.

Epigenetics in CRS

Epigenetics involves heritable changes caused by modification of gene expression rather than alteration of genetic code itself. It is an adaptive response at the genetic level to an altered state of activity. They include mechanisms like DNA methylation, histone modification, and heterochromatin regulation, and act by activating or silencing certain genes and facilitate differentiated cells to express genes that are required for their own activity. Epigenetics have been proposed to play a role in the pathogenesis of heart and kidney disease. Experiments in rats showed a causative role for DNA methylation in causing heart hypertrophy and reduced cardiac contractility and suggested a potential role of demethylation in treating heart disease.[50] Similar animal studies report trimethylation of histone H3 on lysine-4 or lysine-9 in cardiac myocytes leading to development of heart failure.[51] Genome mapping in patients with cardiomyopathy and normal hearts show significant difference in DNA methylation in the promoters of upregulated genes.[52] Similarly in kidney disease as well, the role of epigenetic changes has been described. In ischemia models conducted in mice, there was a transient decrease in histone acetylation in proximal tubular cells due to upregulation of histone deacetylation (HDAC) 5 isoenzyme.[53] The recovery phase was associated with HDAC 5 downregulation and bone morphogenetic protein-7 (BMP7) induction. Inhibition of HDAC 5 by microRNA has been proposed as a therapeutic strategy to facilitate renal recovery by enhancing BMP7 expression.[53] MicroRNAs, which represent a subgroup of small noncoding RNAs, are being studied extensively as possible mediators of organ cross talk. They are secreted by one particular organ and effect functions of cells in a distant organ by binding to untranslated region of target messenger RNA or promoter sequences.[54,55] As an example, experiments in rat models have shown that exposure to the uremic toxin, indoxyl sulfate, was associated with an increase in miR21 and decrease in miR29b, via the angiotensin signalling pathway, leading to cardiac fibrosis.[56] Overall, although these are in no way ready for prime time, there is hope we will have greater insight into the mechanisms and some potential therapeutic targets.

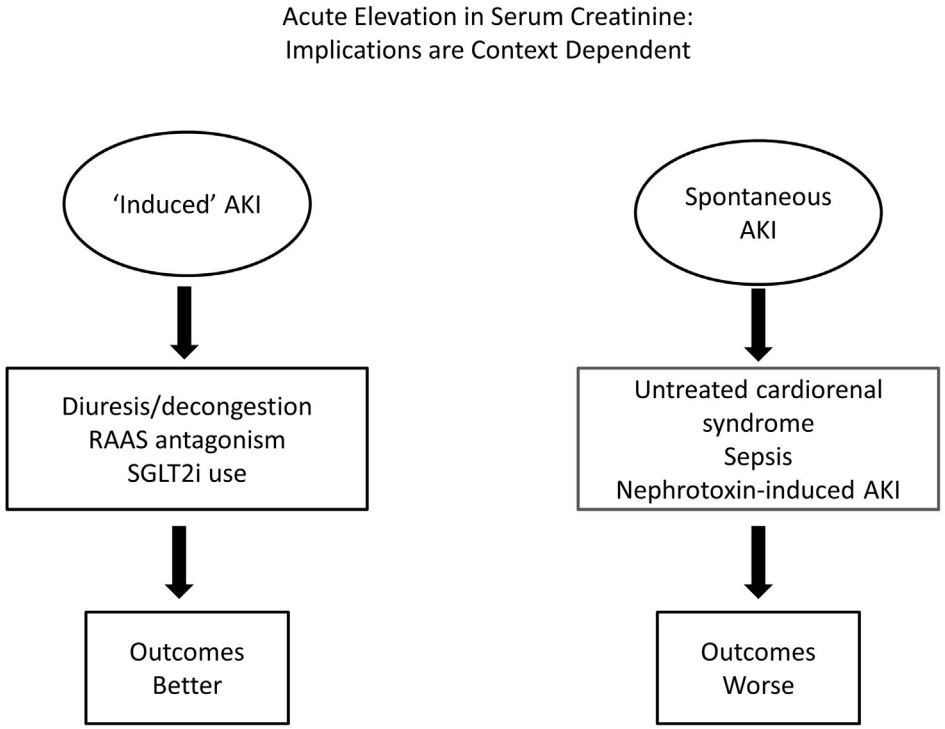

Figure 3. Schematic depicting that the implications of acute elevations in serum creatinine are context-dependent. AKI, acute kidney injury; RAAS, renin angiotensin system; SGLT2i, sodium glucose transporter inhibitors. Modified from Coca[46] with permission from American Society of Nephrology.

Cardiac Surgery-Associated AKI

AKI is a common occurrence after cardiac surgery, with the published incidence ranging from 5% to 42%, mostly varying on the basis of differing definitions, timing, and patient populations.[57,58] The risk of severe AKI needing renal replacement therapy is narrower, at approximately 1%-5%. Because coronary angiography often precedes the need for cardiac surgery, it is important to keep in mind that when contrast-induced AKI (CI-AKI) occurs, it is prudent to wait before surgery to reduce further kidney injury.[59] Unsurprisingly, patients who do develop cardiac surgery-associated AKI (CS-AKI) have higher perioperative mortality as well as long-term mortality, longer length of stay in the intensive care unit, and in-hospital, and subsequently higher costs of care.[15,16] Within cardiac surgery, coronary artery bypass graft (CABG) alone carries a lower risk of AKI compared with valve surgery, or CABG combined with valve surgery.[60] Unlike other causes of postoperative AKI, there are some unique aspects to the development of CS-AKI that are worth elaboration, and are also summarized in Table 3.

Renal hypoperfusion

The kidneys are uniquely susceptible to ischemic damage, with the renal medulla having limited reserve due to low oxygen tension. The MAP itself has not been reported to be associated with the risk of AKI. It is possible that relative hypotension might play a role, and the difference between preoperative MAP and intraoperative MAP might be a more accurate determinant of renal perfusion.[61] Additionally, cardiopulmonary bypass (CPB) provides nonpulsatile perfusion, which might play a role. Data from kidney transplantation surgery suggests decreased incidence of delayed graft function with the use of pulsatile perfusion compared with standard measures.[62] In the CS-AKI literature, the data on amelioration

Table 3. Mechanisms of AKI after cardiac surgery

	Pathway of injury	Mechanism
CPB	Renal hypoperfusion*	Ischemic injury
	Nonpulsatile perfusion	CPB provides nonpulsatile perfusion, which might cause ischemic injury to the medulla
	Decreased oxygen delivery	CPB-induced hemolysis, hemodilution
	Cell lysis	Longer time of CPB associated with hemolysis and rhabdomyolysis; tubular damage from free hemoglobin, nitric oxide depletion
	Embolic phenomenon*	Gaseous and particulate emboli due to CBP
	Ischemia reperfusion injury and inflammation	Activation of inflammatory pathways due to bioincompatible CBP surface free radical release
Other factors	Renal hypoperfusion*	Surgical blood loss, hypotension from other reasons
	Atheroembolic phenomenon*	Dislodgement of cholesterol emboli during surgery

AKI, acute kidney injury; CBP, cardiopulmonary bypass.
* Pathways common to CBP and otherwise.

is not as clear, possibly related to the multifactorial nature of the kidney insult compared with the kidney transplantation scenario.[63,64]

Decreased oxygen delivery

Beyond hypoperfusion, which does contribute to oxygen delivery to tissue, preexisting anemia, blood loss, hemolysis, and hemodilution also contribute to a reduction in oxygen delivery. As mentioned already, the medullary tissue, encompassing tubules and interstitium, has low oxygen tension at baseline, making it susceptible to further insults. Hemodilution during CPB might theoretically exacerbate this, and so would blood loss. Observational studies report a hematocrit of approximately 24% as a threshold, however, this is not supported by trial data.[65] The **T**ransfusion **R**equirements **i**n **C**ardiac **S**urgery (TRICS) III did not report a difference between a liberal (< 95 g/L) or a restrictive transfusion (< 75 g/L) threshold for AKI, nor for any other important clinical outcome.[66]

Potentially protective role of hypothermia

Most cardiac surgeries with CPB are performed using mild to moderate systemic hypothermia (25°C-32°C) and complicated surgeries might require deep hypothermia (15°C-22°C). In the kidney transplantation surgery setting, therapeutic hypothermia in the deceased donor significantly reduces delayed graft function.[67] The association of these hypothermic states with CS-AKI is mixed, possibly relating to measurement error—arterial temperature might be a more accurate determinant than nasopharyngeal, bladder, or rectal temperature.[68] Additionally, damage might be related to ischemia-reperfusion more than hypothermia, and hence the rate of rewarming might play a more important causative role. A small single-centre trial suggested lower incidence of AKI in the arm rewarmed to 34°C vs 37°C (RR, 1.4; 95% CI, 1.0-1.9).[69]

Consequences of cell lysis due to CPB

Longer time of CPB is another risk factor for AKI related to hemolysis and rhabdomyolysis, both of which are directly implicated in tubular damage and AKI.[70] Additionally, intravascular hemolysis leads to free hemoglobin in blood, which scavenges nitric oxide.[71] Depletion of nitric oxide can lead to increased vascular resistance, thrombin formation, fibrin deposition, and platelet activation. Free hemoglobin also induces heme oxygenase-1 expression leading to direct tubular injury.[72] Even damage to red cells short of actual hemolysis can impair their deformability and ability to navigate small capillaries and compromise oxygen delivery.[73]

Embolic phenomenon

Akin to cholesterol emboli with percutaneous diagnostic or therapeutic procedures, cardiac surgery can also dislodge cholesterol from atheromatous plaques with some of these particles making their way into the hapless renal microcirculation.[74] CPB itself also results in macroscopic and microscopic emboli, both gaseous and particulate, which can contribute to AKI. Supporting this is the association of post CABG cerebral emboli and AKI, as well as the association of atheromatous burden in the aorta with AKI.[75]

Ischemia reperfusion and inflammation

CPB is not a biocompatible surface, and results in activation of deleterious inflammatory pathways. A study of complement activation products and cytokines in patients who undergo cardiac surgery showed a biphasic activation of complement, with the first peak (predominantly alternative pathway) occurring during the surgery itself due to contact of blood with extracorporeal circuit and the second peak after 5 days. Subsequent studies on inflammation have shown an association between increase in interleukin 6 and 10 with perioperative risk of AKI.[76] Release of free oxygen radicals during CPB is also associated with toxic AKI.[77] Ischemia reperfusion injury by itself can lead to production of free radicals leading to further myocardial injury and systemic effects.[78]

Off pump vs on pump

As the preceding discussion shows, many of the factors involved in the pathogenesis of CS-AKI have more to do with the events occurring during CPB. Could off-pump surgery represent an overarching intervention to remove all of these pathways? The empiric data are sadly less promising, with the whole being less than what the sum of the parts might lead us to believe. The **Coron**ary **A**rtery Bypass Surgery Off or On Pump **R**evascularization Stud**y** (CORONARY) trial involved approximately 3000 patients with first CABG randomized to off-pump and on-pump.[79] The risk of AKI within 30 days of surgery (> 50% increase in serum creatinine from pre-randomization level) was significantly reduced with off pump (17.5% vs 20.8%; RR, 0.83; 95% CI, 0.72-0.97) but without evidence of better preserved kidney function with off pump at 1 year (17.1% vs 15.3%; RR, 1.10; 95% CI, 0.95-1.29). The **R**andomized **O**n/**O**ff **By**pass (ROOBY) trial, however, did not show a benefit in approximately 2200 patients randomized to the same arms for the 30-day composite outcome, which included AKI (0.8% vs 0.9%).[80] Another perspective can be gained by the examination of AKI rates between surgical and transcatheter aortic valve replacements. The latter could be presumed to have less of the effect on the kidney from mechanisms discussed previously. For this comparison, the observational data are treacherous, because of the decisions underlying surgical vs percutaneous approaches, which result in selection bias that cannot be adjusted away. In the **P**lacement of **A**or**t**ic Tra**n**scathet**er** Valves (PARTNER) trial, there was no difference between surgical or transcatheter approaches with respect to AKI (2.9% and 3.0%).[81] It is possible in this case that the benefit from avoiding CPB might have been offset by the effect of contrast and atheroembolic phenomenon, discussed in the section on *Periprocedural AKI*.

Periprocedural AKI

Cardiac imaging and therapeutic interventions are often followed by AKI, and for long they have been blamed on the iodinated contrast that is administered. In contrast, recent epidemiological studies suggest CI-AKI) does not exist, and is a "myth,"[82] but these do not take into account the clinician decision to avoid contrast in high-risk patients, and are quite susceptible to selection bias, as discussed in the section on *Contrast-Induced Kidney Damage*.[83,84] Table 4 shows a summary of the different mechanisms of AKI in this setting and the features and prognosis.

Table 4. Periprocedural AKI: causes and features

Type	Features	Risk factors	Prognosis
Contrast-induced AKI	Oliguria Rapid rise in creatinine in 24-48 hours	Arterial contrast High volume contrast load Underlying CKD Repeat contrast load	Recovery common within 1-2 weeks (exception: when AKI occurs in the setting of advanced CKD)
Atheroembolic AKI	Step ladder rise in creatinine Might be initially nonoliguric Might be associated with other embolic phenomenon, eosinophilia	Femoral access higher risk than radial access High atheroma burden	Recovery uncommon (exception: partial recovery might occur with resolution of inflammatory changes)
Ischemic ATN	Tubular damage from shock Oliguria	Shock from cardiogenic factors, blood loss	Intermediate (less likely to recover compared with contrast-induced AKI)

AKI, acute kidney injury; ATN, acute tubular necrosis; CKD, chronic kidney disease

Contrast-induced kidney damage

The actual mechanism of contrast-induced kidney damage has not been well characterized until recently, and has been on the basis of animal studies using high doses of high osmolar contrast agents, which are no longer used.[85] Early theories revolved around medullary hypoxia and ischemia, and damage from reactive oxygen species. The physico-chemical properties of the contrast agents, mainly osmolarity but also viscosity are factors thought to play a role in differing toxicity with different agents. The viscous contrast agents can indeed cause intratubular obstruction (seen in the nephrograms associated with this condition) and also ischemia from the agent entering the vasa recta.[86,87] However, most of this research was performed with the older, high-osmolar contrast agents, now completely replaced with low-osmolar and iso-osmolar contrast agents. A recently published study from Calgary used Nod-like receptor pyrin containing 3 (Nlrp3)-deficient mice to shed further light in this area.[88] In this study, ioversol (a low-osmolar agent), as well as diatrizoate (a high-osmolar agent) directly induced tubular cell death and uptake of contrast in resident phagocytes in the kidneys happened in minutes, however, only in wild type mice and not Nlrp3-deficient mice, suggesting a role for this enzyme in CI-AKI pathogenesis. However, applying these contrast agents to primary human proximal tubular epithelial cells showed instead that contrast activates the canonical Nlrp3 inflammasome in macrophages, and that tubular uptake is mediated by renal dipeptidase-1. These insights were supported by detection of inflammasome-related biomarkers in humans who underwent coronary angiography.

These findings also emphasize the existence of CI-AKI which has been called out as a nonexistent entity on the basis of epidemiological studies that cannot exclude selection bias.[84,89] Much of this literature is on the basis of venous contrast administration, mostly computed tomography, and is derived from administrative data sets. First, administrative data sets cannot exclude other possible concomitant causes of AKI (such as prerenal AKI, sepsis, drugs). More importantly, control patients (who are not given contrast) are likely to have not been given contrast because of the ordering clinician's estimate of a patient's risk of AKI. This selection bias cannot be controlled by regression, nor matched away with propensity scores. As an example, one of the epidemiological studies even reported a lower risk of AKI after contrast than in controls (ie, contrast being nephroprotective), a highly unlikely finding.[89] Last, it is indeed true that the risk of AKI after venous contrast has been overstated, however that does not inform us about the risk of AKI with arterial contrast from angiography, which is the area of concern in this setting.

Atheroembolic kidney damage

Often overlooked, but potentially more important is the role of cholesterol emboli and kidney damage. CI-AKI, whether from intratubular damage or from actual tubular injury, should most often recover. Often the episodes labelled as CI-AKI, especially accompanied by nonrecovery, might represent damage from cholesterol emboli.[90] Patients who undergo vascular procedures by definition are more likely to have a high atherosclerotic burden, putting them at high risk for this to occur. Additionally, the kidney does receive approximately 20% of the blood flow, making them more susceptible to be a target of any cholesterol emboli. The damage from cholesterol emboli might occur from immediate ischemia, and subsequently from inflammation, resulting in a "step ladder" form of early and delayed kidney function decline. Additionally, it is also more likely to be irreversible in nature, as expected from its mechanism, unlike CI-AKI. How big a role it plays, however, has not been very clear because the usual stigmata of atheroembolic phenomenon might not always accompany kidney damage, and the presence of, say, livedo reticularis or trash feet, could occur in the absence of AKI. The increase in the use of the radial approach to coronary angiography provides some welcome data, because presumably, it would be less likely to result in cholesterol emboli showering the kidneys, purely from an anatomic perspective. An analysis from the **M**inimizing **A**dverse Haemorrhagic Events by **Tr**ansradial Access Site and Systemic **I**mplementation of Angio**X** (MATRIX) trial revealed that the risk of AKI was lower with the radial approach, most impressively with a halving of the rates of dialysis requirement.[91] A subsequent systematic review from 9 observational cohorts confirmed that the radial approach was associated with approximately half the risk of AKI compared with the femoral approach, with a summary RR of 0.55.[92] Last, the original MATRIX trial also reported a reduction in bleeding and all-cause mortality, along with a reduction in AKI. A recent analysis using multistate and competing risk models reported on the mechanism of the mortality benefit. There were large relative risk reductions in mortality for radial compared with femoral access for the transition from AKI to death (HR, 0.55; 95% CI, 0.31-0.97) and for the pathway from coronary intervention to AKI to death (HR, 0.49; 95% CI, 0.26-0.92). No such risk reduction was seen in the bleeding risk to death pathway.[93]

Admittedly, this lower risk also might stem from a variety of confounders, such as use of radial approach in lower-risk patients,

or by operators with greater technical skill, etc. However, this is backed by some mechanistic data as well. With the advent of transcatheter aortic valve replacement, we have access to computed tomography images in a subsegment of population at high risk of periprocedural AKI. A higher preexisting atherosclerotic plaque burden, measured using these imaging techniques, has been associated with a higher risk of subsequent AKI.[94] Needless to say, this might just be a marker of a sicker patient population. In a recent analysis, Shishikura et al.[95] described a novel method to identify patients at risk for AKI after transcatheter aortic valve replacement through quantitative measurement of aortic atheroma volume. They reported that not just total atheroma volume, but percent atheroma volume, specifically above the renal arteries to be significant predictors of AKI as well as a higher likelihood of attenuated recovery.[95,96]

Other mechanisms

The previous discussion highlights 2 major pathways for AKI around cardiovascular procedures. Other mechanisms include renal hypoperfusion, from decreased effective arterial blood volume (eg, from blood loss), or from cardiogenic shock, both of which would be expected to result in ischemic acute tubular necrosis (ATN). This form of ATN should not be confused with CI-AKI, but is often conflated with it, even in a commonly used risk score, which includes variables such as cardiogenic shock and intra-aortic balloon pump use, which would predispose to ATN, not CI-AKI.[97]

Conclusion

AKI can occur in heart disease by many different mechanisms. Our understanding of the classical CRS is still mostly informed by the neurohormonal consequences of changing hemodynamics, although renal congestion remains an underexplored area. CI-AKI does exist, and the cellular pathways that underpin it are being more clearly elucidated. CS-AKI is a distinct identity with multifactorial mechanisms. Thus, although we have come far from the days of Bright and Starling in terms of our understanding, much remains to be fathomed, especially in the frontiers of genetics and biomarkers.[1,70]

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