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Review

New drugs for acute kidney injury

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ABSTRACT

Acute kidney injury (AKI) presents a significant challenge in the management of critically ill patients, as it is associated with increased mortality, prolonged hospital stays, and increased healthcare costs. In certain conditions, such as during sepsis or after cardiac surgery, AKI is one of the most frequent complications, affecting 30%–50% of patients. Over time, even after the resolution of AKI, it can evolve into chronic kidney disease, a leading global cause of mortality, and cardiovascular complications. Despite significant improvement in the care of critically ill patients over the past two decades, the incidence of AKI remains stable, and novel approaches aiming at reducing its occurrence or improving AKI outcomes are still mostly lacking. However, recent insights into the pathophysiology of AKI within critical care settings have shed light on new pathways for both prevention and treatment, providing various new therapeutic targets aimed to mitigating kidney injury. These advancements highlight the intricate and multifaceted nature of the mechanisms underlying AKI, which could explain the challenge of identifying an effective treatment. Among these targets, modulation of the inflammatory responses and the cellular metabolism, hemodynamic regulation and enhancement of cellular repair mechanisms, have emerged as promising options. These multifaceted approaches offer renewed hope for limiting the incidence and severity of AKI in critically ill patients. Several ongoing clinical trials are evaluating the efficacy of these different strategies and we are facing an exiting time with multiple therapeutic interventions being tested to prevent or treat AKI. In this review, we aim to provide a summary of the new drugs evaluated for preventing or treating AKI in critical care and surgical settings.

Introduction

Acute Kidney Injury (AKI) is a global health concern, affecting over 13 million individuals annually and contributing to approximately 1.7 million deaths worldwide.[1] From a pathophysiological aspect, AKI is characterized by a rapid decline in glomerular filtration rate (GFR), manifesting within hours or days and evidenced by an abrupt increase in serum creatinine levels. Prior to 2004, the lack of a consensual definition for AKI resulted in a broad spectrum of interpretations, spanning from slight creatinine elevation to the requirement for renal replacement therapy (RRT).[2] However, the establishment of classification systems like RIFLE (Risk, Injury, Failure, Loss, and End-stage renal failure), AKIN (Acute Kidney Injury Network), and KDIGO (Kidney Disease: Improving Global Outcomes) has provided a structured approach based on serum creatinine levels and urine output changes, enabling timely recognition and intervention.[3–5] In critical care settings, the incidence of AKI remains heterogeneous with a range from 15% to 60% depending on its definition and the patient's condition.[6] This is a major issue regarding the association between AKI severity and adverse clinical outcomes, including increased mortality rates, prolonged hospital stays, and the risk of the evolution into chronic kidney disease (CKD).[7,8] AKI's heterogeneity extends beyond its definition, encompassing diverse etiologies such as cardiac surgery-associated acute kidney injury (CSA-AKI), sepsis-associated acute kidney injury (SA-AKI) or drug toxicity.[9–11] This complexity poses challenges in identifying suitable drug targets and designing effective therapeutic interventions. Despite notable advancements in the management of crit-

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ically ill patients in the last two decades, randomized controlled trials (RCTs) evaluating therapies for the prevention or the treatment of AKI in critical care settings failed to identify an effective therapeutic intervention. However, recent advancements in understanding AKI pathophysiology have elucidated shared mechanisms underlying its development in critically ill patients, including inflammatory responses, metabolic dysfunction, and impaired cellular repair. These advancements have paved the way for new drugs targeting different mechanisms involved in kidney injury. Overall, new fields of interventions are emerging to offer the most suitable therapy possible to critically ill patients, taking into account the timing of renal injury and the patient's condition. In our review, we aim to provide a comprehensive overview of these new drugs and their primary mechanisms of action (Figure 1/ Table 1).

Inflammation

Inflammatory pathways are activated after different triggers occurring in intensive care unit (ICU), such as sepsis or ischemia/reperfusion injury (IRI). In the early phase of injury, innate response enhances pro-inflammatory cytokine that may trigger organ damage. After this early phase, inflammation may be involved in non-recovery of the AKI, and partial repair leading to fibrosis and CKD.[12,13] Targeting different phases of inflammatory response may prevent or limit the kidney.

Alkaline phosphatase (ALP)

After activation of inflammatory pathways, damage-associated molecular patterns are recognized by Toll-like receptors (TLRs), initiating the inflammatory response by recruiting pro-inflammatory mediators (e.g., Tumor necrosis factor-α (TNF-α), interleukins (IL-6 or IL-18)). This innate response led to the recruitment of neutrophils and macrophages, leading to production of pro-inflammatory cytotoxic mediators which amplify cell damage.[14] ALP are ubiquitous hydrolases in humans, playing a role in the dephosphorylation of different endotoxins, notably lipopolysaccharide (LPS).[15] Dephosphorylated LPS acts as a TLR-4 antagonist and therefore could reduce the innate immune response after bacterial activation.[16] Another mechanism of ALP is the dephosphorylation of extracellular adenosine triphosphate (ATP) and adenosine diphosphate (ADP), inhibiting their pro-inflammatory effect.[17] A phase 2 trial, the STOP-AKI trial, has been conducted in 301 patients with SA-AKI, comparing recombinant ALP (ilofotase alfa) and placebo.[18] In this trial, ilofotase alfa failed to demonstrate an improvement on 7-days renal function, the primary outcome. However, the extended analysis up to day 28 showed an improvement of creatinine clearance of 18.5 mL/min (95% confidence interval [CI]: 5.3 to 31.7, P=0.006) and a reduction of mortality in patients treated with ilofotase alfa (14.4% *vs.* 26.7%, P=0.02). Based on this promising result, a phase 3 trial was conducted to compare the effectiveness of ilofotase

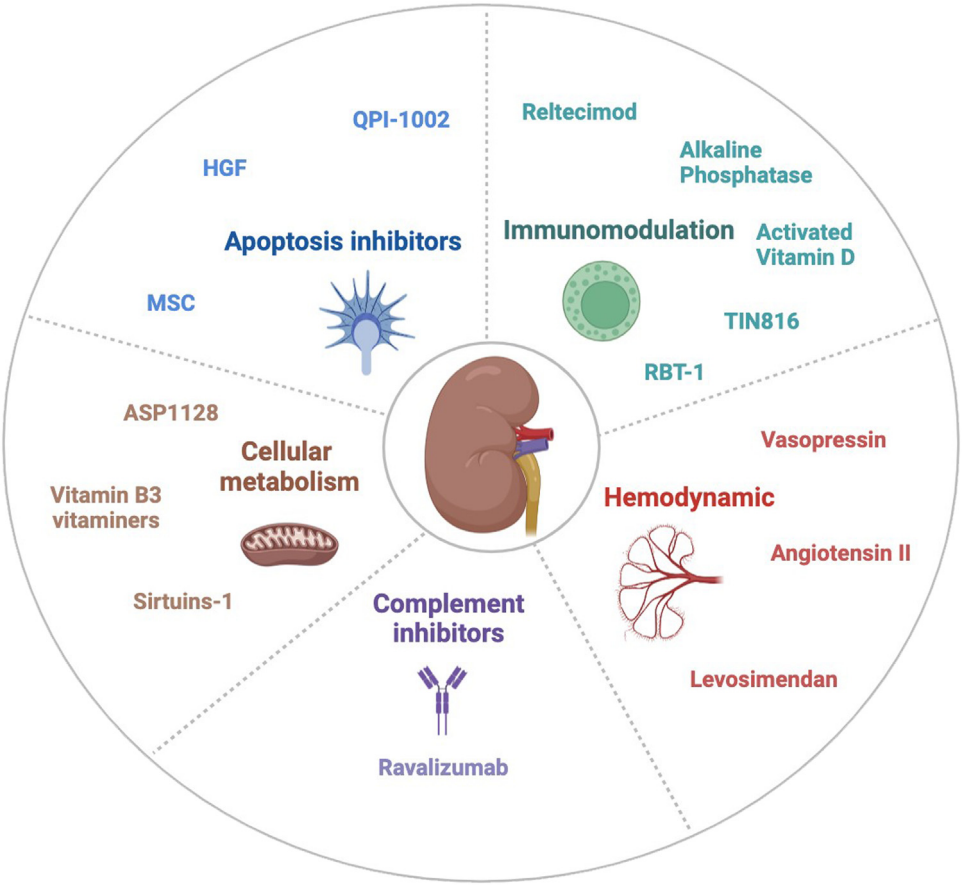

Figure 1. Mechanisms of new drugs assessed in prevention or treatment of acute kidney injury in critical care.
HGF: Hepatocyte growth factor; MSC: Mesenchymal Stem Cells.

Table 1
New drugs assessed for prevention or treatment of AKI in critical care.

Drug	Mechanism	Target	Ongoing RCT	Population
Angiotensin II	Hemodynamic	Renal efferent arteriole	NCT05199493	Prevention of CSA-AKI
			NCT04592744	Prevention of AKI after liver transplantation
			NCT04901169	Prevention of AKI after liver transplantation
Vasopressin			NCT04602767	Prevention of CSA-AKI
			NCT06125184	Prevention of SA-AKI (septic shock)
Levosimendan		Renal afferent arteriole	NCT02531724	CSA-AKI
			NCT01720030	AKI
Reltecimod	Immunomodulation	CD28	NCT03403751	SA-AKI
Activated vitamin D		NF-kb	NCT02962102	Prevention of AKI in high-risk patients
ALP		TLR-4	NCT06168799	Prevention of CSA-AKI
RBT-1		IRI	PROTECT study	Prevention of CSA-AKI
TIN816		ATP/ADP	NCT05996835	SA-AKI
			NCT05524051	Prevention of CSA-AKI
Vitamin B3 vitamers	Cellular metabolism	NAD^+	NCT04750616	Prevention of CSA-AKI
			NCT05513807	Delayed renal graft function
			NCT04589546	Prevention of SA-AKI (septic shock)
			NCT04818216	AKI and COVID-19
ASP1128		PPARδ		
SIRT1			NCT04342975	Prevention of AKI after Aortic arch replacement
Ravulizumab	Complement inhibitors	C5	NCT05746559	Prevention of CSA-AKI
siRNA (QPI-1002)	Apoptosis inhibitors/Cellular repair	P53	NCT02610296	Delayed renal graft function
HGF		Bcl-2	NCT02771509	Prevention of CSA-AKI
MSC			NCT04445220	RRT and COVID-19
			NCT04194671	AKI

ADP: Adenosine di-phosphate; ALP: Alkaline phosphatase; AKI: Acute kidney injury; ATP: Adenosine triphosphate; C5: Complement 5; CSA-AKI: Cardiac surgery-associated acute kidney injury; HGF: Hepatocyte growth factor; IRI: Ischemia-reperfusion injury; MSC: Mesenchymal stem cells; NAD^+: Nicotinamide Adenine Dinucleotide; NF-κb: Nuclear factor kappa b; PPARδ: Peroxisome proliferator-activated receptor delta; RCT: Randomized controlled trial; RRT: Renal Replacement therapy; SA-AKI: Sepsis-associated acute kidney injury; siRNA: Small interfering RNA; SIRT1: Sirtuins; TLR-4: Toll-like receptor 4.

alfa *vs.* placebo in patients with SA-AKI with 28 days and all-cause mortality as primary outcome. After enrolling 655 patients, the REVIVAL trial was stopped for futility on this primary outcome.[19] All-cause mortality was not different in both groups at day 28 (27.9% *vs.* 27.9%, P=0.50) or at day 90 (33.9% *vs.* 34.8%, P=0.47). However, the trial suggests a potential benefit of ilofotase alfa in the reduction of Major adverse kidney events (MAKE) at day 90 (MAKE90) (56.7% *vs.* 64.6%, P=0.02). Notably, this benefit primarily stems from a decrease in the requirement for RRT among patients treated with ilofotase alfa (28.2% *vs.* 36.4%). Remarkably, this effect was even more pronounced among patients with pre-existing altered renal function, implying that enriching the population could hold significant promise. An ongoing phase 2 trial aims to assess the preventive effect of ilofotase alfa on CSA-AKI in 150 patients undergoing prolonged cardiopulmonary bypass (CPB) with a preoperative estimated GFR between 25 mL/(min·m^2) and 65 mL/(min·m^2) (NCT06168799).

Reltecimod

Following the initial immune response, a later injury phase is characterized by the recruitment of natural killer T cells and macrophages. During this adaptative immune response, CD4+ and CD8+ T cells play a role in injury.[12] Reltecimod, a peptide developed by Atox Bio, specifically binds to the co-simulator CD28 on T-cell surface to modulate the inflammatory response during sepsis in animal models.[20–22] In patients with necrotizing soft tissue infections (NSTI), early Reltecimod injection was associated with an improvement of Sequential Organ Failure Assessment (SOFA) score at day 14 in a phase 2 trial compared to placebo, without related adverse events.[23] In a phase 3 trial involving 290 patients, Reltecimod injected within 6 h after the diagnosis of NSTI was compared to placebo. The primary endpoint was a composite outcome evaluating the efficacy of NSTI treatment, including vital status at day 28, extent of debridement at day 14, absence of post-initial operation amputation, and resolution of organ dysfunction as assessed by the SOFA score. While this trial failed to find a benefit in NSTI success of treatment with Reltecimod for the primary endpoint (48.6% *vs.* 39.9%, P=0.14), it shows an improvement in organ dysfunction with a reduction of SOFA score at day 14 (65.1% *vs.* 52.6%, P=0.04).[24]

A phase 3 trial is recruiting patients with confirmed AKI stage 2 or 3 according to the KDIGO criteria (NCT03403751) with confirmed or suspected abdominal sepsis. The primary endpoint is the recovery of AKI at day 28, defined as being alive, free of dialysis, and with less than 37% loss of estimated glomerular filtration rate (eGFR) from baseline.

Activated vitamin D

The role of Vitamin D in kidney function has long been debated, potentially extending beyond its involvement in calcium homeostasis and bone metabolism. Studies suggest that Vitamin D may mitigate inflammatory and profibrotic pathways relevant to kidney disease through various mechanisms.[25–27] In a mice model of sepsis-induced AKI, activated vitamin D may downregulate the expression of nuclear factor-kappa b (NF-κb) in renal tubules, modulating inflammatory responses.[28] Vitamin D insufficiency has widely been identified in patients with CKD, and its supplementation is still debated in this context.[29] While vi-

tamin D can be administrated in different forms, its active form Calcitriol (1,25(OH)2D) or its percussor Calcifediol (25(OH)D), a meta-analysis of four prospective studies found that levels of Calcitriol rather than Calcifediol were significantly lower in patients developing AKI.[30] The formation of calcitriol from calcifediol occurs in the proximal renal tubules, which could explain the decrease in calcitriol levels during AKI. Moreover, patients with AKI have elevated blood levels of fibroblast growth factor 23 (FGF23), an osteocyte-derived hormone that inhibits vitamin D synthesis.[31] Focusing on critically ill patient, an observational study will assess the levels of calcifediol, calcitriol, parathyroid hormone, and FGF23 in patients with and without AKI (NCT02869919). In critically ill patients with high risk of AKI, the phase 2 trial, ACTIVATE-AKI (NCT02962102), has enrolled 150 patients to assess the preventive effect of calcitriol and calcifediol compared to placebo. The first analysis of the primary outcome, death within 7 days, did not show significant differences among the three groups, nor did the need for RRT or changes in serum creatinine levels within the first 7 days.

RBT-1

RBT-1, developed by Renibus therapeutic, is a combination drug composed of stannic protoporfin (SnPP) and iron sucrose (FeS) and may protect from IRI during AKI. Ischemia is characterized by a cessation of nutrient and oxygen supply, leading to a halt in ATP production through oxidative phosphorylation, resulting in cytoplasmic accumulation of hydrogen ions and intracellular acidosis.[32] Adaptive mechanisms lead to an increase in intracellular calcium concentration that participates in the production of inflammatory cytokines and the activation of intracellular proteases. These combined factors lead to the initiation of apoptosis.[33] Quickly, adaptive antioxidative mechanisms are surpassed, and free radical production causes cellular damage. Increased permeability of the mitochondrial membrane results in the release of cytochrome C into the cytoplasm, leading to apoptosis of damaged cells.[34] Ischemia-reperfusion thus induces an inflammatory response, oxidative stress, and protease activation promoting apoptosis participating to AKI.[35] RBT-1 demonstrates a pharmacological preconditioning effect in a phase 2 trial involving 135 patients undergoing cardiac surgery with CPB. This effect manifests as a reduction in IRI biomarkers, achieved through the upregulation of anti-inflammatory, antioxidant, and iron scavenging pathways, including IL-10, Heme-oxygenase 1, and ferritin. However, RBT-1 administration did not lead to a significant reduction in CSA-AKI incidence (9% *vs.* 14%, risk difference=−4.9, 95% CI: −19.5 to 9.1).[36] The PROTECT study is an ongoing phase 3 trial aiming to assess the preventive effect of RBT-1 in 400 patients undergoing cardiac surgery. The primary endpoint is a composite with death, AKI requiring dialysis, ICU length of stay, and 30-day cardiopulmonary readmission rates.[37]

TIN816

Hypoxic conditions during kidney injury result in the release of extracellular ATP. In the extracellular space, ATP acts as a pro-inflammatory factor by recruiting leukocytes and promoting the secretion of pro-inflammatory cytokines such as IL-1β and IL-18 to the site of injury. Furthermore, the dephosphorylation of ATP leads to the production of ADP, which in turn triggers platelet activation and thrombosis, contributing to organ injury[38,39] ATP and ADP are enzymatically phosphohydrolyzed by ectonucleoside-triphosphate-diphosphohydrolase-1 (also known as ectopyrase, CD39), yielding adenosine monophosphate (AMP). AMP is then converted to adenosine by the surface enzyme ecto-5′-nucleotidase (CD73).[40]

TIN816 is an engineered, highly active, soluble, and stabilized recombinant CD39 developed by NOVARTIS that depletes extracellular ATP and ADP into AMP. Recombinant CD39 appears to reduce inflammation, thrombosis, and promotes tissue repair in preclinical studies.[41,42] In human whole blood TIN816 dose dependently inhibited ATP/LPS-induced IL-1β secretion as well as ADP-induced platelet aggregation.

Three ongoing trials are now recruiting patients to assess and investigate the effect of TIN816. A pharmacological trial assesses pharmacokinetic and pharmacodynamic profile of 20 patients with SA-AKI after TIN816 administration (NCT05507437), results are not available yet. The efficacy and safety of TIN816 for the treatment of SA-AKI will be evaluated in a trial of 320 patients. Participants will receive different doses of TIN816 or placebo. The primary endpoint of the trial will be the average of the area under the time-corrected creatinine clearance curve from day 1 to day 8 (NCT05996835). In the setting of cardiac surgery, a trial is currently recruiting patients to assess the potential effect of TIN816 administration during CPB on prevention of CSA-AKI (NCT05524051). The study aims to enroll 120 patients.

Hemodynamic

A decrease in renal perfusion and low blood pressure can impair renal perfusion and contribute to the development of AKI.

Angiotensin II

Angiotensin II plays a pivotal role as a hormone in the renin-angiotensin-aldosterone system (RAAS). Conditions such as reduced renal perfusion or low arterial blood pressure can trigger the activation of RAAS, resulting in the release of angiotensin II and subsequent vasoconstriction. Notably, angiotensin II exerts a selective vasoconstrictive effect on the renal efferent arteriole, thereby enhancing the GFR. Interestingly, several lines of evidence suggest decreased levels of angiotensin II in critical conditions such as CPB or septic shock.[43,44] These low angiotensin II levels could contribute to the development of AKI. Understanding the intricate dynamics of angiotensin II in the RAAS provides valuable insights into the pathophysiology of conditions impacting renal function. During vasoplegic shock, a pilot study involving 20 patients found that angiotensin II was associated with a reduction of catecholamine doses and higher urine output within 8 h after treatment initiation.[45] The ATHOS-3 trial aimed at evaluating the efficacy of angiotensin II in refractory vasodilatory shock.[46] The primary outcome of the ATHOS-3 trial was a response with respect to mean arterial pressure (MAP) at hour 3 after the start of infusion (69.9% in the angiotensin II *vs.* 23.4% in the placebo group, odds ratio (OR)=7.95, 95% CI: 4.76 to 13.3, P <0.001). Death by day 28 occurred in 75 of 163 patients (46%) in the angiotensin II group and in 85 of 158 patients (54%) in the placebo group. In a *post*

hoc analysis of the ATHOS-3 trial in patients requiring RRT, angiotensin II was associated with increased 28-day survival (53% *vs.* 30%, *P*=0.0012) and a higher rate of RRT discontinuation at day 7 (38% *vs.* 15%, *P*=0.0068).[47] The potential beneficial effect of angiotensin II on blood pressure during liver transplantation is currently under investigation in two different trials aiming to recruit, respectively, 30 (NCT04592744) and 50 patients (NCT04901169).[48] In the context of cardiac surgery, a feasibility study compares the use of angiotensin II to norepinephrine to maintain a MAP over 70 mmHg intra-operatively and up to 48 h post-operatively in 61 patients. In this trial, patients treated with angiotensin II had a lower incidence of CSA-AKI, although this difference did not achieve statistical significance (25% *vs.* 38%; *P*=0.31).[49] This potential preventive impact of angiotensin II on CSA-AKI will be explored in an upcoming trial focusing on patients requiring vasopressors after cardiac surgery with elevation of renin level postoperatively (NCT05199493), a biomarker suggestive of angiotensin II deficit.

Vasopressin

Vasopressin exhibits vasoconstrictor effects by modulating the function of ATP-sensitive potassium channels, nitric oxide production, and enhancing vascular response to catecholamines.[50] Unlike norepinephrine, vasopressin acts on the renal efferent arterioles and has potential nephroprotective effects. In ovine model of septic-induced AKI, vasopressin restored MAP but also maintained renal perfusion, leading to sustained improvement in renal function when compared to norepinephrine.[51] A single double-blind RCT involving 330 patients in vasoplegic shock after cardiac surgery demonstrated a reduction of CSA-AKI with vasopressin compared to norepinephrine (10.3% *vs.* 35.8%; *P* <0.0001).[52] However, in the context of septic shock, a large multicenter RCT including 409 patients, vasopressin infusion did not reduce the incidence of AKI compared to norepinephrine.[53] Moreover, a RCT focusing on 250 patients with septic shock and cancer also reported an absence of a significant reduction in AKI when vasopressin was employed compared to norepinephrine (42.4% *vs.* 41.6%; *P*=0.98).[54] In 2019, an individual patient data meta-analysis including 1453 patients of four RCT comparing vasopressin to norepinephrine in septic shock found a potential reduction of the need for RRT with vasopressin (risk ratio=0.86, 95% CI: 0.74 to 0.99). These divergent results underscore the nuanced and context-dependent effects of vasopressin, prompting a careful consideration of its application in distinct clinical scenarios. In cardiac surgery, an ongoing RCT aims at comparing vasopressin to phenylephrine as first line vasopressor intra-operatively, with CSA-AKI as a primary outcome (NCT04602767). In patients with a history of arterial hypertension and septic shock, a trial will compare the adjunction of vasopressin to norepinephrine *vs.* norepinephrine alone on renal outcome (NCT06125184).

Levosimendan

Levosimendan, an inotropic agent, acts by sensitizing troponin C to the action of calcium, thereby improving cardiac contractility. In addition, the vasodilatory effect of levosimendan, in particular in afferent renal arteriole, may participate to the theoretical benefits of AKI.[55] In cardiac surgery, a meta-analysis involving 13 small RCTs shows a reduction in the incidence of CSA-AKI (OR=0.51, 95% CI: 0.34 to 0.76) and RRT (OR=0.43, 95% CI: 0.25 to 0.76) when Levosimendan was used perioperatively.[56] Contrastingly, the administration of Levosimendan within the 48 h post-surgery did not reduce the incidence of CSA-AKI (34% *vs.* 40%; *P*=0.14) or RRT requirement (9.7% *vs.* 12.8%, *P*=0.27) in a larger RCT.[57] During sepsis, Levosimendan also failed to show a potential benefit in the prevention of AKI in a RCT involving 516 patients (45.7% *vs.* 42%, *P*=0.45).[58] As the preventive effects of Levosimendan on AKI remain unproven, there is growing interest in exploring potential therapeutic applications of Levosimendan in the context of established AKI. An ongoing RCT, LEVO-AKI (NCT02531724), is assessing the potential of Levosimendan in the treatment of CSA-AKI, while another trial focuses on all patients with AKI (NCT01720030) (LAKIS trial results have not been published).

Cellular Metabolism

Metabolism impairment in AKI has been increasingly highlighted in recent years. The kidney, being an organ with a high metabolic demand, relies on ATP for active transport and solute reabsorption. Any disruptions in energy availability and utilization can result in cellular dysfunction. Emerging evidence indicates that pathways involving energy metabolism and mitochondrial dysfunction are pivotal contributors to AKI, presenting novel potential targets for therapeutic interventions.

Vitamin B3 vitamers: niacine, nicotinamide, or nicotinamide riboside (NR)

Mitochondrial respiration and function are compromised in AKI, leading to a disruption in the *de novo* biosynthesis of Nicotinamide Adenine Dinucleotide (NAD^+), a factor contributing to the development of AKI. Vitamin B3 includes three forms: Niacin, Nicotinamide (Nam), or NR, which plays a crucial role in NAD^+ production. Poyan Mehr et al.[59] demonstrated that NAD+ protects against AKI, highlighting the significance of its biosynthesis and its impairment as a contributing factor in the pathogenesis of AKI. In a phase 1 pilot study involving 41 patients in cardiac surgery, they found that administration of Nam perioperatively was associated with a 35% decrease in AKI incidence compared to placebo. Building on this finding, a phase 2 trial in cardiac surgery is underway to assess the preventive effect of 3 g of Nam administered on the day of surgery and for 2 days post-surgery compared to placebo in patients at high-risk for CSA-AKI. The study aims to enroll over 300 patients (NCT04750616). In the context of renal transplantation, a phase 3 trial will evaluate the effect of perioperative Nam administration on early graft function (NCT05513807). Additionally, in patients with septic shock, a multicenter RCT is underway to evaluate the preventive effect of 3 days of 1 g Nicotinamide (Nam) on AKI compared to placebo (NCT04589546). Meanwhile, NR, another form of vitamin B3, is being evaluated in the treatment of AKI among 28 patients with coronavirus disease 2019 (COVID-19) in an ongoing RCT (NCT04818216).

ASP1128

Peroxisome proliferator-activated receptor-gamma (PPARγ) is a nuclear hormone receptor that is consistently expressed

across the kidney. Various lines of evidence indicate that the activation of PPARγ can provide kidney protection against IRI, primarily through its anti-inflammatory, antioxidant, and anti-apoptotic effects.[60] ASP118, a selective modulator of peroxisome proliferator-activated receptor-delta (PPARδ), has demonstrated the upregulation of PPARδ/fatty acid oxidation target genes persisting for at least 24 h after administration.[61] This sustained effect holds the potential for providing a renoprotective impact on IRI. However, when evaluated in cardiac surgery patients at high risk of AKI, as defined by one AKI risk factor and elevated postoperative urinary biomarker (TIMP2) × (IGFBP7) levels, the trial involving ASP1128 was stopped for futility after enrolling 151 patients. The primary endpoint, the incidence of CSA-AKI at 72 h, did not differ between the treatment and control groups (24.6% *vs.* 21%, *P*=0.595). Furthermore, ASP1128 did not show associations with a reduction in AKI severity, a decrease in the need for RRT, or a reduction in Major Adverse Kidney Events at days 30 and 90.[62]

Sirtuins (SIRT1)

Sirtuins, comprising seven members (SIRT1–7), are NAD^+ - dependent histone deacetylases. The most studied Sirtuin in AKI is SIRT1. Highly expressed in the kidney, especially in the renal medulla, SIRT1 deficiency amplifies susceptibility to AKI in mice.[63] SIRT1 exhibits a multifaceted potential to prevent AKI. Firstly, it can activate PPARγ, promoting mitochondrial biogenesis and thereby mitigating AKI. Additionally, SIRT1 employs other mechanisms for AKI protection, including the regulation of apoptosis through the deacetylation of p53, contributing to renal cell preservation. Furthermore, SIRT1 acts as an anti-oxidative agent in tubular cells, supporting its protective effects against AKI. These intricate pathways highlight the diverse and comprehensive role of SIRT1 in renal protection.[63–65] In a safety clinical trial involving 24 patients, NRPT, a combination of NR and pterostilbene (PT) acting in synergy on NAD^+ and SIRT-1 activation was tested in patients with AKI. In this study, 20 patients received NRPT, while 4 patients were administered a placebo. Despite no significant difference in GFR observed between the two groups, patients treated with NRPT exhibited lower Blood Urea Nitrogen (BUN) levels 48 h after treatment.[66] In light of these promising results, a Phase 2 trial is currently underway to investigate the potential impact of NRPT supplementation. The trial involves administering NRPT 2 weeks before aortic arch replacement surgery and continuing for 6 weeks afterward, with the aim of preventing AKI (NCT04342975).

Complement Inhibitors

Kidney hypoxia and IRI initiate complement activation on the surface of proximal tubular cells by triggering the lectin pathway. Complement activation leads to the release of anaphylatoxins (C3a and C5a) contributing to interstitial fibrosis. Moreover, complement activation plays a significant role in tubular damage induced by myoglobinuria and hemoglobinuria, as heme can directly activate complement.[67]

Ravulizumab

Ravulizumab inhibits the cleavage of C5 into C5a and C5b on the endothelial cell surface, effectively preventing endothelial dysfunction resulting from complement activation.[68] This long-acting inhibitor of complement C5 is currently approved for treating atypical hemolytic uremic syndrome (aHUS) or paroxysmal nocturnal hemoglobinuria, effectively inhibiting complement-mediated thrombotic microangiopathy. During AKI, the efficacy of Ravulizumab was investigated in a pilot RCT involving 13 patients with COVID-19. Patients who were treated with Ravulizumab had lower dialysis needs 10 days after enrollment (*P*=0.03) and an upward trend in GFR over 30 days compared to the placebo (*P*=0.009). However, those findings need to be balanced with the very small sample size and high risk of type 1 error and the observation of a higher need for hemodialysis by day 30 in patients who received Ravulizumab (18% *vs.* 9%, *P*=0.18).[69] A Phase 3 multicenter RCT, the ARTEMIS trial aims to recruit 736 patients with CKD undergoing cardiac surgery, evaluating the potential benefits of Ravulizumab in preventing CSA-AKI (NCT05746559).

Apoptosis Inhibitors/Cellular Repair

The nature of apoptosis involvement in AKI remains uncertain. However, histological evidence confirms the presence of apoptosis in tubular cells during AKI.[70] Additionally, animal models of induced AKI have shown that inhibition of apoptosis prevents AKI.[71] At the late stage of AKI, cellular repair mechanisms are engaged, however, their impairment can prolong AKI and contribute to partial recovery, potentially leading to CKD.

Small interfering RNA (siRNA) (QPI-1002)

QPI-1002, a synthetic siRNA developed by Quark Pharmaceuticals, serves to transiently inhibit P53, a tumor suppressor protein. The role of P53 is multiple in the process and repair of AKI. Following IRI, P53 is secreted and activated. During the early stages of AKI, P53 may exert a protective effect by inducing renal tubular cell arrest and reducing cell proliferation. However, in cases of prolonged or severe AKI, P53 can trigger tubular cell death, exacerbating AKI, and promote autophagy, thus impeding renal repair following the initial injury.[72] In mice, p53 knockout specifically from proximal tubules demonstrated protection against AKI induced by ischemia and cisplatin.[73] QPI-1002 was evaluated in different contexts. After renal transplantation, QPI-1002 was assessed for its ability to prevent delayed graft dysfunction in 327 patients. Although not statistically significant, there was a relative reduction of 30% in delayed graft function observed among patients who received QPI-1002 (27.3% *vs.* 39.3%), and a significant improvement in GFR at day 30 (34.8 mL/(min·1.73 m^2) *vs.* 21.1 mL/(min·1.73 m^2), *P*=0.035).[74] An ongoing trial to confirm this potential benefit on delayed graft dysfunction after renal transplantation is completed with almost 600 patients (NCT02610296), results are pending. After cardiac surgery, QPI-1002 was assessed for high-risk patients for AKI. QPI-1002 was administered intraoperatively, and the primary endpoint was the incidence of AKI based on creatinine levels measured 5 days postoperatively. A total of 360 patients were enrolled, and the incidence of AKI was reduced by 13% with QPI-1002 (37% *vs.* 50%, *P*=0.02). Additionally, AKI severity and duration were also decreased in patients treated with QPI-1002. However, at 90 days, there was no significant difference in the incidence of Major Adverse Kidney

Events between the two groups (19.3% *vs.* 20.9%, P=0.71).[75] Focusing on MAKE90 as the primary endpoint, a phase 3 clinical trial evaluating QPI-1002 for the prevention of CSA-AKI enrolling over 1000 patients with high-risk for AKI, was stopped for futility (NCT03510897).

Hepatocyte growth factor (HGF)

HGF is a pleiotropic protein that participates in injury repair through the regulation of cell proliferation, survival, and regeneration across various organs, and specifically in the kidney.[76] AKI triggers the upregulation of cMet expression, the receptor of HGF, leading to the formation of the HGF-cMet complex, which suppresses apoptosis by activation of Bcl-2, a critical survival protein.[77] BB3, a small molecule synthesized by Angion Biomedica Corporation (New York, USA) through the reductive distillation of HGF-like peptides, mimics the biological activity of HGF. A preclinical study demonstrated that administration of BB3 24h after IRI in rats improves survival, mitigates tubular injury, BUN and serum creatinine levels, and enhances renal output.[78] In a phase 2 study involving 28 patients with low urine output in the 8 h after renal transplant, recovery of urine output was more frequent and faster after administration of BB3 (84% *vs.* 50%, log-rank test: χ^2=2.799, P=0.09).[79] Interestingly, the authors observe a persistent improvement over time in eGFR in patients who received BB3, from day 14 to 12 months after renal transplantation. These promising results were explored in a phase 3 multicenter RCT assessing the impact of BB3 with eGFR at day 360 after renal transplantation as the primary endpoint. A total of 248 patients were analyzed, 124 in each group, without any difference on the primary endpoint (eGFR [53.2±2.69] mL/(min·1.73 m^2) *vs.* [50.2±2.70] mL/(min·1.73 m^2), P=0.32). Duration and number of dialysis, delayed graft function, and acute rejection were similar in both groups. Those results do not supporting the interest of BB3 after renal transplantation.[80] In another context, Angion Biomedica Corporation is conducting a multicenter, randomized, controlled phase 2 trial, Guard Against Renal Damage (GUARD), assessing the safety and efficacy of BB3 for prevention of CSA-AKI in high-risk AKI patients undergoing cardiac surgery with CPB (NCT02771509).[81] The primary endpoint will be the mean area under the curve (AUC) of the percent increase in serum creatinine above baseline from H24 to day 6 after surgery, they already enrolled 275 patients.

MSC

Mesenchymal Stem Cells (MSC) offer various potential therapeutic benefits in the pathophysiology of AKI, contributing to both the initial injury and the subsequent renal repair processes. These benefits include immunomodulation, inhibition of apoptosis, fibrosis, and oxidative stress. Animal studies have demonstrated that MSCs may mitigate AKI by downregulating factors such as the complement pathway and TNF-α, transforming growth factor beta, while also upregulating others like Bcl-2 and vascular endothelial growth factor, thereby enhancing tubular repair following AKI.[82] A Bone Marrow-MSC (BM-MSC), AC607 (Allocure Inc. Burlington, USA), has been assessed in a phase 2 RCT in patients who developed CSA-AKI within 48 h after the intervention. The primary endpoint was the time to recovery of renal function defined as the return of postintervention creatinine level to baseline. After the enrollment of 156 patients, the trial failed to find a benefit of AC607 and was stopped for futility.[83] An exploratory trial involving 24 patients with AKI requiring dialysis assessed the effect of *ex vivo* administration on another BM-MSC (SB-101). While the sample size was too small to exhibit clinical differences between groups, they found that patients treated with *ex vivo* BM-MSC had immunotherapeutic response triggering accelerated tissue repair and therefore may have clinical effect.[84] This *ex vivo* therapy will be evaluated in patients with SARS-CoV-2 infection requiring RRT (NCT04445220). Another trial will assess the effect of Umbilical cord MSC for the treatment of AKI, aiming to include 100 patients (NCT04194671).

Conclusions

AKI has currently no preventive or therapeutic therapy proving effective with a high level of evidence. However, advancements in understanding the pathophysiology of AKI allow the development of new strategies targeting various pathways that are under investigation. Drugs in development exhibit a wide-ranging impact on pathophysiological processes, from cell death inhibition to inflammation modulation and hemodynamic management. With several drugs now in phase 3 trials, the future appears bright for AKI prevention and treatment in critically ill and surgical patients.

CRediT Authorship Contribution Statement

Geoffroy Hariri: Writing – review & editing, Writing – original draft, Conceptualization. **Matthieu Legrand:** Writing – review & editing, Conceptualization.

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Ethics Statement

Not applicable.

Conflict of Interest

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Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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