Kidney Diseases

Review Article

Kidney Dis
DOI: 10.1159/000533970

Received: January 4, 2023
Accepted: August 23, 2023
Published online: October 18, 2023

The Treatment of Coronary Artery Disease in Patients with Chronic Kidney Disease: Gaps, Challenges, and Solutions

Ilya Losin[a] Keren-Cohen Hagai[b, c] David Pereg[a, c]

[a]Cardiology Department, Meir Medical Center, Kfar Saba, Israel; [b]Department of Nephrology and Hypertension, Meir Medical Center, Kfar Saba, Israel; [c]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Keywords
Chronic kidney disease · Coronary artery disease · Contrast-induced nephropathy · Coronary intervention

Abstract
Background: Chronic kidney disease (CKD) is associated with a high burden of coronary artery disease (CAD), which remains the leading cause of death in CKD patients. Despite the high cardiovascular risk, ACS patients with renal dysfunction are less commonly treated with guideline-based medical therapy and are less frequently referred for coronary revascularization. ***Summary:*** The management of CAD is more challenging in patients with CKD than in the general population due to concerns regarding side effects and renal toxicity, as well as uncertainty regarding clinical benefit of guideline-based medical therapy and interventions. Patients with advanced CKD and especially those receiving dialysis have not traditionally been represented in randomized trials evaluating either medical or revascularization therapies. Thus, only scant data from small prospective studies or retrospective analyses are available. Recently published studies suggest that there are significant opportunities to substantially improve both cardiovascular and renal outcomes of patients with CAD and CKD, including new medications and interventions. Thus, the objective of this review is to summarize the current evidence regarding the management of CAD in CKD patients, in particular with respect to improvement of both cardiovascular and renal outcomes. ***Key Messages:*** Adequate medical therapy and coronary interventions using evidence-based strategies can improve both cardiac and renal outcomes in patients with CAD and CKD.

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality among patients with chronic kidney disease (CKD). Even after adjustment for known cardiovascular risk factors, including diabetes and hypertension, mortality risk progressively increases with worsening CKD. As glomerular filtration rate (GFR) declines the probability of developing coronary artery disease (CAD) increases linearly, and patients with GFR <60 mL/min/1.73 m^2 have 2–3-fold increased CV mortality risk, relative to patients without CKD [1]. Management of CAD is complicated in CKD patients due to the likelihood of comorbid conditions and potential for side effects. Despite their high cardiovascular risk, ACS patients with renal dysfunction are less commonly treated with guideline-based medical therapy and are less frequently referred for coronary revascularization. This

karger@karger.com
www.karger.com/kdd

Correspondence to:
David Pereg, davidpe@tauex.tau.ac.il

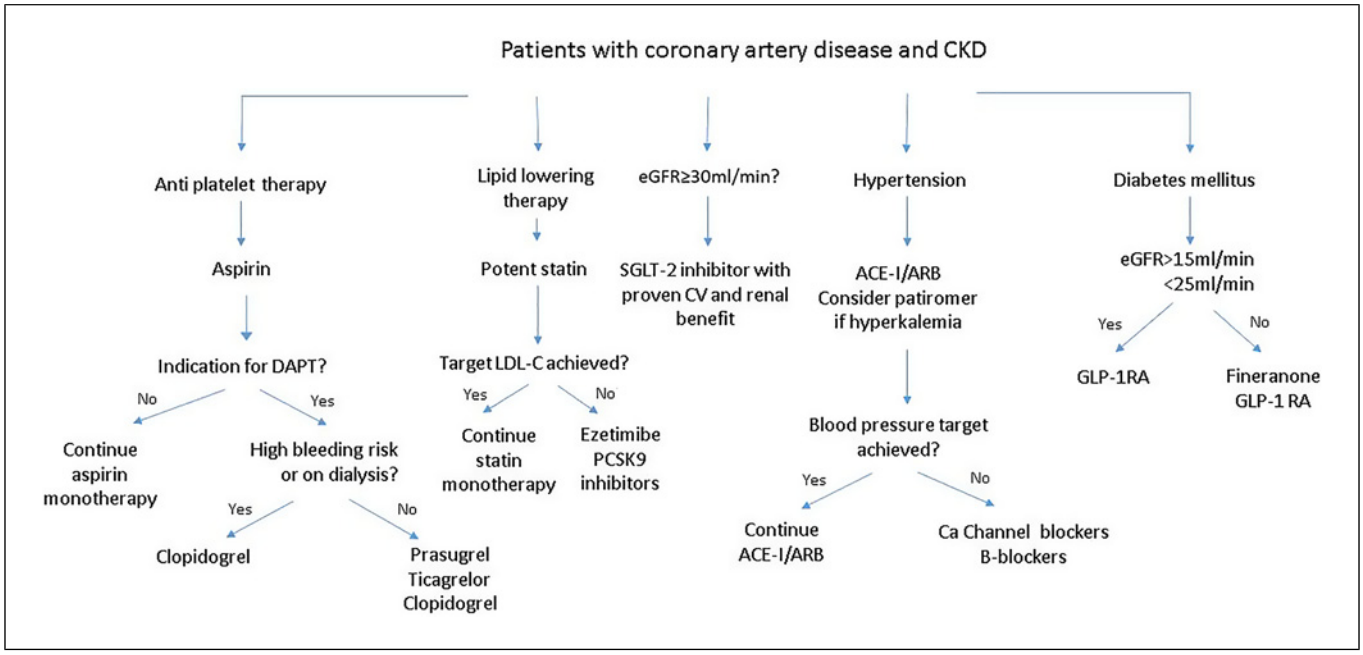

Fig. 1. Algorithm for medical therapy of CKD patients with CAD. CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; SGLT2, sodium glucose co-transporter 2; CV, cardiovascular; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

observation, referred to as the "treatment risk paradox," has been well described and may be explained by physicians' concerns regarding possible nonrenal side effects as well as renal toxicities. Furthermore, patients with severe CKD have traditionally been under-represented in most large cardiovascular clinical trials [2]. Therefore, recommendations for both medical and revascularization of CAD have relied heavily on extrapolation of results from the non-CKD population. This review summarizes the available updated data regarding the treatment of coronary artery in patients with CKD and also identifies knowledge gaps and areas of controversy.

Medical Treatment of Cardiovascular Disorders in Patients with CKD

Medical treatment remains the cornerstone of treatment for patients with CAD and has been associated with improved survival and quality of life. Adequate control of traditional risk factors, including hypertension, dyslipidemia, and diabetes, in patients with CAD and CKD is of particular importance since it not only protects from adverse cardiovascular outcomes but may also delay CKD progression. In this section, we present clinical data and recommendations regarding medical therapy of patients with CAD and CKD, while focusing on new medications. An algorithm for medical therapy of CKD patients with CAD is presented in Figure 1.

Treatment of Cardiovascular Risk Factors

Antihypertensive Medications

Recommended blood pressure targets for patients with CKD vary in the different international clinical guidelines. While the 2018 ESC/ESH guidelines recommended a systolic blood pressure target of 130–139 mm Hg (with a lower target of <130 mm Hg in diabetics), the 2017 ACC/AHA offered a target of <130/80 mm Hg and the more recent 2021 KDIGO guidelines recommended a systolic blood pressure target of <120 mm Hg [3, 4]. For patients with hypertension and CKD, there are randomized controlled trials testing outcomes for renin-angiotensin system inhibitors, calcium channels, and beta blockers [4]. In a large meta-analysis including approximately 65,000 patients with or without diabetes and with or without albuminuria, the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in people with CKD reduced the risk for kidney failure and cardiovascular events

as compared to placebo or other antihypertensive drugs [5]. Among patients with CAD, treatment with ACE inhibitors or ARBs has been associated with improved cardiovascular outcomes, mainly in patients with reduced left ventricular function. Accordingly, ACE inhibitors or ARBs should be considered as first-line drugs for blood pressure control in patients with concomitant CAD and CKD. While advanced renal failure is not a contraindication for ACE inhibitors or ARBs, special attention to prevent hyperkalemia is warranted. Patiromer, a sodium-free potassium-binding polymer, has been demonstrated to be effective in maintaining lower serum potassium levels and allowing optimization of renin-angiotensin system inhibitors dose in patients with heart failure [6]. Recent data support similar effects of patiromer in CKD patients treated with renin-angiotensin system inhibitors for other types of cardiovascular diseases [6].

Lipid-Lowering Therapy

Statin therapy has been associated with improved cardiovascular outcomes in patients with CAD and is therefore recommended to all patients including those with concomitant CKD. Nevertheless, the cardiovascular benefit with statins decreases with the decline of GFR, especially among patients on hemodialysis. The AURORA study was a randomized, double-blind, prospective trial involving 2,776 patients who were undergoing maintenance hemodialysis. Of them, 40% had a history of cardiovascular disease. Patients were randomly assigned to receive rosuvastatin, 10 mg daily, or placebo. Treatment with rosuvastatin lowered the low-density lipoprotein cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke [7]. The SHARP study investigated the cardiovascular effect of ezetimibe therapy in addition to a statin in patients with advanced CKD, including those on dialysis. The addition of ezetimibe to simvastatin reduced the rate of major atherosclerotic events compared with the placebo among a wide range of patients with CKD, including those on dialysis [8]. In recent years, there has been a growing interest in the treatment with PCSK9 inhibitors in addition to statin therapy for further reduction of cardiovascular risk in patients with CAD. A subanalysis of the FOURIER study showed that low-density lipoprotein-lowering therapy with evolocumab was effective and safe across all CKD groups. Interestingly, absolute reduction in the composite of cardiovascular death, MI, or stroke with evolocumab was greater in patients with more advanced CKD [9].

SGLT2 Inhibitors

This new class of drugs was initially developed for glucose lowering in patients with type 2 diabetes. However, the results from randomized controlled trials have demonstrated a significant reduction of different cardiovascular outcomes including cardiovascular mortality, heart failure hospitalizations, and myocardial infarction in different populations of high-risk patients, regardless of the presence of diabetes [10–19]. Furthermore, the SGLT2 inhibitor studies have demonstrated a consistent renoprotective effect regardless of the presence of diabetes, cardiovascular disease, or renal dysfunction at baseline. Among patients with CKD, both empagliflozin and dapagliflozin reduced the risk of the composite outcome of kidney disease progression or cardiovascular death. Accordingly, the 2021 ESC guidelines recommended that an SGLT2 inhibitor with proven outcome benefits should be considered for the prevention of renal deterioration and mortality in patients with CKD, regardless of the presence of diabetes [20]. A summary of renal and cardiovascular outcomes of the different SGLT2 inhibitors randomized control trails is presented in Table 1.

Antiplatelet Therapy

In patients with established cardiovascular disease, antiplatelet therapy significantly reduced the yearly risk of major cardiovascular events. The different pathophysiology of cardiovascular disease and abnormal platelet function has resulted in substantial uncertainty concerning the risks and benefits of antiplatelet therapy in patients with CKD. Some randomized control trials involving CKD population showed that more intensive antiplatelet therapy could be of reduced benefit in preventing major cardiovascular events [21], whereas others suggested benefits of similar or even greater magnitude [22, 23]. A large meta-analysis including 27,773 patients with CKD with and without coexisting CAD who were treated with different antiplatelet drugs, including aspirin and P2Y12 receptor inhibitors, demonstrated the association of antiplatelet therapy with a 15% reduction in the risk of major cardiovascular events and a 48% reduction of dialysis access failure [24]. Antiplatelet therapy had no significant effect on all-cause death or kidney failure events. Not surprisingly, both major and minor bleeding events were significantly more common with antiplatelet therapy. For every 1,000 persons with CKD treated with antiplatelet therapy for 12 months, 23 major cardiovascular events will be prevented, while nine major bleeding events will occur. These data suggest that patients with CAD and concomitant CKD should receive antiplatelet therapy. However, special attention should be given to

Table 1. Summary of cardiovascular and renal outcomes of the different SGLT2 inhibitors RCTs

Study	Drug	Patient characteristics	*N*	Cardiovascular outcomes	Renal outcomes
EMPA-REG OUTCOMES [10]	Empagliflozin	Diabetic patients with CV disease eGFR >30 mL/min/1.73 m^2 History of CAD: 77%	7,020	14% reduction of MACE (0.74–0.99) 34% reduction of heart failure hospitalizations (0.5–0.85)	39% reduction of Incident or worsening nephropathy
DECLARE [11]	Dapagliflozin	Diabetic patients who had or were at risk of CV disease eGFR >60 mL/min/1.73 m^2 History of CV disease: 40% History of CAD: 33%	17,160	17% reduction in the composite of CV death or hospitalization for heart failure	26% reduction in the composite renal outcome (≥40% decrease in eGFR to <60 mL/min/1.73 m^2, new ESRD, or death from renal or CV causes
DAPA-CKD [12]	Dapagliflozin	Diabetics and nondiabetics eGFR = 25–75 mL/min/1.73 m^2 and a UACR = 200–5,000 History of CV disease: 37%	4,304	29% reduction of CV death + hospitalization for HF	46% reduction in progression of CKD (composite of eGFR decline ≥50%, ESRD, or death from renal causes)
DAPA-HF [13]	Dapagliflozin	Symptomatic HF patients with an EF ≤40% eGFR >30 mL/min/1.73 m^2 (eGFR <60 in 41%) History of CAD: 56%	4,744	26% reduction of CV death + hospitalization for HF	
EMPEROR REDUCED [14]	Empagliflozin	Symptomatic HF patients with an EF ≤40% eGFR >20 mL/min/1.73 m^2 (GFR <60 in 48%) History of CAD: 52%	3,730	25% reduction for CV death + hospitalization for HF	50% reduction of composite renal outcome (chronic dialysis or renal transplantation or a sustained profound reduction in the eGFR)
EMPEROR PRESERVED [15]	Empagliflozin	Symptomatic HF patients with an EF >40% eGFR >20 mL/min/1.73 m^2 (GFR <60 in 50%) History of CAD: 35%	5,988	21% reduction of CV death + hospitalizations for HF	Annual rate of decline in eGFR was slower in the empagliflozin group than in the placebo group (−1.25 vs. −2.62 mL/min/1.73 m^2/year; $p < 0.001$)
EMPULSE [16]	Empagliflozin	Acute heart failure regardless of EF	530	36% increase in clinical benefit- composite of death, hospitalizations for HF and improved symptoms	
CANVAS [17]	Canagliflozin	Diabetic patients who had or were at risk of CV disease eGFR >30 mL/min/1.73 m^2 History of CAD: 56%	10,142	14% reduction of MACE 33% reduction of heart failure hospitalizations	40% reduction of composite renal outcome (sustained 40% reduction in eGFR, the need for renal replacement therapy, or death from renal causes)
CREDENCE [18]	Canagliflozin	Diabetic patients with albuminuria eGFR >30 mL/min/1.73 m^2 History of CV disease: 37%	4,401	20% reduction of MACE 39% reduction of heart failure hospitalizations	34% reduction of composite renal outcome (ESRD, a doubling of the creatinine level or death from renal causes)

Table 1 (continued)

Study	Drug	Patient characteristics	*N*	Cardiovascular outcomes	Renal outcomes
EMPA-KIDNEY [19]	Empagliflozin	Patients with CKD: eGFR 20–45 mL/min/1.73 m^2, or eGFR 45–90 mL/min/1.73 m^2 with a urinary albumin-to-creatinine ratio >200	6,609	28% reduction of kidney disease progression or death from cardiovascular causes	29% reduction of kidney disease progression

ASCVD, atherosclerotic cardiovascular disease; CHF, chronic heart failure; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EF, ejection fraction; ESRD, end-stage renal disease; HF, heart failure; MACE, major adverse cardiovascular events; CAD, coronary artery disease; UACR, urinary albumin-to-creatinine ratio.

bleeding risk assessment and strategies to prevent bleeding events. Among CKD patients with ACS or those following coronary revascularization, the decision regarding the type of P2Y12 receptor inhibitor (prasugrel, ticagrelor, or clopidogrel) in addition to aspirin should be made following a careful assessment of bleeding and thrombotic risks. Among patients on hemodialysis, clopidogrel should be preferred over prasugrel and ticagrelor.

Treatment for Patients with Diabetes Mellitus

Glucagon-Like Protein 1 Receptor Agonists

Liraglutide, semaglutide, and dulaglutide have been associated with a reduction in the risk of major adverse cardiovascular events among diabetic patients at high cardiovascular risk including those with concomitant CAD. The cardiovascular benefit with glucagon-like protein 1 (GLP-1) receptor agonists' treatment remained constant in patients with CKD. Moreover, treatment with GLP-1 receptor agonists has been associated with a significant renoprotective effect including a lower rate of new onset or worsening proteinuria. Accordingly, GLP-1 receptor agonists have been approved for high-risk diabetic patients with an eGFR>15 mL/min/1.73 m^2 [25].

Finerenone

Finerenone, a new nonsteroidal mineralocorticoid receptor antagonist, has recently demonstrated a significant improvement in renal and cardiovascular outcomes in diabetes patients with CKD [26, 27]. The FIDELIO-DKD study included 5,734 diabetic patients with CKD (a UACR of 30–300 with eGFR of 25–59 mL/min/1.73 m^2 or UACR of >300 with an eGFR of 25–75 mL/min/1.73 m^2) who were randomly assigned to receive finerenone or placebo. Of them, 2,605 (45.9%) had a history of cardiovascular disease. The study demonstrated that in diabetic patients with predominantly stage 3–4 CKD, treatment with finerenone resulted in a lower risk of CKD progression (end stage renal failure, a sustained decrease of at least 40% in the eGFR from baseline or death from renal causes) and cardiovascular events (the composite of CV death, nonfatal myocardial infarction, stroke, or hospitalization for heart failure) than placebo [26]. The FIGARO-DKD study randomly assigned 7,437 diabetic patients with a wide range of CKD to receive finerenone or placebo. Eligible patients had stage 2–4 CKD with moderate albuminuria or stage 1–2 CKD with severe albuminuria. Of them, 3,330 (45.3%) had a history of cardiovascular disease. The study demonstrated that among diabetic patients with a wide range of CKD, treatment with finerenone significantly reduced the primary cardiovascular composite outcome, as well as the secondary composite renal outcome [27]. These consistent results strongly support finerenone treatment in diabetic patients with CKD, including those with previous CAD, for the reduction of both cardiovascular and renal adverse outcomes.

Coronary Revascularization

The choice of medical therapy alone or revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in symptomatic patients with CKD is controversial. Despite the lack of dedicated data, CKD patients presenting with a STEMI undergo primary PCI similar to those with normal kidney function. Among patients with non-ST-segment elevation-ACS, observational studies support an early invasive strategy with coronary angiography and subsequent coronary revascularization over a conservative approach [28]. However, the early invasive approach was not associated with survival benefit among patients with eGFR<60 mL/min/1.73 m^2.

Short- and long-term procedural risks of both PCI and CABG are greater among patients with CKD compared to those with normal renal function. The data to support PCI or CABG in patients with CKD are limited and are taken

mainly from observational studies. A meta-analysis including 3,993 patients encompassing 526 patients with stage 3–5 CKD suggested some benefits to CABG over PCI in moderate CKD [29]. Among dialysis patients, observational studies suggest a short-term higher risk of mortality and stroke with CABG versus PCI, but a long-term higher risk of adverse outcomes with PCI versus CABG. Decisions regarding the type of revascularization (surgical vs. percutaneous) should be made individually for each patient following consideration of short- and long-term risks and benefits of each intervention. Special attention should be given to comorbidity burden, CKD and overall related-prognosis, frailty, and patient preference.

Percutaneous Coronary Interventions

Patients with CKD, who are planned for coronary angiography and subsequent PCI, represent an important high-risk group for both cardiovascular and renal adverse outcomes. Main causes of acute kidney injury (AKI) in patients undergoing PCI include the exposure to contrast media, hemodynamic instability, and atheroembolization.

Contrast-induced nephropathy (CIN) is defined as the development of AKI following contrast media administration in the absence of an alternative etiology [30]. The most widely adopted definition of CIN is the Kidney Disease Improving Global Outcomes (KDIGO) definition: an increase in serum creatinine by ≥0.3 mg/dL within 48 h after contrast media exposure or an increase to ≥50% within 7 days [31]. The incidence of CIN in patients undergoing PCI varies in different populations and may be as high as 15% in high-risk groups. In the majority of patients with CIN, renal function returns to baseline values. However, the development of CIN has been associated with worse outcomes, including prolonged hospital stay, irreversible kidney injury including the need for dialysis, and death [30, 31].

Several risk factors for the development of CIN have been identified. Of them, baseline renal function appears to be the strongest predictor. Patients with estimated GFRs (eGFRs) ≥45 mL/min/1.73 m^2 are at negligible risk for CIN, while in patients with eGFRs <30 mL/min/1.73 m^2, the risk for CIN may be as high as 27% [32]. The presence of diabetes mellitus may further increase this risk. Other risk factors include renal hypoperfusion (due to volume depletion, cardiogenic shock, acute heart failure), advanced age, diabetes mellitus, anemia, and low left ventricular ejection fraction [33]. CIN risk assessment can be done using validated scores, which incorporate the aforementioned predictors [34, 35].

Once the diagnosis of CIN is established, there is no specific treatment; hence the main goal is prevention. Prevention of CIN is based on pre-procedural, procedural, and post-procedural strategies.

Prevention of PCI-Related AKI

Pre-Procedural Strategies

Discontinuation of Nephrotoxic Medications

Ideally, in nonurgent cases, potentially nephrotoxic medications (metformin, nonsteroidal anti-inflammatory drugs, diuretics) should be discontinued at least 48 h before exposure to contrast media [36].

Intravenous Fluids

Adequate hydration with intravenous infusion of normal saline remains a key instrument for CIN prevention. While the dosing, duration, or injection rate for pre- and post-procedural fluid administration have not been well established, the European Society of Cardiology guidelines recommend the routine administration of intravenous isotonic saline at a rate of 1 to 1 mL/kg/h for 12 h before and up to 24 h after the procedure [37]. Several studies have demonstrated that tailoring hydration rate and total volume according to invasive left ventricular end-diastolic or central venous pressure monitoring [38, 39] or bioimpedance vector analysis [40] can reduce the risk of CIN compared with a standard hydration protocol. Moreover, the RenalGuard system (RenalGuard Solutions, Milford, MA, USA) is a novel device that allows the maximization of intravenous hydration by matching the infused volume to the patient's urine output that allow the dilution of contrast media without volume overexpansion according to the urine output. Randomized trials showed benefit in CI-AKI prevention using RenalGuard versus standard hydration protocols [41].

High-Dose Statins

High-dose statins are the only pharmacological agents that have been shown to decrease the risk of CIN in different randomized controlled trials on patients with CKD undergoing coronary interventions [42]. Possible mechanisms for this renoprotective effect may include improved endothelial function, antioxidant, anti-inflammatory, and antithrombotic effects. Therefore, in statin-naïve patients, pretreatment with high-dose statins (rosuvastatin 20/40 mg or atorvastatin 80 mg) should be strongly considered. Other pharmacological agents, including N-acetylcysteine, bicarbonate, trimetazidine, and fenoldopam, have failed to show consistent renoprotective effect and are therefore not recommended.

Procedural Strategies

Vascular Access

Several large trials have showed that radial access is associated with lower incidence of PCI-related AKI as compared with femoral access [43]. The mechanism behind this benefit appears to be multifactorial and includes lower rates of major bleeding and hemodynamic instability and reduction of atheroma embolization to the renal arteries by avoiding manipulating the abdominal aorta [42] Therefore, radial access should be preferred over femoral access, when feasible, to decrease the risk of AKI.

Contrast Media Volume Reduction

There is a direct association between contrast media volume and the risk of CIN [44]. A contrast volume-to-creatinine clearance (CV/CrCl) ratio >2 has been identified as an independent predictor of CI-AKI in patients with an eGFR <30 mL/min/1.73 m^2 [45]. Coronary procedures using ultralow contrast volume techniques with CV/CrCl ratio <1 are ideal to minimize the risk for CI-AKI. Several studies have demonstrated that these techniques may be successfully utilized in most patients with CKD undergoing PCI with excellent renal outcomes and without jeopardizing coronary outcomes. The reduction of contrast media administration can be achieved by using diluted contrast, 5-French catheters with no side holes, avoidance of test injections, use of biplane angiography and stent enhancement techniques, increased acquisition rates (15 or 25 frames/s) to improve image quality during diagnostic angiogram and extensive use of intracoronary imaging with intravascular ultrasound (IVUS) and dextran-based optical coherence tomography. The latter may allow zero contrast PCI procedures that can be performed if coronary anatomy is known. In the MOZART trial, zero contrast PCI was safely performed through IVUS imaging and significantly reduced the dose of iodine contrast in comparison to an angiography-only approach. However, no clinical benefit (including reduction of CIN) was observed [46].

Several other technologies for the reduction of contrast media exposure have been introduced. Among them is the DyeVert PLUS system that collects contrast media from the aortic root into a reservoir chamber, which leads to 15–40% reduction of contrast media exposure and contrast media aspiration from the coronary sinus immediately following contrast injection. However, both technologies have not shown any clinical benefit yet [47].

Type of Contrast Media

Recent data on patients with CKD undergoing PCI have showed no significant benefit of the iso-osmolar iodixanol over low-osmolar contrast media in preventing CI-AKI [48]. Accordingly, there is no evidence to recommend iodixanol over low-osmolar CM for CI-AKI prevention.

Hemodynamic Support

Hypotension during coronary procedures is an important cause of AKI. Hemodynamic support with a percutaneous left ventricular assist device such as Impella (Abiomed, Danvers, MA, USA) is a feasible strategy for maintaining hemodynamic stability during high-risk PCI. In a single-center retrospective study on 230 patients with left ventricular ejection fraction <35% including 115 subjects supported with Impella and 115 unsupported matched controls undergoing high-risk PCI, CI-AKI was observed in 5.2% of Impella-supported subjects versus 27.8% in the unsupported group (adjusted OR: 0.13; 95% confidence interval: 0.09–0.31; $p < 0.001$) [49]. Impella use was associated with lower incidence of all stages of AKI, including AKI requiring dialysis and there was no association between CKD severity and CI-AKI in the Impella-supported group. The promising result of this study warrants confirmation in large prospective registries. Currently, there are no studies showing any effect of hemodynamic support during high-risk PCI using intra-aortic balloon pump on the risk of AKI.

Remote Ischemic Conditioning

The mechanism of the renoprotective effect of remote ischemic conditioning remains largely unknown but may include reduced renal ischemia/reperfusion injury [50]. Preconditioning with alternating 5-min inflation and 5-min deflation of an upper-arm blood pressure cuff or by inflating/deflating the stent balloon for 30 s after stenting the culprit lesion were associated with a significant reduction of AKI. Nevertheless, given the relatively small studies on remote ischemic conditioning, the feasibility and efficacy of this technique in routine clinical practice remains to be proven.

Cardiac Surgery and Renal Failure

AKI complicates recovery from cardiac surgery in up to 30% of patients [51]. Renal ischemia, reperfusion, inflammation, hemolysis, oxidative stress, cholesterol emboli, and toxins contribute to the development and progression of AKI. As many as 2–5% of patients with cardiac surgery-related AKI require renal replacement therapy and this serious complication is associated with a 10-fold increased mortality [52]. In a propensity-matched cohort based on a

nationally representative database in the US, CABG for multi-vessel disease was associated with twice more likelihood of developing post-procedural AKI including the need for renal replacement therapy as compared with PCI [53]. Therefore, in patients with CKD and multi-vascular CAD who may be treated with either surgical or percutaneous revascularization, the presence of high risk for procedure-related AKI is a strong argument supporting PCI.

Risk factors for cardiac surgery-related AKI may be divided into preoperative (urgent surgery, advanced age, female gender, pre-existing CKD, diabetes mellitus, and anemia), intraoperative (cardiopulmonary bypass (CPB) duration and a need to return to CPB, hypovolemia, and hypoperfusion), and postoperative factors (shock, use of inotropes, vasopressors, or diuretics). Several risk stratification systems exist for prediction of cardiac surgery-related AKI [54–56]. Of them, the Cleveland Clinic score offers the best prediction [56].

Prevention of Cardiac Surgery-Related AKI

Timing of Surgery

The association between the time from coronary angiography to cardiac surgery and the risk for cardiac surgery-related AKI is controversial. While some studies have demonstrated that a short period (<3 days) was associated with the increased risk of AKI, other studies have failed to show such an association [57, 58]. Accordingly, surgical intervention should not be delayed in emergency or urgent cases. The optimization of renal function and correction of other predisposing factors seem to be the correct strategy in clinically stable patients with risk factors for AKI.

Pre-Procedural Prevention of Cardiac Surgery-Related AKI

Discontinuation of Potentially Nephrotoxic Drugs

Discontinuation of potentially nephrotoxic drugs, including NSAIDS, metformin, and diuretics, prior to surgery is strongly recommended [59]. Recommendations regarding discontinuation of ACE inhibitors and ARBs are less clear end evidence exists suggesting that these drugs may be safely continued until the day of surgery [60]. Some evidence exists regarding the renal protective effect of preoperative statin therapy [61].

Anemia and Transfusion

Studies have demonstrated that preoperative anemia is significantly associated with AKI during cardiac surgery [62]. Decreased hemoglobin concentration with an effect cut-off value of <9 g/dL and volume of transfused RBC, especially on the day of surgery, were independent risk factors for cardiac surgery-related AKI [63]. Accordingly, severe hemodilution and blood transfusion in patients with hemoglobin levels >8 g/dL should be avoided. When RBC transfusion cannot be avoided, it should be minimized and administered at least 1–2 days before surgery [64]. Among elective patients, the preoperative optimization of anemia using the infusion of erythropoietin (300 IU/kg) reduced the risk of AKI and improved postoperative renal function [65].

Hydration

Maintenance of volume status is extremely important in the prevention of AKI in cardiac surgery. Appropriate fluid management after cardiac surgery is complex, especially in patients in whom the cardiopulmonary bypass machine is used since fluid can be sequestered in the extracellular space while intravascular space remains volume-depleted. Using diuretics in these patients leads to further intravascular dehydration. A low urine flow rate after furosemide administration was independently associated with AKI in post cardiac surgery patients [66]. The RenalGuard is a novel device that allows the maximization of intravenous hydration by matching the infused volume to the patient's urine output. It has been shown to reduce the rate of AKI and is safe to use in patients undergoing cardiac surgery [67].

Cardiopulmonary Bypass

Cardiopulmonary bypass may contribute to the pathogenesis of AKI by activating a systemic inflammatory response, altering regional blood flow and vasomotor tone in kidneys, and generating microemboli [67]. The duration of cardiopulmonary bypass is an important independent risk factor for AKI in the postoperative setting [68]. On the other hand, the routine use of pulsatile perfusion during cardiopulmonary bypass and a target MAP >60 mm Hg might be beneficial in renal preservation [69]. Off-pump cardiac surgery appears to be a logical step toward minimizing the risk of postoperative AKI. However, studies have provided conflicting results. The CORONARY trial found that off-pump compared with on-pump CABG surgery reduced the risk of postoperative AKI but did not alter 1-year kidney function [70]. These findings were further supported by other studies [71, 72]. Evidence from small studies has suggested that minimally invasive surgery might also be renoprotective [73].

Conclusions

The combination of CKD with CAD is associated with poor outcomes and poses a great challenge to the treating physician. Treatment decisions should be tailored

individually to each patient following a multi-disciplinary discussion and consideration of relevant risks and benefits, as well as patient preference. While the clinical benefit from several guideline-based therapies may be unclear, several studies suggest that there are significant opportunities to substantially improve both cardiovascular and renal outcomes of these patients, including treatment with new lipid-lowering medications, SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone. Furthermore, several strategies have resulted in lower rates of both CABG- and PCI-related AKI. Ongoing work is needed for further understanding of the efficacy and safety of different interventions and drugs that may further improve the outcome of patients with CAD and CKD.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received by the authors.

Author Contributions

Ilya Losin and Keren-Cohen Hagai: data collection, manuscript design, manuscript writing, critical revision of the manuscript, and approval of the final version. David Pereg: data collection, manuscript design and conception, manuscript writing, and approval of the final version.

References

1 Sarnak MJ, Amann K, Bangalore S, Cavalcante JL, Charytan DM, Craig JC, et al. Chronic kidney disease and coronary artery disease: JACC state-of-the-art review. J Am Coll Cardiol. 2019;74(14):1823–38.
2 Konstantinidis I, Nadkarni GN, Yacoub R, Saha A, Simoes P, Parikh CR, et al. Representation of patients with kidney disease in trials of cardiovascular interventions: an updated systematic review. JAMA Intern Med. 2016;176(1):121–4.
3 Williams, B (Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European society of Cardiology and the European society of hypertension: the task force for the management of arterial hypertension of the European society of Cardiology and the European society of hypertension. J Hypertens. 2018;36(10):1953–2041.
4 Drawz PE, Beddhu S, Bignall ONR 2nd, Cohen JB, Flynn JT, Ku E, et al. KDOQI US commentary on the 2021 KDIGO clinical practice guideline for the management of blood pressure in CKD. Am J Kidney Dis. 2022;79(3):311–27.
5 Xie X, Liu Y, Perkovic V, Li X, Ninomiya T, Hou W, et al Renin-angiotensin system inhibitors and kidney and cardiovascular outcomes in patients with CKD: a bayesian network meta-analysis of randomized clinical trials. Am J Kidney Dis. 2016;67(5):728–41.
6 Silva-Cardoso J, Brito D, Frazão JM, Ferreira A, Bettencourt P, Branco P, et al. Management of RAASi-associated hyperkalemia in patients with cardiovascular disease. Heart Fail Rev. 2021;26(4):891–6.
7 Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360(14):1395–407.
8 Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181–92.
9 Charytan DM, Sabatine MS, Pedersen TR, Im K, Park JG, Pineda AL, et al. Efficacy and safety of evolocumab in Chronic kidney disease in the FOURIER Trial. J Am Coll Cardiol. 2019;73(23):2961–70.
10 Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28.
11 Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–57.
12 Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46.
13 McMurray JV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008.
14 Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–24.
15 Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385(16):1451–61.
16 Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med. 2022;28(3):568–74.
17 Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57.
18 Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295–306.
19 The EMPA-KIDNEY Collaborative Group; Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, et al. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2023;388(2):117–27.
20 Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227–337.
21 Best PJ, Steinhubl SR, Berger PB, Dasgupta A, Brennan DM, Szczech LA, et al. The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: results from the Clopidogrel for the reduction of events during observation (CREDO) trial. Am Heart J. 2008;155(4):687–93.
22 James S, Budaj A, Aylward P, Buck KK, Cannon CP, Cornel JH, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the platelet inhibition and patient outcomes (PLATO) trial. Circulation. 2010;122(11):1056–67.
23 Dixon BS, Beck GJ, Vazquez MA, Greenberg A, Delmez JA, Allon M, et al. Effect of dipyridamole plus aspirin on hemodialysis graft patency. N Engl J Med. 2009;360(21):2191–201.

24 Su X, Yan B, Wang L, Lv J, Cheng H, Chen Y. Effect of antiplatelet therapy on cardiovascular and kidney outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. BMC Nephrol. 2019;20(1):309.
25 Tuttle KR, Lakshmanan MC, Rayner B, Busch RS, Zimmermann AG, Woodward DB, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol. 2018;6(8):605–17.
26 Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383(23):2219–29.
27 Investigators FIGARO-DKD; Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med. 2021;385(24):2252–63.
28 Shaw C, Nitsch D, Lee J, Fogarty D, Sharpe CC. Impact of an early invasive strategy versus conservative strategy for unstable angina and non-ST elevation acute coronary syndrome in patients with chronic kidney disease: a systematic review. PLoS One. 2016;11(5):e0153478.
29 Charytan DM, Desai M, Mathur M, Stern NM, Brooks MM, Krzych LJ, et al. Reduced risk of myocardial infarct and revascularization following coronary artery bypass grafting compared with percutaneous coronary intervention in patients with chronic kidney disease. Kidney Int. 2016;90(2):411–21.
30 Mehran R, Dangas GD, Weisbord SD. Contrast-associated acute kidney injury. N Engl J Med. 2019;380(22):2146–55.
31 Almendarez M, Gurm HS, Mariani J Jr, Montorfano M, Brilakis ES, Mehran R, et al. Procedural strategies to reduce the incidence of contrast-induced acute kidney injury during percutaneous coronary intervention. JACC Cardiovasc Interv. 2019;12(19):1877–88.
32 Rudnick MR, Leonberg-Yoo AK, Litt HI, Cohen RM, Hilton S, Reese PP. The controversy of contrast-induced nephropathy with intravenous contrast: what is the risk? Am J Kidney Dis. 2020;75(1):105–13.
33 Azzalini L, Spagnoli V, Ly HQ. Contrast-induced nephropathy: from pathophysiology to preventive strategies. Can J Cardiol. 2016;32(2):247–55.
34 Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME, et al. Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR Cath-PCI registry. JACC Cardiovasc Interv. 2014;7:1–9.
35 Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol. 2004;44(7):1393–9.
36 McCullough PA, Choi JP, Feghali GA, Schussler JM, Stoler RM, Vallabahn RC, et al. Contrast-induced acute kidney injury. J Am Coll Cardiol. 2016;68(13):1465–73.
37 Mullasari A, Victor SM. Update on contrast induced nephropathy. E J ESC Counc Cardiol Pract. 2014;4:13.
38 Brar SS, Aharonian V, Mansukhani P, Moore N, Shen AYJ, Jorgensen M, et al. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. Lancet. 2014;383(9931):1814–23.
39 Qian G, Fu Z, Guo J, Cao F, Chen Y. Prevention of contrast-induced nephropathy by central venous pressure-guided fluid administration in chronic kidney disease and congestive heart failure patients. JACC Cardiovasc Interv. 2016;9(1):89–96.
40 Maioli M, Toso A, Leoncini M, Musilli N, Grippo G, Ronco C, et al. Bioimpedance-guided hydration for the prevention of contrast-induced kidney injury; the HYDRA study. J Am Coll Cardiol. 2018;71(25):2880–9.
41 Briguori C, Visconti G, Focaccio A, Airoldi F, Valgimigli M, Sangiorgi GM, et al. Renal insufficiency after contrast media administration trial II (REMEDIAL II): RenalGuard system in highrisk patients for contrast-induced acute kidney injury. Circulation. 2011;124(11):1260–9.
42 Cho A, Lee YK, Sohn SY. Beneficial effect of statin on preventing contrast-induced acute kidney injury in patients with renal insufficiency: a meta-analysis. Medicine. 2020;99.
43 Andò G, Costa F, Trio O, Oreto G, Valgimigli M. Impact of vascular access on acute kidney injury after percutaneous coronary intervention. Cardiovasc Revasc Med. 2016;17(5):333–8.
44 Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation. 2002;105(19):2259–64.
45 Gurm HS, Dixon SR, Smith DE, Share D, Lalonde T, Greenbaum A, et al. Renal function-based contrast dosing to define safe limits of radiographic contrast media in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol. 2011;58(9):907–14.
46 Mariani J Jr, Guedes C, Soares P, Zalc S, Campos CM, Lopes AC, et al. Intravascular ultrasound guidance to minimize the use of iodine contrast in percutaneous coronary intervention: the MOZART (Minimizing cOntrast utiliZation with IVUS Guidance in coRonary angioplasTy) randomized controlled trial. JACC Cardiovasc Interv. 2014;7(11):1287–93.
47 Gurm H, Mavromatis K, Bertolet B, Kereiakes DJ, Amin AP, Shah AP, et al. Minimizing radiographic contrast administration during coronary angiography using a novel contrast reduction system: a multicenter observational study of the DyeVert™ plus contrast reduction system. Catheter Cardiovasc Interv. 2019;93(7):1228–35.
48 Reed M, Meier P, Tamhane UU, Welch KB, Moscucci M, Gurm HS. The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials. JACC Cardiovasc Interv. 2009;2(7):645–54.
49 Flaherty MP, Pant S, Patel SV, Kilgore T, Dassanayaka S, Loughran JH, et al. Hemodynamic support with a microaxial percutaneous left ventricular assist device (Impella) protects against acute kidney injury in patients undergoing high-risk percutaneous coronary intervention. Circ Res. 2017;120(4):692–700.
50 Er F, Nia AM, Dopp H, Hellmich M, Dahlem KM, Caglayan E, et al. Ischemic preconditioning for prevention of contrast medium-induced nephropathy: randomized pilot RenPro trial (renal Protection trial). Circulation. 2012;126(3):296–303.
51 Lagny MG, Jouret F, Koch JN, Blaffart F, Donneau AF, Albert A, et al. Incidence and outcomes of acute kidney injury after cardiac surgery using either criteria of the RIFLE classification. BMC Nephrol. 2015;16:76.
52 Landoni G, Zangrillo A, Franco A, Aletti G, Roberti A, Calabrò MG, et al. Long-term outcome of patients who require renal replacement therapy after cardiac surgery. Eur J Anaesthesiol. 2006;23(1):17–22.
53 Shen W, Aguilar R, Montero AR, Fernandez SJ, Taylor AJ, Wilcox CS, et al. Acute kidney injury and in-hospital mortality after coronary artery bypass graft versus percutaneous coronary intervention: a nationwide study. Am J Nephrol. 2017;45(3):217–25.
54 Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. J Am Soc Nephrol. 2005;16(1):162–8.
55 Mehta RH, Grab JD, O'Brien SM, Bridges CR, Gammie JS, Haan CK, et al. Bedside tool for predicting the risk of postoperative dialysis in patients undergoing cardiac surgery. Circulation. 2006;114(21):2208–16; quiz 2208.
56 Kiers HD, van den Boogaard M, Schoenmakers MC, van der Hoeven JG, van Swieten HA, Heemskerk S, et al. Comparison and clinical suitability of eight prediction models for cardiac surgery-related acute kidney injury. Nephrol Dial Transplant. 2013;28(2):345–51.
57 Liu K, Li M, Li L, Wu B, Xu X, Ge Y, et al. The effect of coronary angiography timing on cardiac surgery associated acute kidney injury incidence and prognosis. Front Med. 2021;8:619210.

58 Ozkaynak B, Kayalar N, Gümüş F, Yücel C, Mert B, Boyacıoğlu K, et al. Time from cardiac catheterization to cardiac surgery: a risk factor for acute kidney injury? Interact Cardiovasc Thorac Surg. 2014;18(6):706–11.
59 Kellum JA, Lameire N; KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013; 17(1):204.
60 Billings FT 4th, Balaguer JMCY, Yu C, Wright P, Petracek MR, Byrne JG, et al. Comparative effects of angiotensin receptor blockade and ACE inhibition on the fibrinolytic and inflammatory responses to cardiopulmonary bypass. Clin Pharmacol Ther. 2012;91(6): 1065–73.
61 Singh I, Rajagopalan S, Srinivasan A, Achuthan S, Dhamija P, Hota D, et al. Preoperative statin therapy is associated with lower requirement of renal replacement therapy in patients undergoing cardiac surgery: a meta-analysis of observational studies. Interact Cardiovasc Thorac Surg. 2013;17(2):345–52.
62 Oprea AD, Del Rio JM, Cooter M, Green CL, Karhausen JA, Nailer P, et al. Pre- and postoperative anemia, acute kidney injury, and mortality after coronary artery bypass grafting surgery: a retrospective observational study. Can J Anaesth. 2018;65(1):46–59.
63 Haase M, Bellomo R, Story D, Letis A, Klemz K, Matalanis G, et al. Effect of mean arterial pressure, haemoglobin and blood transfusion during cardiopulmonary bypass on postoperative acute kidney injury. Nephrol Dial Transplant. 2012;27(1):153–60.
64 Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, Chan CT, Wong PY, et al. Advance targeted transfusion in anemic cardiac surgical patients for kidney protection: an unblinded randomized pilot clinical trial. Anesthesiology. 2012;116(3): 613–21.
65 Song YR, Lee T, You SJ, Chin HJ, Chae DW, Lim C, et al. Prevention of acute kidney injury by erythropoietin in patients undergoing coronary artery bypass grafting: a pilot study. Am J Nephrol. 2009;30(3):253–60.
66 PenkJ, GistKM, WaldEL, KitzmillerL, WebbTN, LiY, et al. Furosemide response predicts acute kidney injury in children after cardiac surgery. J Thorac Cardiovasc Surg. 2019;157(6):2444–51.
67 Luckraz H, Giri R, Wrigley B, Nagarajan K, Senanayake E, Sharman E, et al. Reduction in acute kidney injury post cardiac surgery using balanced forced diuresis: a randomized, controlled trial. Eur J Cardio Thorac Surg. 2021;59(3):562–9.
68 Pickering JW, James MT, Palmer SC. Acute kidney injury and prognosis after cardiopulmonary bypass: a meta-analysis of cohort studies. Am J Kidney Dis. 2015;65(2):283–93.
69 Sievert A, Sistino J. A meta-analysis of renal benefits to pulsatile perfusion in cardiac surgery. J Extracorp Technol. 2012; 44(1):10–4.
70 Garg AX, Devereaux PJ, Yusuf S, Cuerden MS, Parikh CR, Coca SG, et al. Kidney function after off-pump or on-pump coronary artery bypass graft surgery: a randomized clinical trial. JAMA. 2014;311(21):2191–8.
71 Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al. Off-pump or on-pump coronaryartery bypass grafting at 30 days. N Engl J Med. 2012;366(16):1489–97.
72 Schopka S, Diez C, Camboni D, Floerchinger B, Schmid C, Hilker M. Impact of cardiopulmonary by- pass on acute kidney injury following coronary artery bypass grafting: a matched pair analysis. J Cardiothorac Surg. 2014;9:20.
73 Benedetto U, Luciani R, Goracci M, Capuano F, Refice S, Angeloni E, et al. Miniaturized cardiopulmonary bypass and acute kidney injury in coronary artery bypass graft surgery. Ann Thorac Surg. 2009;88(2):529–35.