

# Results of Protocol-based Perioperative Management in Off-Pump Coronary Artery Bypass Grafting for Patients with Non-dialysis-dependent Chronic Kidney Disease

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**Background:** Recent studies have demonstrated the benefits of off-pump coronary bypass grafting over the on-pump technique in patients with chronic kidney disease (CKD). To further reduce the risk of acute kidney injury and the need for renal replacement therapy, even in patients undergoing off-pump coronary artery bypass grafting, we adopted protocol-based perioperative management for patients with CKD. **Methods:** From December 2012 to March 2015, 265 patients underwent isolated off-pump coronary artery bypass grafting. To analyze renal function in a stable condition, we excluded 12 dialysis-dependent end stage renal failure and 10 emergency or urgent cases. Among the remaining 243 patients, 208 patients had normal kidney function (normal group), and 35 patients had CKD (CKD group). Minimizing contrast exposure, ensuring adequate hydration, using strict drug dosage adjustment, and optimizing hemodynamic status were key elements of the protocol for the CKD group. **Results:** The risk of acute kidney injury was about ×3 higher in the CKD group than in the normal group ( $p=0.01$ ). Estimated glomerular filtration rates and serum creatinine levels deteriorated until the third postoperative day in the CKD group. However, by adopting protocol-based perioperative management, this transient renal dysfunction recovered to preoperative levels by the fifth postoperative day without requiring renal replacement therapy in all cases. **Conclusion:** Off-pump coronary bypass surgery combined with this protocol-based perioperative management strategy in patients with non-dialysis-dependent CKD could mostly be performed without renal replacement therapy.

**Key words:** 1. Coronary artery bypass surgery  
2. Off-pump  
3. Renal insufficiency, chronic  
4. Acute kidney injury  
5. Perioperative care

## Introduction

Patients with chronic kidney disease (CKD) who require coronary revascularization tend to have advanced cardiovascular disease and more accelerated

coronary artery atherosclerosis than patients with normal kidney function [1]. Furthermore, CKD is an independent risk factor for postoperative renal dysfunction after coronary artery bypass grafting (CABG). The occurrence of CKD is also known as an important

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predictor of postoperative morbidity and poor long-term outcomes [2-5]. Most recent studies have focused on the effects of surgical techniques (on-pump vs. off-pump CABG) on postoperative outcomes in patients with CKD [6-8]. The impact of off-pump coronary artery bypass (OPCAB) on postoperative renal function in CKD patients has been sparsely reported in the literature [5,9,10]. However, those studies have analyzed the risk factors for postoperative renal replacement therapy (RRT) using a heterogeneous population by including dialysis-dependent and non-dialysis CKD patients [11,12].

Recently, protocol-based management has become broadly adopted as a means of improving clinical outcomes in a number of different clinical settings. So far, the available studies are limited to demonstrating the superior features of protocol-based management compared to individual protocols [13]. To prevent the development or worsening of acute kidney injury (AKI) in high-risk patients in the perioperative setting, guidelines suggest that "using protocol-based management is superior to no protocol" [14]. Although several guidelines and articles have suggested methods for the appropriate management of AKI, this has yet to be elucidated and properly tested. There are no previous studies in the literature concerning how to manage these patients, not even those reporting excellent postoperative outcomes. The aim of this study is to verify the effects of protocol-based management on postoperative kidney function in patients with non-dialysis-dependent CKD undergoing OPCAB.

## Methods

Between December 2012 and March 2015, 265 patients underwent isolated CABG at Sejong General Hospital. To evaluate renal function in a stable clinical condition, we excluded 12 patients with dialysis-dependent end stage renal failure and 10 patients with emergency or urgent cases. The remaining 243 patients were included in this study, and categorized into 2 groups (the normal group and CKD group) according to the presence of CKD. The institutional review board of Sejong General Hospital approved this retrospective study and waived the requirement for individual patient consent (IRB approval number: 1534).

### 1) Definition

We defined CKD, according to guidelines in *Kidney Disease: Improving Global Outcomes* [12], as an estimated glomerular filtration rate (eGFR)  $<60$  mL/min/1.73 m<sup>2</sup> for  $>3$  months according to the Modification of Diet in Renal Disease equation [15]. The occurrence of AKI was defined as an increase in the serum creatinine level of  $>0.3$  mg/dL within 48 hours or an increase of  $>1.5\times$  above baseline known or presumed to have occurred within the previous 7 days [14].

### 2) Surgical technique

OPCAB using skeletonized bilateral internal thoracic arteries was performed in most cases. Heparin was administered just before taking down the grafts, and an activated clotting time of  $>300$  seconds was maintained during surgery. After graft harvesting, composite Y or I grafts were constructed using continuous 8-0 polypropylene sutures. In most cases, the in situ left internal thoracic artery was used for the territory of the left anterior descending artery. A sequential anastomosis technique was used for revascularization in the additional territories. The ascending aorta was not touched in any case.

### 3) Standardized protocol-based perioperative management

**(1) Preoperative management:** In the normal group, computed tomography (CT) was the preferred imaging method for evaluating any abnormalities in the brain, carotid, aorta and arch vessels, iliofemoral arteries, and peripheral vessels. In the CKD group, alternative imaging methods were used. If the eGFR was within 30–60 mL/min/1.73 m<sup>2</sup>, we delayed surgery until kidney function was recovered to baseline, if possible. If the eGFR was  $<30$  mL/min/1.73 m<sup>2</sup>, carotid Doppler ultrasonography and one-stage angiography to evaluate carotid arteries, subclavian arteries, internal thoracic arteries, and iliofemoral vessels during coronary angiography were preferred over contrast CT in order to minimize radiocontrast exposure. All CKD patients were hydrated using potassium-free fluid.

**(2) Intraoperative management:** To maintain optimal hemodynamic performance, every effort was made, especially during manipulation of the beating heart, to keep the target mean blood pressure at a minimum of 65 mm Hg using a potassium-free fluid infusion

**Table 1.** Baseline characteristics of patients in the normal group and the CKD group

Characteristic	Normal group (N=208)	CKD group (N=35)	p-value
Age (yr)	64.0±9.5	66.4±8.2	0.158
Sex (women)	42 (20.2)	15 (42.9)	0.003
New York Heart Association class III or IV	17 (8.2)	6 (17.1)	0.115
Canadian Cardiovascular Society of Angina class III or IV	23 (11.1)	7 (20.0)	0.162
<b>Medical history</b>			
Hypertension	132 (63.5)	26 (74.3)	0.214
Diabetes	107 (51.4)	24 (68.6)	0.060
Smoking	119 (57.2)	15 (42.9)	0.114
Hyperlipidemia	93 (44.7)	17 (48.6)	0.671
Stroke	23 (11.1)	5 (14.3)	0.570
Peripheral vascular disease	21 (10.1)	5 (14.3)	0.383
<b>Cardiac history</b>			
Percutaneous angioplasty	27 (13.0)	2 (5.7)	0.273
Myocardial infarction	15 (7.2)	3 (8.6)	0.730
Atrial fibrillation	6 (2.9)	0	0.597
<b>Diseased coronary vessels</b>			
0.126			
Left main	65 (31.3)	4 (11.4)	0.016
Triple	151 (72.6)	31 (88.6)	0.044
Double	48 (23.1)	4 (11.4)	0.179
Single	9 (4.3)	0	0.635
Left ventricular ejection fraction	53.7 (15.1)	46.5 (16.8)	0.012
Left ventricular ejection fraction ≤35%	40 (19.2)	13 (37.1)	0.018
Serum creatinine concentration (mg/dL)	0.88±0.16	1.58±0.74	<0.001
Estimated glomerular filtration rate (mL/min/1.73 m <sup>2</sup> )	95.9±20.0	44.0±11.6	<0.001

Values are presented as mean±standard deviation or number of patients (%).  
CKD, chronic kidney disease.

with or without inotropes. To optimize oxygen delivery, we used a transfusion of red blood cells to maintain a hematocrit of >30%. We used isotonic crystalloids rather than colloids to manage the expansion of intravascular volume in patients at risk for AKI.

**(3) Postoperative management:** Dehydration was avoided to maintain sufficient kidney blood flow. Rigorous physical examination was performed to detect signs of dehydration, including dehydrated tongue, tachycardia, and decreased urine output. If any signs were present, positive input-output balance was achieved using potassium-free fluid hydration (about 500 mL positive) for the first 3 days after surgery. Fentanyl-based pain medication rather than non-steroidal anti-inflammatory drugs was used. Doses were strictly adjusted based on eGFR, especially when using prophylactic antibiotics. Tight insulin therapy was performed to maintain plasma glucose levels <180 mg/dL.

#### 4) Data collection and statistical analysis

The eGFR and serum creatinine levels were measured preoperatively, on postoperative days (POD) 1, 2, 3, and 5, and prior to discharge. Statistical analyses were performed with IBM SPSS ver. 22.0 software (IBM Co., Armonk, NY, USA). Preoperative characteristics, operative data, and postoperative outcomes were compared between the normal and CKD groups. Categorical variables are expressed as numbers and percentages of patients. Continuous variables are expressed as means±standard deviations. Statistical analysis comparing 2 groups was performed with the independent t-test or the Mann-Whitney U-test for continuous variables. The Pearson chi-square or Fisher exact test was used to compare categorical variables. Univariate and multivariate logistic regression models were used to determine independent risk factors for AKI. All variables with a p-value <0.10 were entered into a subsequent multivariate analysis. On multivariate analysis, variables

that retained a p-value <0.05 were defined as independent risk factors for AKI. A linear mixed model was used to analyze the serial changes in serum creatinine levels and eGFR. A p-value <0.05 was considered statistically significant.

## Results

The baseline characteristics of the 2 groups are shown in Table 1. The CKD group had more female patients (p=0.003) and lower left ventricle ejection fractions (p=0.012) than the normal group. The CKD

**Table 2.** Operative characteristics and postoperative outcomes of patients in the normal group and the CKD group

Characteristic	Normal group	CKD group	p-value
No. of grafts per patient	3.48±0.98	3.46±0.92	0.719
Grafts used			
Bilateral ITAs	198 (95.2)	34 (97.1)	
Bilateral ITAs+right saphenous vein	1 (0.5)	1 (2.9)	
Inotrope use	49 (23.6)	12 (34.3)	0.176
Transfusion	44 (21.2)	15 (42.9)	0.006
New onset atrial fibrillation	17 (8.2)	6 (17.1)	0.115
Wound complications	7 (3.4)	4 (11.4)	0.057
Stroke	5 (2.4)	0	>0.999
Re-exploration for bleeding	2 (1.0)	2 (5.7)	0.100
Perioperative intra-aortic balloon pump	2 (1.0)	1 (2.9)	0.374
Mechanical ventilation (hr)	8.6±6.8	9.4±5.6	0.444
Total intensive care unit stay (day)	1.1±0.6	1.1±0.3	0.752
Postoperative length of stay (day)	9.9±9.0	10.5±10.3	0.106
In-hospital mortality	1 (0.5)	0	>0.999

Values are presented as mean±standard deviation or number of patients (%).

CKD, chronic kidney disease; ITA, internal thoracic artery.

group tended to have more diabetic patients, but this was not statistically significant (p=0.06). The normal group had a higher rate of left main coronary lesions. However, the CKD group had more diffuse coronary lesions presenting as triple vessel disease. In the CKD group, the mean serum creatinine concentration was 1.58±0.74 mg/dL, and the mean eGFR was 44.0±11.6 mL/min/1.73 m<sup>2</sup>.

Operative data and postoperative outcomes are shown in Table 2. The mean number of grafts was similar between the 2 groups (3.48±0.98 in the normal group vs. 3.46±0.92 in the CKD group, p=0.719). Bilateral internal thoracic arteries were used in most patients (normal group, 95.2%; CKD group, 97.1%).

Patients in the CKD group received more transfusions than those in the normal group (p=0.006). There was a slightly higher incidence of wound complications in the CKD group (p=0.057). However, the occurrence of mediastinitis did not significantly differ between the 2 groups. Re-exploration for bleeding, ventilation hours, and postoperative length of hospital stay did not significantly differ between the 2 groups. In-hospital mortality occurred in only 1 patient in the normal group (overall mortality, 0.004%) and in none in the CKD group.

### 1) Risk factors for postoperative acute kidney injury

The overall incidence of AKI after OPCAB is reported in Table 3. Cases of AKI occurred in 34 patients (13.9%). Most of these presented on or before POD 2. Patients in the CKD group were at a ×3 higher risk of developing AKI than those in the normal group (odds ratio [OR], 3.07; 95% confidence interval [CI], 1.31 to 7.16; p=0.01), especially on POD 1 (OR, 5.17; 95% CI, 1.67 to 15.98; p=0.04). However, none of these patients needed RRT.

The risk factors for AKI are represented in Table 4.

**Table 3.** AKI after off-pump coronary artery bypass surgery

Variable	Normal group	Chronic kidney disease group	Odds ratio (95% confidence interval)	p-value
Overall AKI	24 (11.5)	10 (28.6)	3.07 (1.31-7.16)	0.010
POD #1	8 (3.8)	6 (17.1)	5.17 (1.67-15.98)	0.004
POD #2	16 (7.7)	3 (8.6)	1.13 (0.31-4.08)	0.858
POD #3	4 (1.9)	0	-	
POD #5	0	1 (2.9)	-	
Renal replacement therapy	0	0		

Values are presented as number of patients (%).

AKI, acute kidney injury; POD, postoperative days.

**Table 4.** Risk factors for postoperative acute kidney injury after off-pump coronary artery bypass surgery

Variable	Unadjusted		Adjusted	
	OR (95% CI)	p-value	OR (95% CI)	p-value
<b>Normal group</b>				
Chronic kidney disease	3.07 (1.31–7.16)	0.010	0.73 (0.16–3.26)	0.680
Preoperative atrial fibrillation	6.65 (1.28–34.40)	0.024	9.64 (1.77–52.66)	0.009
Preoperative estimated glomerular filtration rate (mL/min/1.73 m <sup>2</sup> )	0.98 (0.97–0.99)	0.002	0.99 (0.97–1.01)	0.412
Preoperative creatinine (mg/dL)	5.71 (1.95–16.74)	0.002	4.65 (0.72–30.21)	0.107
<b>Chronic kidney disease group</b>				
Sex (male)	4.33 (0.76–24.61)	0.098	27.87 (1.76–442.41)	0.018
Age	1.11 (0.99–1.23)	0.052	1.24 (1.04–1.48)	0.014

OR, odds ratio; CI, confidence interval.

**Table 5.** Postoperative serial changes in eGFR

Variable	Estimated marginal means <sup>a)</sup>	Standard error	t	p-value
<b>Chronic kidney disease group</b>				
POD #1	−0.958	2.423	−0.40	0.693
POD #2	−1.366	2.760	−0.49	0.621
POD #3	1.685	2.729	0.62	0.538
POD #5	9.408	2.569	3.66	<0.001
Discharge	10.696	2.332	4.59	<0.001
<b>Normal group</b>				
POD #1	−0.719	0.994	−0.72	0.470
POD #2	−4.242	1.132	−3.75	<0.001
POD #3	−1.077	1.119	−0.96	0.337
POD #5	0.824	1.055	0.78	0.436
Discharge	1.121	0.957	1.17	0.243

eGFR, estimated glomerular filtration rate; POD, postoperative day.

<sup>a)</sup>Differences of eGFR between preoperative values and postoperative values at each time were calculated by estimated marginal means.

Univariate analysis revealed that CKD, atrial fibrillation, preoperative eGFR, and serum creatinine level were risk factors for AKI in all patients. However, in multivariate analysis, CKD was not a risk factor for AKI. Preoperative atrial fibrillation was the only independent risk factor for AKI (OR, 9.64; 95% CI, 1.77 to 52.66;  $p=0.009$ ). In subgroup analysis in the CKD group, male gender and older age were independent risk factors for AKI after OPCAB (OR, 27.87; 95% CI, 1.76 to 442.41;  $p=0.018$ ; and OR, 1.24; 95% CI, 1.04 to 1.48;  $p=0.014$ , respectively). Left ventricle ejection fraction, preoperative eGFR, and serum creatinine level did not affect the occurrence of AKI.

## 2) Serial changes of postoperative renal function

Postoperative serial changes of measured eGFR and serum creatinine levels are shown in Tables 5 and 6.

**(1) Estimated glomerular filtration rate:** In the CKD group, eGFR decreased until POD 2. After POD 3, eGFR was slightly increased, and further increased significantly compared to preoperative values until prior to discharge, indicating recovery of renal function ( $p<0.001$ ). The normal group also showed similar recovery patterns with respect to renal function. However, the worst eGFRs compared to preoperative values were recorded on POD 2, and these differences were statistically significant ( $p<0.001$ ).

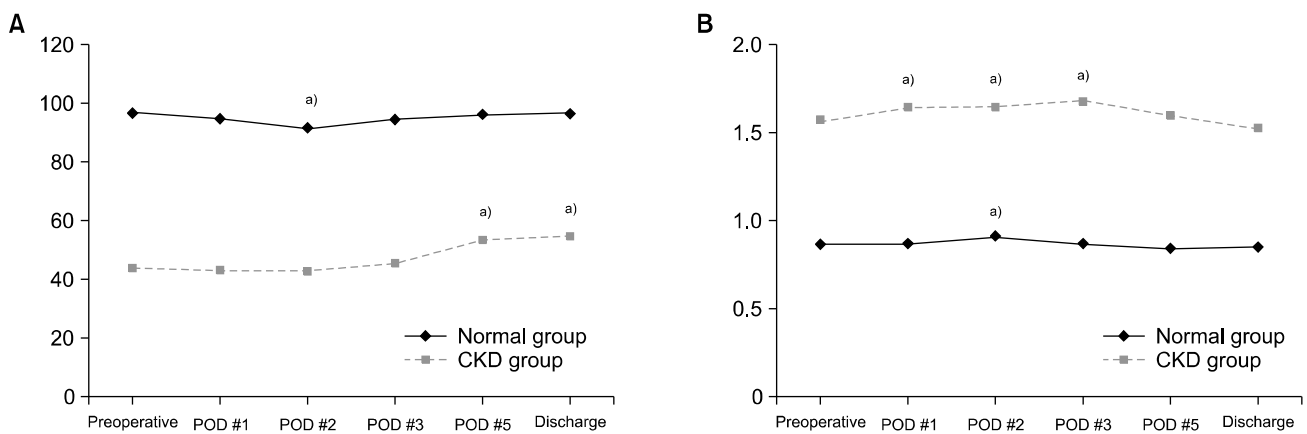
**(2) Serum creatinine levels:** In the CKD group, serum creatinine levels were elevated until POD 3 and decreased after POD 5 until discharge, but statistically significant differences compared to preoperative values were noted from POD 1 to 3 ( $p<0.05$ ). In the normal group, serum creatinine levels were elevated until POD 2, and decreased until prior to discharge.

**Table 6.** Postoperative serial changes in serum creatinine levels

Variable	Estimated marginal means <sup>a)</sup>	Standard error	t	p-value
<b>Chronic kidney disease group</b>				
POD #1	0.070	0.034	2.02	0.044
POD #2	0.072	0.035	2.03	0.044
POD #3	0.106	0.036	2.97	0.003
POD #5	0.020	0.037	0.54	0.590
Discharge	-0.044	0.031	-1.42	0.157
<b>Normal group</b>				
POD #1	0.002	0.014	0.15	0.884
POD #2	0.044	0.015	3.03	0.003
POD #3	0.004	0.015	0.27	0.788
POD #5	-0.028	0.015	-1.82	0.070
Discharge	-0.021	0.013	-1.64	0.102

POD, postoperative day.

<sup>a)</sup>Differences of serum creatinine levels between preoperative values and postoperative values at each time were calculated by estimated marginal means.



**Fig. 1.** The changes in (A) estimated glomerular filtration rate and (B) serum creatinine levels on different postoperative days. CKD group (dotted line); normal group (solid line). CKD, chronic kidney disease; POD, postoperative day. <sup>a)</sup>Significant difference compared to preoperative values ( $p < 0.05$ ).

The only significant difference compared to preoperative value was on POD 2 ( $p = 0.003$ ). The changes in eGFR and serum creatinine levels after surgery are shown in Fig. 1.

### Discussion

Patients with CKD who require CABG are attracting more interest, and there have been a number of recent advances in surgical techniques and perioperative management. Previous studies have demonstrated that CKD is an independent risk factor for postoperative renal dysfunction, in which poor outcomes trigger a necessity for RRT [3,4,16-18]. Recently, the off-pump

technique has been consistently reported to cause fewer incidences of postoperative AKI compared to the standard on-pump technique [6,7,10,19]. However, a major issue of concern now is how to prevent postoperative AKI and manage those at high risk for AKI in the perioperative period.

Consistent and focused standard care might be more important than individual surgical skill in the drive for improved outcomes. Hence, we conducted protocol-based management in CKD patients who underwent OPCAB based on well-established evidence and current guidelines [14,20]. Our protocol-based perioperative care approach for preventing renal injury requiring RRT can be divided into 3 phases: the

preoperative phase, in which radiocontrast exposure is minimized while carrying out risk evaluation; the intraoperative phase, in which optimal hemodynamic status and oxygen carrying capacity are maintained; and the postoperative phase, in which dehydration is prevented, omitting nephrotoxic drugs, and sufficient kidney blood flow is maintained to prevent pre-renal and renal AKI. The question at hand is whether, by adopting these protocols, we can successfully reduce the incidence of postoperative AKI and improve clinical outcomes in CKD patients who undergo CABG.

The incidences of AKI in all patients and CKD patients in this study were 13.9% and 28.6%, respectively. Recently published studies reported the overall incidence of postoperative AKI after OPCAB as 17.5%, and as 19.2% in CKD patients, specifically. Postoperative dialysis was required in 1.4% of cases [6]. Other studies reported an incidence of AKI in CKD patients of 12.5%, and a rate of dialysis of 4.3% [19]. Compared to these results, our results suggest a slightly higher incidence of postoperative AKI. However, this finding could be explained by the different definitions of AKI used, and therefore the true incidence of AKI should be compared cautiously for each study. It is worth noting the fact that CKD patients are at higher risk of postoperative AKI after CABG. Our results confirmed that patients in the CKD group were more susceptible to AKI, even after OPCAB, than those in the normal group (OR, 3.07; 95% CI, 1.31 to 7.16;  $p=0.01$ ). However, multivariate analysis failed to elicit CKD itself as an independent predictor of postoperative AKI. This may suggest that perioperative management has a substantial effect on the result.

Another parameter supporting the benefit of protocol-based management is the incidence of postoperative RRT. Our decision of when to start RRT was most often based on clinical features, including volume overload presented with pulmonary edema, and biochemical features—for example, solute imbalances such as uremic complications, azotemia, hyperkalemia, and severe acidosis combined with oliguria or anuria—as recommended by the current guidelines [14]. In our study, no patients needed RRT in either the CKD or normal groups. In the subgroup analysis of CKD patients, independent risk factors for AKI were male gender and older age. In these patients, more intensive perioperative management should be

applied to avoid AKI, since these risk factors are not modifiable.

In this study, we investigated the effect of protocol-based management on the recovery of kidney function using serial estimation of eGFR and serum creatinine levels. In CKD patients, eGFR decreased on POD 2, and serum creatinine level increased until POD 3. Recovery of kidney function, indicated by decreased serum creatinine levels and increased eGFR, appeared after POD 5. Sajja et al. [10] also reported the recovery of kidney function after OPCAB and on-pump CABG. However, their data were not sufficient to allow estimation of serial changes in postoperative kidney function, since they estimated eGFR and serum creatinine on POD 1, 5, and 15. Mean length of hospital stay was about 10 days in the present study, and we measured eGFR and serum creatinine levels prior to discharge. This was enough to allow the estimation of serial changes in postoperative kidney function. Consequently, the serial changes of postoperative kidney function showed that protocol-based management seems to be effective in minimizing further deterioration of kidney function even if AKI develops after OPCAB.

This study has several limitations. It was retrospective in design, non-randomized, and from a single institution. Ideally, to determine if these protocol-based perioperative managements are effective, the cohorts of patients with CKD would be divided into 2 groups with applied protocols and with standard management. However, the definition of ‘standard management’ could be quite ambiguous; it does not mean ‘never do anything.’ Several guidelines and articles have already suggested methods for the appropriate management of AKI; thus, standard management could result in protocol-based management. Hence, we adopted these protocol-based perioperative management strategies in patients with non-dialysis-dependent CKD undergoing OPCAB to verify their effects on postoperative kidney function.

Another significant limitation is the small sample size, as only 35 of the total included patients are in the CKD group. As our results indicated, CKD patients were more susceptible to AKI than patients in the normal group. However, protocol-based perioperative management had consistent effects on further deterioration of postoperative kidney function even if AKI developed in CKD patients; thus, all of them

could be saved from the necessity of RRT. This result strengthens the evidence for protocol-based perioperative management, even though our cohort contained a small number of CKD patients. We did not include time intervals in the analysis of the risk factors for AKI between preoperative coronary angiography or contrast CT angiography and surgery. This might affect the development of radiocontrast-induced AKI, and thus represents one possible confounder of true-surgery related AKI.

In conclusion, OPCAB combined with protocol-based perioperative management could mostly prevent further deterioration of postoperative kidney function and reduce the need for RRT.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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