

Prophylactic dialysis improves short-term clinical outcome in patients with non-dialysis-dependent chronic kidney disease undergoing cardiac surgery: a meta-analysis of randomized controlled trials

Xiuping An, Nan Ye, Weijing Bian and Hong Cheng

Background Several studies have reported that prophylactic dialysis can reduce the mortality of non-dialysis-dependent chronic kidney disease (CKD) patients after cardiac surgery. However, the results of complications in these randomized controlled trials (RCTs) were not consistent. We aimed to perform a meta-analysis to systematically evaluate the effect of prophylactic dialysis in these non-dialysis-dependent CKD patients.

Methods We systematically searched Medline, Embase, Cochrane's Library and other online sources for related RCTs. Effects of prophylactic dialysis on the incidence of 30 days' mortality and postoperative complications were analyzed.

Results Four RCTs comprising 395 patients were included, all of them treated by coronary artery bypass grafting. Treatment of preoperative and intraoperative prophylactic dialysis significantly reduced the rate of 30-day all-cause mortality (risk ratio [RR]: 0.27, 95% confidence interval [CI], 0.13–0.58, $P < 0.001$, $I^2 = 0\%$) and the incidence of pulmonary complications (RR: 0.39, 95% CI, 0.20–0.77, $P = 0.007$, $I^2 = 0\%$), low cardiac output (RR: 0.29, 95% CI, 0.09–0.99, $P = 0.05$, $I^2 = 0\%$), and acute kidney injury (RR: 0.19, 95% CI: 0.07–0.52, $P = 0.001$,

$I^2 = 0\%$). However, there were no statistically significant differences between the dialysis group and the control group in gastrointestinal bleeding, sepsis or multiple organ failure, wound infection, arrhythmia, transient neurologic deficit, stroke and re-exploration for bleeding.

Conclusion Prophylactic dialysis can improve the 30-day clinical outcomes of non-dialysis-dependent CKD patients undergoing cardiac surgery, it was associated with the 30-day mortality benefit and led to a decrease in the incidence of pulmonary complications, as well as low cardiac output, and acute kidney injury. *Coron Artery Dis* 33: e73–e79 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Patients with chronic kidney disease not only have traditional risk factors for cardiovascular disease (CVD) such as hypertension, diabetes mellitus but also have uremia-specific risk factors such as renal dysfunction, anemia and hyperparathyroidism [1]. Two important features of CVD in chronic kidney disease (CKD) include increased calcific density of atherosclerotic plaques and coronary artery calcification [2]. As a result, they are at increased risks of coronary heart disease [3], all-cause mortality of them are significantly higher than that of patients with normal renal function [4], and CVD is the most important contributor to morbidity and mortality in patients with CKD or end-stage renal disease [2,5,6].

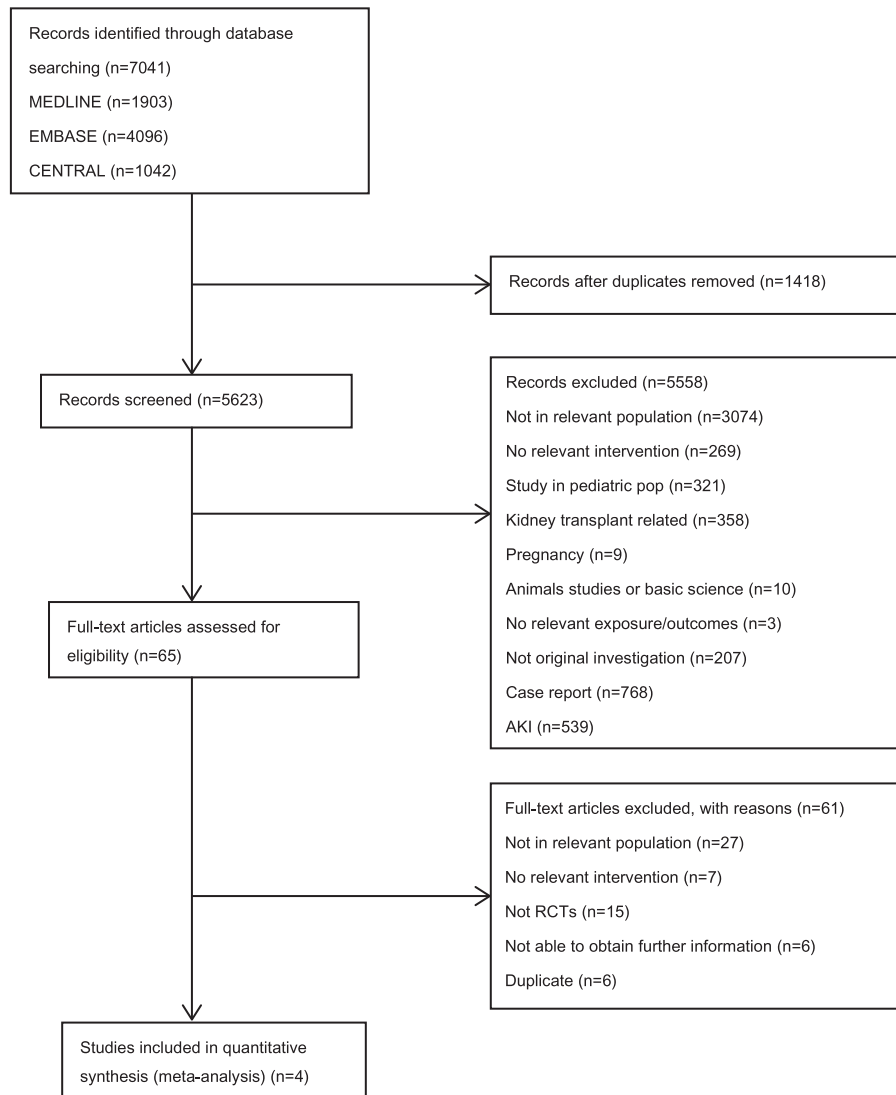
Cardiac surgery, including coronary artery bypass grafting (CABG), heart valve surgery, aortic surgery, etc, are

generally applied for the treatment of CVD in patients with CKD in recent years, and these techniques are relatively mature [7]. Some studies even demonstrate that CABG may be preferred over PCI in individuals with CKD, despite lacking sufficient evidence [8–10]. As a result, an increasing number of CKD patients receiving cardiac surgery. Numerous studies have shown that preoperative renal insufficiency is closely related to in-hospital death and long-term dialysis after cardiac surgery [11–14], so it is vitally important to take early preventive measures.

Measures to improve the clinical outcomes in CKD patients undergoing cardiac surgery include hydration [15], infusions of low dose dopamine [16], maintenance of high perfusion pressure during cardiopulmonary bypass (CPB) [17] and close monitoring of liquid electrolyte balance during the perioperative period. However, the prognosis of patients with CKD is still not satisfactory through the preventive measures mentioned above. Studies have confirmed that early aggressive use of postoperative continuous venovenous hemofiltration (CVVH) can reduce

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Fig 1



Preferred reporting items for systematic reviews and meta-analyses flowchart showing the search strategy.

the mortality of CAD in CKD patients [18], but the cost of using CVVH is high, and it is also related to the longer time of ICU. It has also been confirmed by some studies that prophylactic dialysis can protect postoperative renal function, but the sample size of each study is small, and some conclusions are inconsistent. Therefore, we aimed to perform an updated meta-analysis of all the published randomized controlled trials to evaluate the effect of prophylactic dialysis on the prognosis of non-dialysis-independent CKD patients treated with cardiac surgery.

Methods

Medline, Embase and the Cochrane Library (Cochrane Center Register of Controlled Trials) databases were systematically searched for relevant randomized controlled

trials (RCTs). Besides, the references of the original articles and reviews were also screened as a complementary process. The date of the final database search was 12 July 2020.

Inclusion criteria

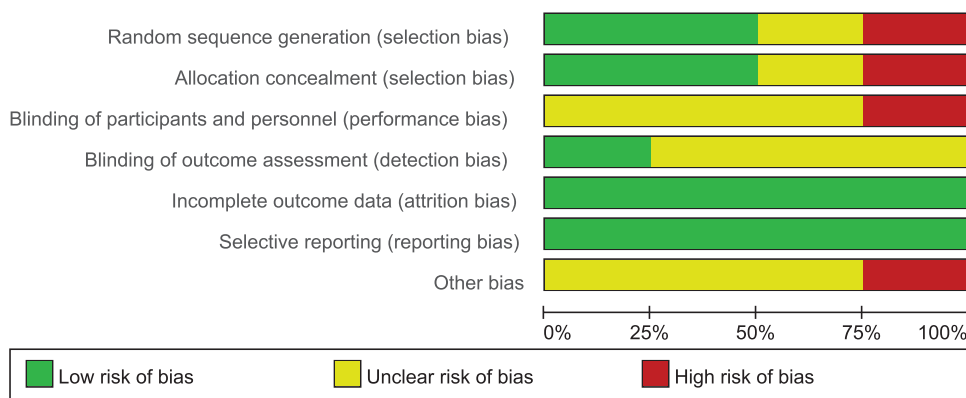
(1) Designed as RCTs to evaluate the effect of prophylactic dialysis on the prognosis of non-dialysis-independent CKD patients (serum creatinine ≥ 2 mg/dl or estimated glomerular filtration rate [eGFR] ≤ 60 ml/min/1.73m²) treated with cardiac surgery including coronary artery surgery, heart valve surgery, open-heart surgery, aortic surgery, arterial switch operation, heart aneurysmectomy, heart transplantation and so on. (2) Pre- or intraoperative prophylactic dialysis was performed in the dialysis group, while the control group only received emergency dialysis because

Table 1 Study characteristics

Study	Country	Years	Type	Intervention	Time of intervention	Group	Simple	Age(mean/medium, years)	Male (%)	DM (%)	HBP (%)	smoking (%)	Hyperlipidemia (%)	Mean LVEF (%)	SCr (mg/dL)
Matata <i>et al.</i> [21]	United Kingdom	2015	RCT	Hemodialysis	during operation	Dialysis	97	76 (54, 87)	58.8	31.9	68.4	61.9	70.1	NR	1.29
						Control	102	73 (50, 86)	59.8	32.4	67	44.1	74.5	NR	1.34
Durmaz <i>et al.</i> [19]	Turkey	2003	RCT	Hemodialysis	preoperation	Dialysis	21	58.1 ± 11.8	76.2	66.7	76.2	61.9	52.4	44.1	3.46
						Control	23	54.3 ± 11.1	82.6	56.5	65.2	65.2	52.2	46.95	3.25
Bingol <i>et al.</i> [20]	Turkey	2007	RCT	Hemodialysis	preoperation	Dialysis	31	76.1 ± 5.4	74.2	61.2	64.5	83.8	70.9	41.1	2.9
						Control	33	77.6 ± 7.3	66.7	66.6	69.6	78.7	78.7	44.6	2.7
Borji <i>et al.</i> [22]	Iran	2017	RCT	Hemodialysis	preoperation	Dialysis	39	66.1 ± 7.8	82.1	64.1	76.9	38.5	76.9	41.4	2.3
						Control	49	63.5 ± 10.3	79.6	63.3	89.8	26.5	63.3	43.7	2.2

DM, diabetes mellitus; HBP, high blood pressure; LVEF, left ventricular ejection fraction; NR, not report; RCT, randomized controlled trial; SCr, serum creatinine.

Fig 2



Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

of postoperative acute kidney injury (AKI) or other complications. Dialytic modalities including hemodialysis, high-flux hemodialysis, hemodiafiltration, hemofiltration, plasma exchange, continuous blood purification, etc.

Quality assessment and data extraction

Two investigators independently abstracted data from studies meeting inclusion criteria and any disagreements were resolved by a third reviewer. A structured data collection form was used to abstract the baseline characteristics of the study populations and outcomes of interest. The quality of the included trials was assessed using previously published criteria. Extracted data included study design, first author, publication date, sample size, baseline clinical characteristics, intervention measures, time of ICU stay, proportions of patients with complications and 30-day mortality. For quality evaluation of the included RCTs, the seven domains of the Cochrane Risk of Bias Tool were applied, which quantified the included RCTs with the following aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other potential threats to validity.

Outcome measures

The primary outcome was 30-day all-cause mortality. The secondary outcomes included the time of ICU stay and the incidence of postoperative complications.

Statistical analysis

Continuous data was evaluated via weighted mean difference (MD), whereas categorized data was analyzed using risk ratios (RR) with a 95% confidence interval (CI). For the test of heterogeneity, Cochrane's *Q* test was used, which indicated a significant heterogeneity if *P* < 0.10. *I*² statistic, which reflected the percentage of total variation among studies that is caused by heterogeneity rather than chance, was also calculated in the test. If significant heterogeneity was detected, stepwise exclusion of 1 study at a time was used to perform a sensitivity analysis to determine the impact of an individual study on the outcomes. Data analysis was performed using the Review Manager (version 5.4).

Results

Database searching

The flowchart of the literature search is presented in Fig. 1. A total of 5623 studies were identified via initial

Fig 3

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bashir M.2015	+	+	-	+	+	+	?
Hakan 2007	?	?	?	?	+	+	?
Isa 2003	-	-	?	?	+	+	-
Roghayeh 2017	+	+	?	?	+	+	?

Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

database search, and 5558 studies were excluded after reading titles and abstracts because of their irrelevance. Of the remaining 65 studies that underwent full-text review, 61 were further excluded with the reasons listed in Fig. 1. Finally, 4 RCTs [19–22] were included in the meta-analysis with a total of 395 patients (dialysis group, $n = 188$; control group, $n = 207$) (Table 1). All types of cardiac surgery in these studies are CABG, and all types of intervention of which are conventional dialysis. However, the dialytic modality in one study [21] was intraoperative dialysis, while that of the other studies were performed two or three times within 72 h before the operations.

Quality evaluation

The details of quality evaluation in each domain of Cochrane’s Risk of Bias Tool are listed in Figs. 2,3. Overall, the quality of the included RCTs was moderate. Two of the researches reported the generation of random sequences, and the strategies for allocation concealment were reported in them [21,22]. It was impossible to blind surgeons and other clinicians in the operating room from noticing the presence of a dialysis device and blinded to the intervention allocation.

All-cause mortality

4 trials comprising 395 patients reported all-cause mortality data. A total of 8 (4.3%) events occurred among 188 patients in the dialysis group versus 32 (15.5%) events among 207 patients in the control group. On the basis of the fixed-effect model, prophylactic dialysis can significantly reduce the rate of all-cause death within 30 days of non-dialysis-dependent CKD patients treated with cardiac surgery (RR: 0.27, 95% CI, 0.13–0.58, $P < 0.001$, $I^2 = 0\%$; Fig. 4).

Postoperative complications

The benefit of prophylactic dialysis in preventing postoperative complications was observed by comparing with nondialysis CKD patients undergoing cardiac surgery. Results of meta-analysis with a fixed-effect model showed that prophylactic dialysis significantly reduced the incidence of pulmonary complications (RR: 0.39, 95% CI, 0.20–0.77, $P = 0.007$, $I^2 = 0\%$), low cardiac output (RR: 0.29, 95% CI: 0.09–0.99, $P = 0.05$, $I^2 = 0\%$), and AKI (RR: 0.19, 95% CI: 0.07–0.52, $P = 0.001$, $I^2 = 0\%$) (Fig. 4). However, prophylactic dialysis did not result in a statistically significant benefit in preventing gastrointestinal bleeding, sepsis or multiple organ failure, wound infection, arrhythmia, transient neurologic deficit, stroke and re-exploration for bleeding.

ICU stay

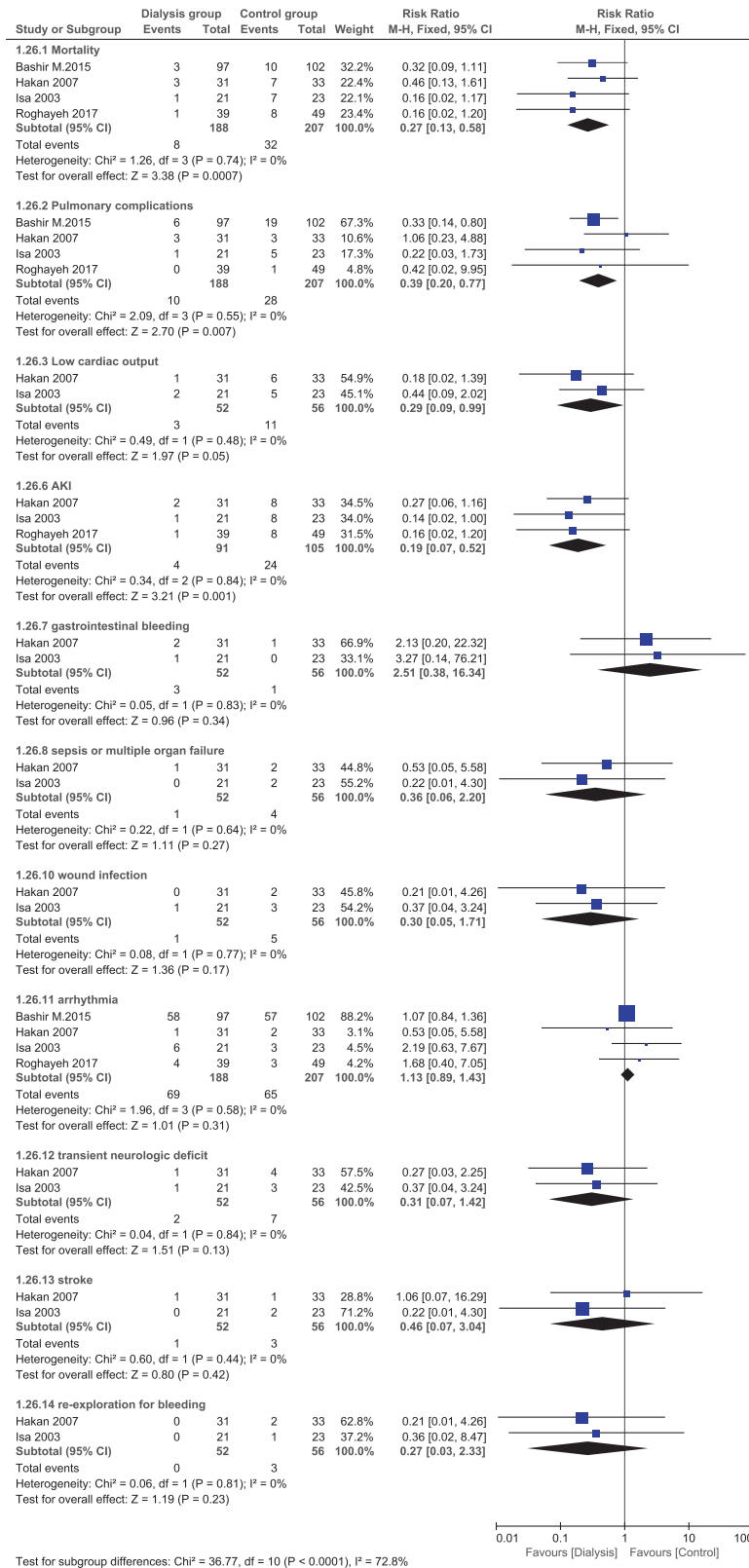
Compared with the control group, prophylactic dialysis decreased the time of ICU stay dramatically (MD: -52.75, 95% CI: -68.80 to -36.71, $P < 0.001$, $I^2 = 0\%$; Fig. 5). Therefore, prophylactic dialysis can significantly shorten the observation time in ICU, which may contribute greatly to reducing the burden of medical treatment.

Discussion

Cardiac and renal function is closely related to each other, CKD patients have a higher risk of cardiovascular disease than the general population. With the improvements in preoperative management and surgical technique of CABG, a large number of CKD patients receive cardiac surgery in recent years. However, the patients with renal insufficiency are more susceptible to cardiopulmonary bypass, thus the mortality and morbidity remain higher in this high-risk group. They are more vulnerable to anesthesia, hemodynamic changes caused by cardiopulmonary bypass and toxic effects of drugs caused by drug accumulation, which obligated us to investigate specific preventive measures that could potentially improve surgical outcomes.

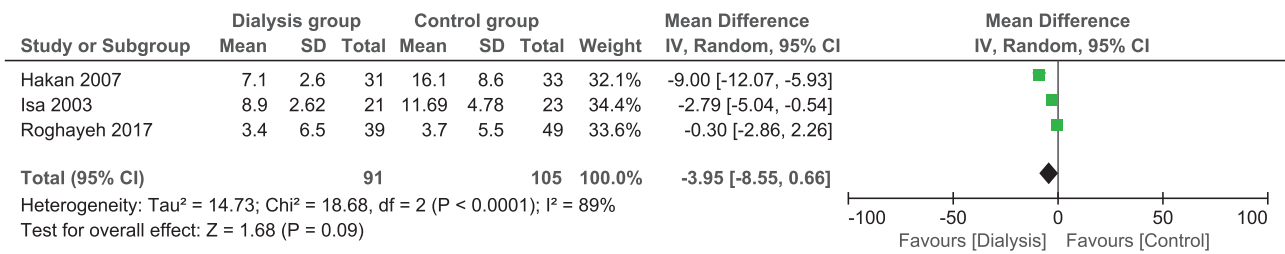
In recent years, there were few studies on prophylactic dialysis in non-dialysis-dependent patients undergoing cardiac surgery, and RCTs were even rarer. Besides, all the relevant RCTs are single-center studies and lack relevant meta-analysis. Four RCTs on non-dialysis-dependent CKD patients were analyzed in this meta-analysis, they are from three centers and of different races. Furthermore, the intervention measures

Fig 4



Forest plot showing outcomes with dialysis group vs. control group.

Fig 5



Forest plot showing ICU stay with dialysis group vs. control group.

were roughly the same, and the heterogeneity of outcomes was small.

Multiple mechanisms are responsible for improving prognosis through prophylactic dialysis. First, hemodialysis, the effective method of attenuating volume overload, safely maintains hemodynamic stability and electrolyte balance [23]. Compared to high-dose diuretics, it can suppress neurohormonal activation and greatly shorten the duration of hospitalization [24]. Besides, hemodialysis could improve ventricular function [19, 22]. As a result, prophylactic dialysis can improve clinical outcomes and decrease adverse events significantly, especially for those with previous renal dysfunction.

In this meta-analysis, we have shown that for non-dialysis-dependent CKD patients, prophylactic dialysis is associated with a mortality benefit, and it was also closely associated with the reduction in the morbidity of postoperative complications including pulmonary complications, low cardiac output and AKI. Several possible reasons may contribute to the reduced incidence of pulmonary complications. First, volume overload, acid-base and electrolyte disorders caused by renal failure are related to the increase of susceptibility to infection in other organ systems. And the accumulation of proinflammatory factors may induce anti-inflammatory responses, so the CKD patients have decreased immunity to infections [25]. As a result, the incidence of severe pulmonary infection is higher in CKD patients than that in the general population. Furthermore, there is a high incidence of delayed extubation because of pulmonary congestion caused by impaired water clearance [19] and delayed anesthetic drug metabolism [19], which may contribute to a higher incidence of pulmonary complications. Dialysis could also favorably affect contractility, the most likely mechanisms include the removal of the uremic toxins, increases of plasma ionized calcium and increase of bicarbonate concentrations [19,22]. In conclusion, prophylactic dialysis can improve clinical outcomes of non-dialysis-dependent CKD patients undergoing cardiac surgery, and the most likely cause is the cardio-renal protection of dialysis. Prophylactic dialysis can also shorten the duration of ICU stay, suggesting that patients

in the dialysis group can recover faster. However, the decision-making process of discharging patients to a lower level of care is also influenced by some objective reasons such as acute shortage of ICU beds and availability or lack of ward beds [21].

There is a marked difference between stage III (eGFR 30–60 ml/min/1.73 m²) and stage IV/V (eGFR <30 ml/min/1.73 m²) CKD patients, for patients with stage IV/V CKD suffering higher risk owing to cardio-cerebrovascular diseases which are associated with a worse outcome [25]. However, all of these 4 RCTs included in this meta-analysis lack the data between stage III and stage IV/V. A retrospective study concluded that intraoperative continuous venovenous hemofiltration might be useful in patients with preoperative renal dysfunction (defined as a GFR of 30–60 mL/min/1.73 m²) [26]. And another retrospective review concluded that non-dialysis renal failure patients, particularly those with higher creatinine concentrations (creatinine clearance of 30 mL or less), may benefit from elective perioperative dialysis in terms of decreased rates of complications and shorter postoperative length of stay [25]. In conclusion, both stage III and stage IV/V CKD patients can benefit from prophylactic dialysis, further studies are needed to figure out the differences between them.

Prophylactic dialysis therapy can reduce the incidence of postoperative AKI in non-dialysis-dependent CKD patients, and may be considered into the clinical practice for these high-risk groups of AKI undergoing cardiac surgery. We have developed a clinical prediction score system for AKI in patients who have undergone cardiac surgery, which can identify the high-risk groups of AKI [27]. A collaborative platform of the department and cardiovascular surgery can be created to make a preliminary assessment of AKI in CKD patients who are prepared to be treated by cardiac surgery, and nephrologists can make prophylactic dialysis strategies and other preventive measures to reduce the risk of postoperative AKI.

Our study has some limitations. First, there were no other types of cardiac surgery except for CABG, but a retrospective study including all types of cardiac surgery in

a single-center also showed that perioperative prophylactic dialysis can reduce the incidence of complications, postoperative hospital stay and in-hospital mortality of non-dialysis-dependent CKD patients [25]. Therefore, the results of this study are also applicable to other cardiac surgeries. Second, the time and modalities of intervention in these studies are not identical, so the optimal time of dialysis cannot be defined clearly. Thirdly, the studies included in this meta-analysis lack adequate follow-up, so the long-term prognosis of prophylactic dialysis on CABG in non-dialysis-dependent CKD patients is still unclear. Last but not least, individual patient data were not available to us, so we were limited by the use of available summary data from published studies. Patients had variable backgrounds and pharmacological therapies, which had the potential to confound our results. Finally, both the number and sample size of the included studies were small, and these results were not based on high-quality evidence from RCTs. However, there was no heterogeneity presented in the majority of our reported outcomes, suggesting consistency in the results of the included trials. This conclusion should be revalidated in future high-quality RCTs.

Conclusion

To sum up, this meta-analysis showed that prophylactic dialysis can improve the short-term prognosis in non-dialysis-dependent CKD patients receiving cardiac surgery. In other words, preoperative or intraoperative dialysis was associated with all-cause mortality benefit and led to a decrease in the incidence of pulmonary complications, as well as low cardiac output, and AKI. Treatment with prophylactic dialysis before or during cardiac surgery should be recommended in clinics.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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