

# Rationale and Strategies for Preserving Residual Kidney Function in Dialysis Patients

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## Keywords

Urine volume · Renal Kt/V · Glomerular filtration rate ·  
End-stage renal disease · Incremental dialysis

## Abstract

**Background:** Residual kidney function (RKF) conveys a survival benefit among dialysis patients, but the mechanism remains unclear. Improved volume control, clearance of protein-bound and middle molecules, reduced inflammation and preserved erythropoietin and vitamin D production are among the proposed mechanisms. Preservation of RKF requires techniques to measure it accurately to be able to uncover factors that accelerate its loss and interventions that preserve it and ultimately to individualize therapy. The average of renal creatinine and urea clearance provides a superior estimate of RKF in dialysis patients, when compared with daily urine volume. However, both involve the difficult task of obtaining an accurate 24-h urine sample. **Summary:** In this article, we first review the definition and measurement of RKF, including newly proposed markers such as serum levels of beta2-microglobulin, cystatin C and beta-trace protein. We then discuss the predictors of RKF loss in new dialysis patients. We review several strategies to preserve RKF such as renin-angiotensin-aldosterone system blockade, in-

cremental dialysis, use of biocompatible membranes and ultrapure dialysate in hemodialysis (HD) patients, and use of biocompatible solutions in peritoneal dialysis (PD) patients. Despite their generally adverse effects on renal function, aminoglycoside antibiotics have not been shown to have adverse effects on RKF in well-hydrated patients with end-stage renal disease (ESRD). Presently, the roles of better blood pressure control, diuretic usage, diet, and dialysis modality on RKF remain to be clearly established. **Key Messages:** RKF is an important and favorable prognostic indicator of reduced morbidity, mortality, and higher quality of life in both PD and HD patients. Further investigation is warranted to uncover factors that protect or impair RKF. This should lead to improved quality of life and prolonged lifespan in patients with ESRD and cost-reduction through patient centeredness, individualized therapy, and precision medicine approaches.

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## Introduction

### Background

The number of people receiving peritoneal dialysis (PD) and hemodialysis (HD) and the annual cost con-

tinue to increase each year [1]. The adjusted mortality rate for dialysis patients in the United States in 2016 remains high at 164 per 1,000 patient-years, but the causes are not clear. Trials to decrease cardiovascular (CV) morbidity or mortality have been disappointing. No significant benefit was reported with higher HD dose or membrane flux on a 3 times a week basis in the HEMO trial [2], with the calcimimetic agent cinacalcet in the EVOLVE trial [3] or with 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors in several trials despite the consistent positive effects seen in the general population and in patients with chronic kidney disease (CKD) not requiring dialysis [4–6]. Furthermore, the normalization of the hemoglobin through recombinant human erythropoietin therapy resulted in higher mortality, CV events, and vascular access thrombosis [7]; a recent meta-analysis suggested that partial correction as opposed to normalization of hemoglobin had neither adverse effects nor positive benefits, except for a tendency toward less fistula thrombosis [8]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) have shown some benefit in reducing mortality independent of attained blood pressure in HD and PD patients [9, 10]. A small sample meta-analysis identified mineralocorticoid receptor antagonists as a potential benefit to reduce CV mortality for dialysis patients [11].

#### *Clinical Importance*

Clinical trials have shown residual kidney function (RKF) to be an important and favorable prognostic indicator of reduced morbidity, mortality, and higher quality of life in both PD and HD [12–14]. Three trials in end-stage renal disease (ESRD) patients including the Canada-United States PD study group trial, the Netherlands Cooperative Study on the Adequacy of Dialysis, and a large cohort trial have addressed the importance of RKF [13–15]. The survival benefit was attributed to renal clearance rather than dialysis clearance [14]. The benefits of RKF have been related to greater volume removal, protein-bound solute clearance, middle molecule clearance, and reduced inflammation [12, 14, 16].

Current data have confirmed the favorable clinical effect of RKF but have not clearly established the underlying mechanisms. In the United States, the RKF in PD is monitored every 3 months to calculate Kt/V. Unfortunately, the importance of RKF is still not well appreciated in HD, in part because the ESRD Quality Incentive Program does not accept Kt/V adjustment for RKF, despite Kidney Disease Outcomes Quality Initia-

tive guideline suggesting that  $Kt/V_{\text{urea}}$  targets can be reduced for patients with a residual renal urea clearance  $>2$  mL/min/1.73 m<sup>2</sup> [17]. Therefore, clinical trials that investigate how best to maintain RKF are important. Moreover, RKF should be considered a functional endpoint or covariate in outcome trials of patients with ESRD.

#### *Definition*

There is no uniform definition of RKF. According to 2018 United States Renal Data System Report, the mean estimated glomerular filtration rate (GFR) at initiation of dialysis in 2016 was 9.7 mL/min/1.73 m<sup>2</sup>, down from a peak of 10.4 in 2010 [1]. Anephric was defined as GFR  $<1$  mL/min/1.73 m<sup>2</sup> in the ADEquacy of PD in MEXico study [12] but as a urine volume  $<100$  mL/day or creatinine clearance  $<1.0$  mL/min in another [18]. In agreement with current clinical practice guidelines, any urine volume  $>100$  mL or estimated GFR  $\geq 1$  mL/min/1.73 m<sup>2</sup> are valuable and should not be ignored [19–21].

#### *Measurement of RKF*

For both PD and HD patients, the guidelines advocate measuring RKF by calculating the mean of the 24-h creatinine clearance and urea clearance, but many confounding influences remain. Thus, the clearance of inulin, iohexol, ethylenediaminetetraacetic acid, and iothalamate are deemed superior methods to quantitate GFR, but they are not suitable for clinical practice. Currently, many practitioners measure 24-h urine volume to assess RKF, but this has wide variability. Thus, alternative methods of estimating RKF based on single serum samples have been studied. Efforts are made to quantify RKF without the need for 24-h urine collection. Ideal markers of RKF should be filtered by the glomerulus and not secreted by the tubules and cleared into the urine without the complication of clearance through HD or PD membranes. There are recent reports that the serum concentrations of middle molecular weight proteins, such as beta2-microglobulin (B2M), cystatin C and beta-trace protein (BTP) are highly correlated with measured GFR and have been proposed as new GFR markers [22, 23] but some are cleared from the circulation by HD or PD (Table 1).

B2M is filtered by the glomerulus and not secreted by the tubules [24]. Its use is confounded by increased levels in patients with several malignancies and infectious diseases. Cystatin C is freely filtered by the glom-

**Table 1.** RKF study equations for estimating  $C_{Urea}$  and  $C_{Urea, Cr}$  validated in the NECOSAD external cohort [25]

Endogenous filtration marker	$C_{Urea}$ , mL/min	$C_{Urea, Cr}$ , mL/min/1.73 m <sup>2</sup>
Urea, Cr, mg/dL	$1.1 \times UN^{0.949} \times Cr^{-1.544}$	$2.4 \times UN^{0.984} \times Cr^{-1.868}$
BTP	$69 \times BTP^{-2.114} \times 1.677$ if male	$95 \times BTP^{-2.16} \times 1.652$ if male
B2M	$1711 \times B2M^{-2.328} \times 1.610$ if male	$2,852 \times B2M^{-2.417} \times 1.592$ if male
Cystatin C	$64 \times cystatin\ C^{-2.211}$	$123 \times cystatin\ C^{-2.468}$
BTP, B2M	$385 \times BTP^{-1.450} \times B2M^{-0.965} \times 1.694$ if male	$673 \times BTP^{-1.406} \times B2M^{-1.096} \times 1.670$ if male

RKF, residual kidney function;  $C_{Urea}$ , urinary urea clearance (mL/min);  $C_{Urea, Cr}$ , average of urinary urea and creatinine clearance (mL/min/1.73 m<sup>2</sup>); NECOSAD, Netherlands Cooperative Study on the Adequacy of Dialysis; Cr, serum creatinine; UN, serum urea nitrogen; BTP, Beta-trace protein; B2M, Beta2-microglobulin.

erulus without tubular secretion [24]. Some studies suggest its levels can be increased by steroids and inflammation, and may be affected by age, female sex, greater weight, diabetes mellitus and thyroid hormone levels [25, 26]. BTP is a glycoprotein enzyme involved in prostaglandin metabolism. It is filtered by the glomerulus with minimal secretion. BTP levels are decreased by corticosteroids and are increased by inflammation but are not affected by body composition or thyroid function [27].

B2M and Cystatin C are not effectively cleared by low-flux HD or by PD, but they are cleared by high-flux HD and hemodiafiltration. Although it is not removed by conventional low or high-flux HD, BTP is removed by hemodiafiltration and super high-flux HD [28, 29]. Consequently, compared to B2M or cystatin C, levels of BTP are more stable and less influenced by dialysis [24]. Serum BTP may be the most reliable marker for assessing RKF and recently a commercial assay has been launched but presently is available only in Europe [24] (Table 2).

The inadequacies of existing markers have led to a search for improved methods. The C-terminal fragment of agrin, p-cresyl sulfate (PCS), and indoxyl sulfate (IndS) have also been investigated as novel markers for RKF in PD and HD [30, 31]. C-terminal fragment of agrin is a major heparan sulfate proteoglycan of the glomerular basement membrane. Its serum concentrations are not influenced by new high-flux membranes but some is removed by Elisio19H dialyzers [30].

PCS and IndS are protein-bound uremic solutes [31] that are cleared by tubular secretion but not effectively removed by dialysis. The renal clearances of

IndS and PCS showed strong positive correlation with the renal clearances of urea and creatinine in PD patients [32].

The concept that RKF should be defined by clearance of unreabsorbed glomerular filtrate markers such as creatinine, Cystatin C, or BTP fails to recognize the importance of residual tubular secretion of organic anions by the organic anion transporter (OAT) pathways [24]. There is an emerging shift in emphasis from the exclusive “glomerulocentric” view of RKF to a concept that RKF is best described by combined glomerular and tubular functions [33]. Creatinine is secreted into the proximal tubule by the OAT 2 [34] and by the electrogenic organic cation transporter 2 that is expressed on the basolateral membrane of proximal tubule cells [35]. Various xenobiotics and drugs can compete for transport with creatinine by these transporters, and thereby alter creatinine clearance; for example, many of the drugs used to treat patients with HIV [36], but their effect on RKF has not yet been studied.

Many unfiltered organic anions are protein-bound and secreted by renal tubular OATs. Since the relative contribution of renal tubular secretion to overall clearance increases as GFR declines, the input of OATs should be incorporated into the measurement of RKF. A combined evaluation of both glomerular and tubular function may be achieved by assessing creatinine and hippurate clearance [33]. If this concept is validated, drugs such as penicillin, cephalothin, and thiazide derivatives as well as certain dietary substances that compete for OAT secretion should be limited in dialysis patients [33], since reducing competition for OAT transport may facilitate excretion of uremic toxins.

**Table 2.** Proposed GFR markers for estimation of RKF in dialysis patients

Endogenous filtration marker	Molecular weight, Da	Tubular secretion	Low-flux HD clearance	High-flux HD clearance	Super high-flux HD clearance	HDF clearance	PD clearance	Confounders
B2M	11,600	No	No	Yes 62±8%	Yes	Yes	No	↑By inflammation ↑By some malignancies
Cystatin C	13,300	No	No	Yes 73±9%	Yes	Yes	No	↑By inflammation ↑By steroids Affected by age, female sex, greater weight, diabetes mellitus, thyroid hormone levels
BTP	23,000–29,000*	Minimal	No	Minimal 26±19%	Yes	Yes	No	↑By inflammation ↓By steroids

\* Depends on the glycosylation of the molecule.

GFR, glomerular filtration rate; RKF, residual kidney function; HD, hemodialysis; HDF, hemodiafiltration; PD, peritoneal dialysis; B2M, beta2-microglobulin; BTP, beta-trace protein.

### Predictors of Loss of RKF among Incident Dialysis Patients

Patients treated by PD were reported to have a 65% lower risk of loss of RKF than those treated with HD. This was attributed to better hemodynamic stability [37]. Female sex, non-white race, prior history of diabetes, or congestive heart failure and time to follow-up were shown to be independent predictors of loss of RKF. HD patients were reported to have a better preservation of RKF in patients with higher post-dialysis mean arterial pressure (MAP), higher pre-dialysis serum calcium, and usage of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (Table 3). Female sex was associated with a greater rate of RKF loss among PD patients, which was independent of body mass index, MAP, albumin, estrogen use, or menopausal status [38].

### Prevention of Loss of RKF

#### Renin-Angiotensin-Aldosterone System Blockade

The effect of ACE inhibitors and ARB in slowing the progression of CKD and in reducing proteinuria in non-dialysis CKD patients is well established. The protection by ACE inhibitors appears to be in addition to blood pressure control [38, 39].

A recent meta-analysis of 6 open-label studies in 257 patients treated with continuous ambulatory PD (CAPD) reported that, compared with other antihyper-

**Table 3.** Predictors of loss of RKF among incident dialysis patients

Effects on RKF	Factors
Deleterious	Female sex Non-white race Prior history of diabetes mellitus Prior history of congestive heart failure Time to follow-up
Beneficial	PD modality Higher post-dialysis MAP (in HD patients) Higher pre-dialysis serum calcium (in HD patients) Use of ACE inhibitor (in PD patients) Use of calcium channel blocker (in PD patients) Use of HMG CoA reductase inhibitor (in HD patients)

RKF, residual kidney function; PD, peritoneal dialysis; MAP, mean arterial pressure; HD, hemodialysis; ACE, angiotensin-converting enzyme; HMG CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A.

tensive drugs, the long-term use (>12 months) of ACE inhibitors and ARB had additional and similar benefits in preserving RKF, but no effect on reducing proteinuria [40].

Loss of RKF generally occurs faster in HD than PD patients. There has been only limited data on the effect of ACE inhibitors or ARBs in HD patients. A 1-year open-



label study of 42 HD patients reported that enalapril was associated with greater preservation of RKF [41], while another study in HD patients reported that irbesartan was not associated with the same benefit [42]. Thus, presently it is prudent to use an ACE inhibitor or perhaps an ARB for dialysis patients requiring antihypertensive treatment.

#### *Diuretics and Volume Control*

Diuretics are often used to prevent excessive volume overload in dialysis patients. Recent studies have reported that within 3 months of starting HD, patients who had evidence of fluid overload had a 26% excess risk for mortality [43]. Meanwhile, aggressive ultrafiltration in HD patients is a risk factor for loss of RKF [44]. Increasing use of whole body bio-impedance spectroscopy to assess volume status may provide more precise data [45], but this is not yet approved for use by the United States Food and Drug Administration.

The data on the effects of diuretics on RKF are not consistent. Two large studies of CAPD patients from China reported that use of diuretics was associated with a more rapid decline in RKF [46, 47]. However, the Dialysis Outcomes and Practice Patterns Study cohort of 16,420 HD patients reported that those receiving diuretics were more likely to avoid large intradialytic weight gains and had a 14% reduced cardiac-specific mortality risk and a decreased risk of hyperkalemia [48]. Patients receiving diuretics were twice as likely to retain urine volume after 1 year in this study [48]. In the long term, the beneficial effect of diuretics diminishes because progression of the underlying renal disease decreases the tubular response [49].

The use of diuretics in patients treated by PD can improve volume status and minimize the need for higher glucose-containing solution. Meanwhile, a prospective trial of CAPD patients randomized to daily furosemide (250 mg/day) found a significantly better preservation of urine volume over 12 months, but no beneficial effects on urea and creatinine clearance [47, 50]. Acute high dose of furosemide (2 g) over 24 h is effective in increasing urine volume and electrolyte excretion in CAPD patient but with no effect on urea and creatinine clearance [51]. Thus, prudent use of loop diuretics in both HD and PD patients may lessen the adverse effects associated with hypervolemia and may increase urine output, but long-term effects on RKF are unclear.

A recent novel approach has been to use tolvaptan to increase urine flow. Tolvaptan is currently approved for the treatment of hyponatremia secondary to

syndrome of inappropriate antidiuretic hormone and heart failure as well as autosomal dominant polycystic kidney disease. It may emerge as a possible agent for preserving RKF through volume control. One study of PD patients reported that tolvaptan (15 mg/day) given for 2 weeks increased urine volume while maintaining renal Kt/V, renal creatinine clearance, and B2M level, and decreasing C-reactive protein [52]. This finding was limited by small sample size (total 24 PD patients) and very short duration and is yet to be validated by other studies.

#### *Blood Pressure Control*

Both hypotension and hypertension are risk factors for decline of RKF in dialysis patients [44]. The effect of blood pressure control on RKF can be confounded by the occurrence of acute kidney injury during episodes of hypotension, especially intradialytic hypotension. Both intradialytic hypotension in HD and hypovolemia episodes in PD were associated with poor residual GFR in the first 3 months of dialysis [44]. This suggested that intravascular volume depletion is an important determinant for the decline in residual GFR [44]. At the same time, a MAP >110 mm Hg in PD patients was associated with a faster decline of residual GFR, which might be explained by volume overload, since the MAP was correlated with atrial natriuretic peptide levels [53]. However, a study evaluating systolic blood pressure as a time-varying covariate using longitudinal data reported that slightly higher systolic blood pressure values were associated with better preservation of RKF and residual urine volume [54]. Presently, BP goals in dialysis patients are not clearly established. The effects of BP on RKF are not clear but care is needed to avoid excessive swings and prolonged hypotension or hypertension.

#### *Peritonitis and Use of Aminoglycosides*

The number of peritonitis episodes in patients treated with PD was reported to be an independent predictor for the development of anuria [47]. Each episode of peritonitis was associated with a 3.8% increased risk of anuria [47]. This might be explained by the hypotension and relative hypovolemia caused by peritonitis [55].

Aminoglycosides are used widely to treat PD-associated peritonitis because of their low cost, excellent coverage of gram-negative organisms and synergy benefit in severe cases caused by gram-positive organisms. In a large Australian observational cohort of 2,715 PD

patients, treatment with aminoglycosides did not reduce RKF [56]. Short courses of aminoglycosides probably do not accelerate the loss of residual renal function.

#### *PD Modality and Glucose Exposure*

The effects of CAPD and automated PD (APD) on RKF and technique survival are controversial. One study reported a higher risk of loss of RKF in the first year of APD compared with CAPD [57], but this may be influenced by selection bias, since older and sicker patients were treated with APD.

Patients treated with APD are generally exposed to higher glucose dialysates compared with CAPD, and glucose exposure has been associated with faster loss of RKF and anuria [58]. Thus, for every 10 g/day higher glucose exposure, there was a 2.5% increase in the risk of anuria [47]. Larger randomized trials are needed to understand the effects on RKF of CAPD versus APD.

#### *Biocompatible PD Solution*

A high level of glucose degradation products (GDP) was associated with increased serum levels of advanced glycation end products and progressive renal injury. A new biocompatible peritoneal fluid with a neutral pH and reduced GDP dialysate was reported to better preserve renal creatinine clearance and urine volume than conventional PD solution [59]. The balANZ study reported that the use of biocompatible PD solutions conferred 27% better preservation of residual GFR and 37% better preservation of residual urine volume independent of peritoneal ultrafiltration [54]. This result supported the fact that the guidelines of the International Society for PD that PD solution with neutral pH and lower GDP are preferred in an attempt to preserve RKF [60].

#### *Icodextrin and Incremental PD*

Icodextrin is a glucose polymer osmotic agent used to provide sustained ultrafiltration during dwells for PD. Absorbed icodextrin is metabolized to oligosaccharides [61]. Icodextrin has been reported to reduce fluid overload and improve peritoneal ultrafiltration without compromising RKF or urine volume [62]. Chang et al. [61] confirmed that icodextrin solution attenuated the rate of decline of daily urine volume that they attributed to a maintained atrial natriuretic peptide level and to prevention of inferior vena cava collapse but did not detect any effect on residual GFR. A reanalysis of the Canada-United States PD study group trial showed that for each 5 L/

week/1.73 m<sup>2</sup> increment in GFR, there is a 12% decrease in the relative risk of death but no association with peritoneal creatinine clearance. Furthermore, it was found that for a 250 mL increment in 24-h urine volume, there is a 36% decrease in the relative risk of death and the association of patient survival with GFR disappeared. In other words, residual urine volume was more important than residual GFR in predicting adverse outcomes in patients on PD; this would indicate that icodextrin may be preferable to dextrose PD solutions [14]. Some authors advocate incremental PD by initiating carefully selected patients on a regimen of single daily icodextrin exchange as only dialytic therapy [63]; a randomized prospective study is warranted to evaluate whether this strategy confers a survival benefit.

#### *Biocompatible HD Membranes and Ultrapure Dialysate*

Overall, patients treated with PD have a better preservation of RKF than those treated with HD. This has been attributed to fewer episodes of hypotension and a more biocompatible membrane. Repetitive exposure of blood to dialysis membranes during HD can cause inflammation that could affect RKF adversely. Indeed, compared to HD patients treated with cellulose acetate membrane, those patients with the more biocompatible polysulfone membrane had a slower decline in creatinine clearances and a better-maintained urine volume [64]. A cohort study in the United Kingdom reported that RKF declined at an identical rate in HD patients treated with high-flux biocompatible membranes and in CAPD patients [65]. However, some studies have not replicated this result [66]. In addition to the reduction of inflammatory nephrotoxic mediators by biocompatible membranes, ultrapure dialysate fluid combined with high-flux synthetic membranes is reported to slow the loss of RKF in HD patients [65, 67]. This might be explained by decreased inflammation, since the levels of C-reactive protein and interleukin-6 were lower in the group exposed to ultrapure water. More investigations are needed to validate the benefit of biocompatible membranes.

#### *Incremental HD and Combined Diet and Dialysis Programs*

Incremental dialysis refers to “smooth transition” from CKD to dialysis therapy. When compared to the conventional thrice-weekly schedule, incremental HD in the first 3 months is associated with greater preservation of RKF and urine volume and lower interdialytic

**Table 4.** Incremental (twice-weekly) HD treatment criteria [69]

1. Adequate residual kidney function with urine output >600 mL/day (transition to thrice-weekly if urine output drops to <500 mL/day)
2. Limited fluid retention between 2 consecutive HD treatments with a fluid gain <2.5 kg (or <5% of the ideal dry weight) without HD for 3–4 days
3. Limited or readily manageable cardiovascular or pulmonary symptoms without clinically significant fluid overload
4. Suitable body size relative to residual renal function; patients with larger body size may be suitable for twice-weekly HD if not hypercatabolic
5. Hyperkalemia (K >5.5 mEq/L) infrequent or readily manageable
6. Hyperphosphatemia (P > 5.5 mg/dL) infrequent or readily manageable
7. Good nutritional status without florid hypercatabolic state
8. Lack of profound anemia (hemoglobin >8 g/dL) and appropriate responsiveness to anemia therapy
9. Infrequent hospitalization and easily manageable comorbid conditions
10. Satisfactory health-related quality of life and functional status
11. KRU >3 mL/min/1.73 m<sup>2</sup> (transition to thrice-weekly if KRU <2 mL/min/1.73 m<sup>2</sup>)

HD, hemodialysis; K, serum potassium; P, serum phosphorus; KRU, residual urea clearance.

weight gain independent of other clinically relevant factors [15].

Despite the potential benefits that incremental dialysis brings, an individualized approach is required for patients on this protocol. Kalantar-Zadeh et al. [68] have proposed eleven criteria to screen incident ESRD patients as suitable candidates for incremental HD (Table 4). Two were considered mandatory (urine volume and urea clearance) and 5 additional criteria among the remaining 9 were required.

Recent strategies have been proposed to quantify guidelines for incremental practice. In relatively healthy patients, HD can be started once weekly, while renal urea clearance (Kru) is between 4 and 5 mL/min/1.73 m<sup>2</sup>. This can be increased to twice weekly when Kru is between 2 and 4 mL/min/1.73 m<sup>2</sup> and thrice weekly when Kru falls below 2 mL/min/1.73 m<sup>2</sup> [69].

Meanwhile, Combined Diet and Dialysis Programs combine once weekly HD with a relatively less restrictive low-protein diet (0.6 g/kg/day) compared to the Integrated Dialysis Diet Program (0.3–0.4 g/kg/day). This strategy has been reported to elicit more favorable outcomes including better overall survival and preserved RKF, reduced rate of hospitalization, lower B2M levels, improved phosphorus control and lower doses of erythropoiesis-stimulating agents [70]. As with other incremental dialysis programs, Combined Diet and Dialysis

Programs should be individualized and is suitable only for highly motivated patients who would adhere to the strict diet.

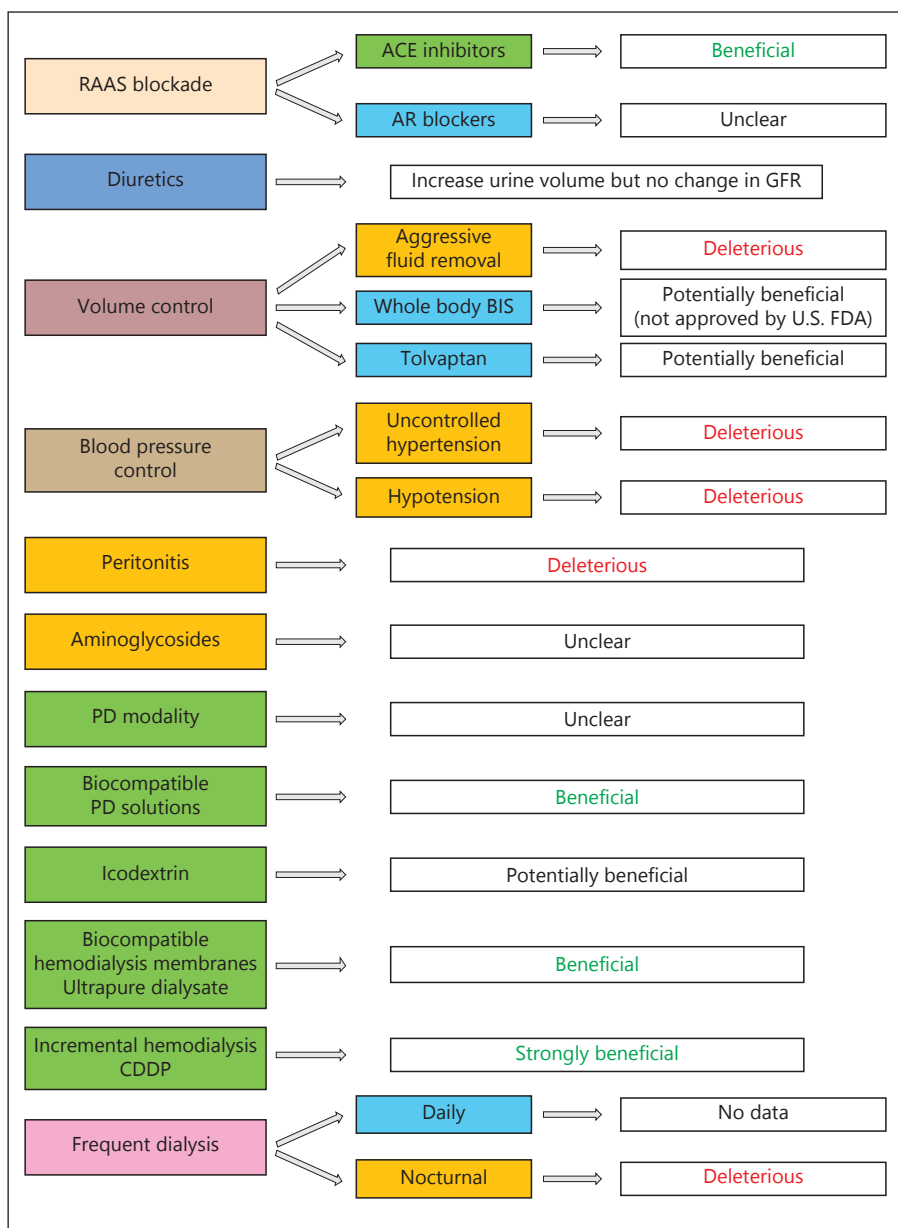
Despite all the promising benefits, larger size, double-blinded, and randomized clinical trials are warranted to validate the long-term safety and implications of this approach to dialysis transition.

#### *Frequent Dialysis*

The Frequent HD Network daily trial showed that frequent HD (6 times per week), as compared with conventional HD (3 times per week), was associated with favorable effects on the composite outcomes of death or change in left ventricular mass and death or change in physical-health composite score [71]. Frequent nocturnal HD appears to promote a more rapid loss of RKF (perhaps due to reduced extracellular volume, blood pressure and osmotic load as well as discontinuation of ACE inhibitors) but whether increased session length or session frequency is to blame remains to be determined [72].

#### **Conclusion**

RKF is an independent prognostic factor predicting morbidity, mortality, and quality of life. In practice, we measure RKF based on 24-h urine volume, but this has



**Fig. 1.** Effects of various factors on RKF. RAAS, renin-angiotensin-aldosterone system; ACE, angiotensin-converting enzyme; AR, angiotensin receptor; GFR, glomerular filtration rate; BIS, bio-impedance spectroscopy; US FDA, United States Food and Drug Administration; PD, peritoneal dialysis; CDDP, combined diet and dialysis program; HD, hemodialysis.

wide variability. Several studies and Kidney Disease Outcomes Quality Initiative guideline define RKF as the composite of 24-h creatinine and urea clearance. Plasma levels of B2M, cystatin C and BTP are promising RKF biomarkers. After acknowledging the contribution of tubular secretion to RKF, a new perspective of combining measurements of glomerular and tubular function to assess RKF has been proposed. Clinical studies have reported that the use of Renin-Angiotensin-Aldosterone System inhibitors, incremental dialysis, biocompatible solutions, and membranes have beneficial effects on RKF but

need to be validated. Proper control and close monitoring of blood pressure and volume status and avoiding intradialytic hypotension episodes may help better preserve RKF and urine volume. Icodextrin and diuretic usage in patients treated by PD are shown to improve urine volume but not change clearance. Surprisingly, aminoglycosides in ESRD patients appear not to worsen RKF. More investigations are needed in this field to validate some of the above proposed agents and mechanisms (Fig. 1). RKF should be a focus in long-term management of both PD and HD patients. RKF should be monitored



regularly in all modalities and dialysis prescriptions should be tailored periodically to the gradual loss of renal clearance.

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### Statement of Ethics

The authors have no ethical conflicts to disclose.

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### Author Contributions

T.L.: wrote and re-edited the manuscript. C.S.W.: planned the review and provided critical review. M.L. and J.G.-C.: critical review. S.D.: drafted the work and revised it critically for important intellectual content.

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