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

Tian Li[a]    Christopher S. Wilcox[b]    Michael S. Lipkowitz[b]

Judit Gordon-Cappitelli[c]    Serban Dragoi[c]

[a]Department of Medicine, State University of New York Downstate Medical Center, Brooklyn, NY, USA;
[b]Division of Nephrology and Hypertension, Georgetown University, Washington, DC, USA;
[c]Division of Nephrology and Hypertension, Georgetown University Hospital, Washington, DC, USA

**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 an 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.

© 2019 S. Karger AG, Basel

## Introduction

*Background*

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

Serban Dragoi, MD, PhD
Division of Nephrology and Hypertension
Georgetown University Hospital, 6-PHC/F-6003A
3800 Reservoir Rd NW, Washington DC 20007 (USA)
E-Mail serban.a.dragoi @ gunet.georgetown.edu

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 $Kt/V_{urea}$ targets can be reduced for patients with a residual renal urea clearance >2 mL/min/1.73 m$^2$ [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$^2$, down from a peak of 10.4 in 2010 [1]. Anephric was defined as GFR <1 mL/min/1.73 m$^2$ 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 ≥1 mL/min/1.73 m$^2$ 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-

Li/Wilcox/Lipkowitz/Gordon-Cappitelli/ Dragoi

**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$^2$ |
|---|---|---|
| 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$^2$); 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<br>↑By some malignancies |
| Cystatin C | 13,300 | No | No | Yes 73±9% | Yes | Yes | No | ↑By inflammation<br>↑By steroids<br>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<br>↓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<br>Non-white race<br>Prior history of diabetes mellitus<br>Prior history of congestive heart failure<br>Time to follow-up |
| Beneficial | PD modality<br>Higher post-dialysis MAP (in HD patients)<br>Higher pre-dialysis serum calcium (in HD patients)<br>Use of ACE inhibitor (in PD patients)<br>Use of calcium channel blocker (in PD patients)<br>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$^2$ 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$^2$ (transition to thrice-weekly if KRU <2 mL/min/1.73 m$^2$) |

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$^2$. This can be increased to twice weekly when Kru is between 2 and 4 mL/min/1.73 m$^2$ and thrice weekly when Kru falls below 2 mL/min/1.73 m$^2$ [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.
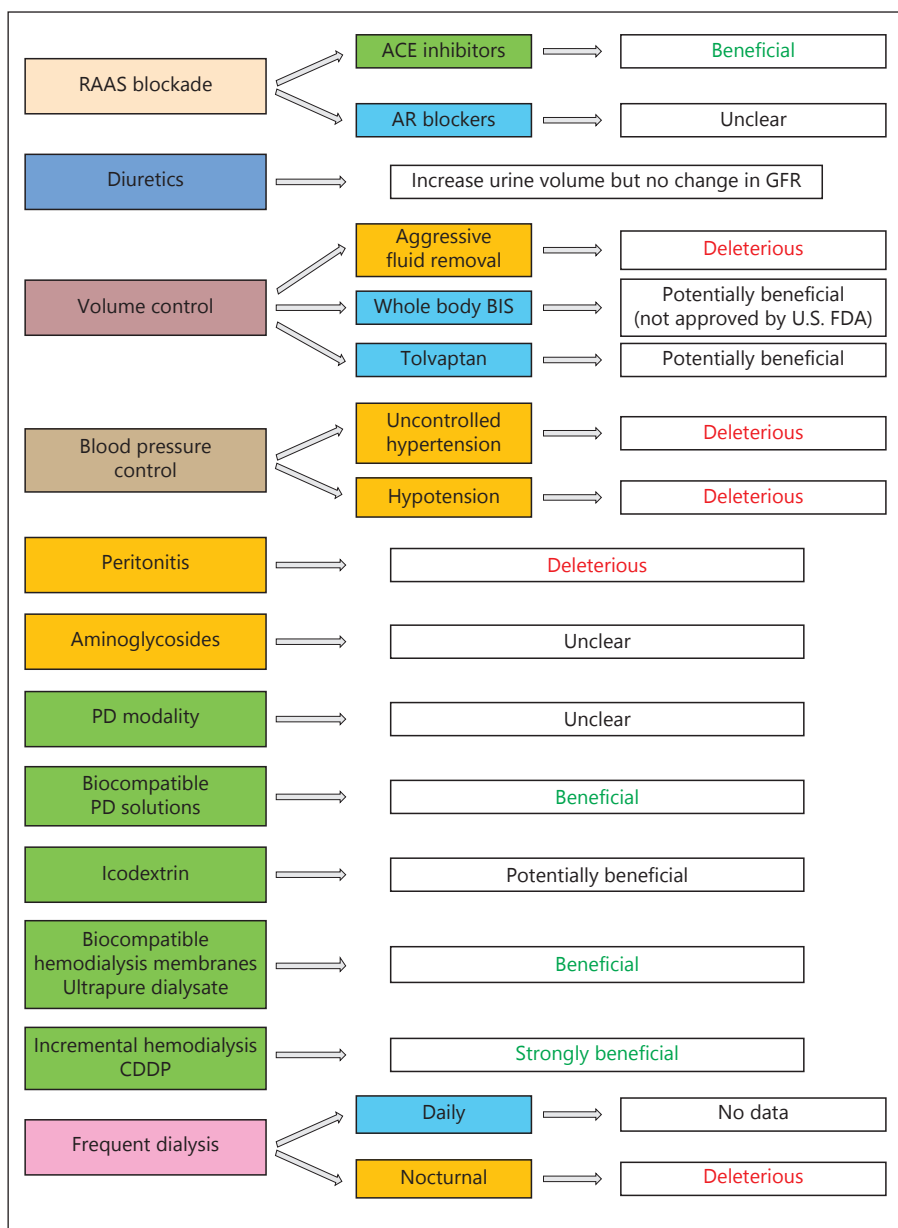
Despite all the promising benefits, larger size, double-blinded, and randomized clinical trials are warranted to validate the long-term safety and implications of this approach to dialysis transition.

*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

RAAS blockade → ACE inhibitors → Beneficial

RAAS blockade → AR blockers → Unclear

Diuretics → Increase urine volume but no change in GFR

Volume control → Aggressive fluid removal → Deleterious

Volume control → Whole body BIS → Potentially beneficial (not approved by U.S. FDA)

Volume control → Tolvaptan → Potentially beneficial

Blood pressure control → Uncontrolled hypertension → Deleterious

Blood pressure control → Hypotension → Deleterious

Peritonitis → Deleterious

Aminoglycosides → Unclear

PD modality → Unclear

Biocompatible PD solutions → Beneficial

Icodextrin → Potentially beneficial

Biocompatible hemodialysis membranes Ultrapure dialysate → Beneficial

Incremental hemodialysis CDDP → Strongly beneficial

Frequent dialysis → Daily → No data

Frequent dialysis → Nocturnal → Deleterious

**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.

## References

1 USRDS 2018 Annual Data Repost: Atlas of End-Stage Renal Disease in the United States. Volume 2. Bethesda (MD): National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Disease; 2018.

2 Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, et al.; Hemodialysis (HEMO) Study Group. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med. 2002 Dec;347(25):2010–9.

3 Chertow GM, Block GA, Correa-Rotter R, Drüeke TB, Floege J, Goodman WG, et al.; EVOLVE Trial Investigators. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med. 2012 Dec; 367(26):2482–94.

4 Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, et al.; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005 Jul; 353(3):238–48.

5 Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al.; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009 Apr;360(14): 1395–407.

6 Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al.; SHARP Investigators. 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 Jun; 377(9784):2181–92.

7 Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. N Engl J Med. 1987 Jan;316(2):73–8.

8 Ye Y, Liu H, Chen Y, Zhang Y, Li S, Hu W, et al. Hemoglobin targets for the anemia in patients with dialysis-dependent chronic kidney disease: a meta-analysis of randomized, controlled trials. Ren Fail. 2018 Nov;40(1):671–9.

9 Shen JI, Saxena AB, Montez-Rath ME, Chang TI, Winkelmayer WC. Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use and cardiovascular outcomes in patients initiating peritoneal dialysis. Nephrol Dial Transplant. 2017 May;32(5):862–9.

10 Wu CK, Yang YH, Juang JM, Wang YC, Tsai CT, Lai LP, et al. Effects of angiotensin converting enzyme inhibition or angiotensin receptor blockade in dialysis patients: a nationwide data survey and propensity analysis. Medicine (Baltimore). 2015 Jan;94(3):e424.

11 Quach K, Lvtvyn L, Baigent C, Bueti J, Garg AX, Hawley C, et al. The Safety and Efficacy of Mineralocorticoid Receptor Antagonists in Patients Who Require Dialysis: A Systematic Review and Meta-analysis. Am J Kidney Dis. 2016 Oct;68(4):591–8.

12 Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, et al.; Mexican Nephrology Collaborative Study Group. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol. 2002 May;13(5):1307–20.

13 Termorshuizen F, Korevaar JC, Dekker FW, van Manen JG, Boeschoten EW, Krediet RT; NECOSAD Study Group. The relative importance of residual renal function compared with peritoneal clearance for patient survival and quality of life: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD )-2. Am J Kidney Dis. 2003 Jun;41(6):1293–302.

14 Bargman JM, Thorpe KE, Churchill DN; CANUSA Peritoneal Dialysis Study Group. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. J Am Soc Nephrol. 2001 Oct;12(10):2158–62.

15 Obi Y, Streja E, Rhee CM, Ravel V, Amin AN, Cupisti A, et al. Incremental Hemodialysis, Residual Kidney Function, and Mortality Risk in Incident Dialysis Patients: A Cohort Study. Am J Kidney Dis. 2016 Aug;68(2):256–65.

16 Shafi T, Jaar BG, Plantinga LC, Fink NE, Sadler JH, Parekh RS, et al. Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. Am J Kidney Dis. 2010 Aug;56(2):348–58.

17 Daugirdas JT, Depner TA, Inrig J, Mehrotra R, Rocco MV, Suri RS, et al.; National Kidney Foundation. KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 update. Am J Kidney Dis. 2015 Nov;66(5):884–930.

18 Singhal MK, Bhaskaran S, Vidgen E, Bargman JM, Vas SI, Oreopoulos DG. Rate of decline of residual renal function in patients on continuous peritoneal dialysis and factors affecting it. Perit Dial Int. 2000 Jul-Aug;20(4): 429–38.

19 Szeto CC. The new ISPD peritonitis guideline. Ren Replace Ther. 2018;4(1):7.

20 Mathew AT, Fishbane S, Obi Y, Kalantar-Zadeh K. Preservation of residual kidney function in hemodialysis patients: reviving an old concept. Kidney Int. 2016 Aug;90(2):262–71.

21 Shemin D, Bostom AG, Laliberty P, Dworkin LD. Residual renal function and mortality risk in hemodialysis patients. Am J Kidney Dis. 2001 Jul;38(1):85–90.

22 White CA, Ghazan-Shahi S, Adams MA. β-Trace protein: a marker of GFR and other biological pathways. Am J Kidney Dis. 2015 Jan;65(1):131–46.

23 Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al.; CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012 Jul;367(1):20–9.

24 Shafi T, Michels WM, Levey AS, Inker LA, Dekker FW, Krediet RT, et al. Estimating residual kidney function in dialysis patients without urine collection. Kidney Int. 2016 May;89(5):1099–110.

25 Stevens LA, Schmid CH, Greene T, Li L, Beck GJ, Joffe MM, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. Kidney Int. 2009 Mar;75(6):652–60.

26 Curhan G. Cystatin C: a marker of renal function or something more? Clin Chem. 2005 Feb;51(2):293–4.

27 Davenport A. Measuring residual renal function in dialysis patients: can we dispense with 24-hour urine collections? Kidney Int. 2016 May;89(5):978–80.

28 Lindström V, Grubb A, Alquist Hegbrant M, Christensson A. Different elimination patterns of β-trace protein, β2-microglobulin and cystatin C in haemodialysis, haemodiafiltration and haemofiltration. Scand J Clin Lab Invest. 2008;68(8):685–91.

29 Donadio C, Tognotti D, Caponi L, Paolicchi A. β-trace protein is highly removed during haemodialysis with high-flux and super high-flux membranes. BMC Nephrol. 2017 Feb; 18(1):68.

30 Steubl D, Hettwer S, Dahinden P, Luppa P, Rondak IC, Regenbogen C, et al. C-terminal agrin fragment (CAF) as a serum biomarker for residual renal function in peritoneal dialysis patients. Int Urol Nephrol. 2015 Feb;47(2):391–6.

31 Viaene L, Meijers BK, Bammens B, Vanrenterghem Y, Evenepoel P. Serum concentrations of p-cresyl sulfate and indoxyl sulfate, but not inflammatory markers, increase in incident peritoneal dialysis patients in parallel with loss of residual renal function. Perit Dial Int. 2014 Jan-Feb;34(1):71–8.

32 Huang WH, Hung CC, Yang CW, Huang JY; High Correlation Between Clearance of Renal Protein-Bound Uremic Toxins. High correlation between clearance of renal protein-bound uremic toxins (indoxyl sulfate and p-cresyl sulfate) and renal water-soluble toxins in peritoneal dialysis patients. Ther Apher Dial. 2012 Aug;16(4):361–7.

33 Lowenstein J, Grantham JJ. Residual renal function: a paradigm shift. Kidney Int. 2017 Mar;91(3):561–5.

34 Nakada T, Kudo T, Kume T, Kusuhara H, Ito K. Estimation of changes in serum creatinine and creatinine clearance caused by renal transporter inhibition in healthy subjects. Drug Metab Pharmacokinet. 2019 Aug;34(4): 233–8.

35 Urakami Y, Kimura N, Okuda M, Inui K. Creatinine transport by basolateral organic cation transporter hOCT2 in the human kidney. Pharm Res. 2004 Jun;21(6):976–81.

36 Casado JL, Monsalvo M, Vizcarra P, Fontecha M, Serrano-Villar S, Moreno S. Evaluation of kidney function in HIV-infected patients receiving an antiretroviral regimen containing one or two inhibitors of the tubular secretion of creatinine. HIV Med. 2019, Epub ahead of print.

37 Shahab I, Khanna R, Nolph KD. Peritoneal dialysis or hemodialysis? A dilemma for the nephrologist. Adv Perit Dial. 2006;22:180–5.

38 Moist LM, Port FK, Orzol SM, Young EW, Ostbye T, Wolfe RA, et al. Predictors of loss of residual renal function among new dialysis patients. J Am Soc Nephrol. 2000 Mar;11(3): 556–64.

39 Suzuki H, Kanno Y, Sugahara S, Okada H, Nakamoto H. Effects of an angiotensin II receptor blocker, valsartan, on residual renal function in patients on CAPD. Am J Kidney Dis. 2004 Jun;43(6):1056–64.

40 Zhang L, Zeng X, Fu P, Wu HM. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for preserving residual kidney function in peritoneal dialysis patients. Cochrane Database Syst Rev. 2014 Jun;(6):CD009120.

41 Xydakis D, Papadogiannakis A, SSfakianaki M, Kostakis K, Stylianou K, Petrakis I, et al. Residual renal function in hemodialysis patients: the role of angiotensin-converting enzyme inhibitor in its preservation. ISRN Nephrol. 2012 Dec;2013:184527.

42 Kjaergaard KD, Peters CD, Jespersen B, Tietze IN, Madsen JK, Pedersen BB, et al. Angiotensin blockade and progressive loss of kidney function in hemodialysis patients: a randomized controlled trial. Am J Kidney Dis. 2014 Dec;64(6):892–901.

43 Zoccali C, Moissl U, Chazot C, Mallamaci F, Tripepi G, Arkossy O, et al. Chronic Fluid Overload and Mortality in ESRD. J Am Soc Nephrol. 2017 Aug;28(8):2491–7.

44 Jansen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT; NECOSAD Study Group. Predictors of the rate of decline of residual renal function in incident dialysis patients. Kidney Int. 2002 Sep;62(3):1046–53.

45 Onofriescu M, Hogas S, Voroneanu L, Apetrii M, Nistor I, Kanbay M, et al. Bioimpedance-guided fluid management in maintenance hemodialysis: a pilot randomized controlled trial. Am J Kidney Dis. 2014 Jul;64(1):111–8.

46 Liao CT, Shiao CC, Huang JW, Hung KY, Chuang HF, Chen YM, et al. Predictors of faster decline of residual renal function in taiwanese peritoneal dialysis patients. Perit Dial Int. 2008 Jun;28 Suppl 3:S191–5.

47 Szeto CC, Kwan BC, Chow KM, Chung S, Yu V, Cheng PM, et al. Predictors of residual renal function decline in patients undergoing continuous ambulatory peritoneal dialysis. Perit Dial Int. 2015 Mar-Apr;35(2):180–8.

48 Bragg-Gresham JL, Fissell RB, Mason NA, Bailie GR, Gillespie BW, Wizemann V, et al.; Diuretic Use, Residual Renal Function, and Mortality Among Hemodialysis Patients in the Dialysis Outcomes and Practice Pattern Study (DOPPS). Diuretic use, residual renal function, and mortality among hemodialysis patients in the Dialysis Outcomes and Practice Pattern Study (DOPPS). Am J Kidney Dis. 2007 Mar;49(3):426–31.

49 van Olden RW, van Meyel JJ, Gerlag PG. Acute and long-term effects of therapy with high-dose furosemide in chronic hemodialysis patients. Am J Nephrol. 1992;12(5):351–6.

50 Medcalf JF, Harris KP, Walls J. Role of diuretics in the preservation of residual renal function in patients on continuous ambulatory peritoneal dialysis. Kidney Int. 2001 Mar; 59(3):1128–33.

51 van Olden RW, Guchelaar HJ, Struijk DG, Krediet RT, Arisz L. Acute effects of high-dose furosemide on residual renal function in CAPD patients. Perit Dial Int. 2003 Jul-Aug; 23(4):339–47.

52 Hiramatsu T, Hobo A, Hayasaki T, Kabu K, Furuta S. A pilot study examining the effects of tolvaptan on residual renal function in peritoneal dialysis for diabetics. Perit Dial Int. 2015 Sep-Oct;35(5):552–8.

53 Hidaka H, Nakao T. Preservation of residual renal function and factors affecting its decline in patients on peritoneal dialysis. Nephrology (Carlton). 2003 Aug;8(4):184–91.

54 Htay H, Cho Y, Pascoe EM, Darssan D, Hawley C, Johnson DW; balANZ trial investigators. Predictors of Residual Renal Function Decline in Peritoneal Dialysis Patients: The balANZ Trial. Perit Dial Int. 2017 May-Jun; 37(3):283–9.

55 Johnson DW, Mudge DW, Sturtevant JM, Hawley CM, Campbell SB, Isbel NM, et al. Predictors of decline of residual renal function in new peritoneal dialysis patients. Perit Dial Int. 2003 May-Jun;23(3):276–83.

56 Badve SV, Hawley CM, McDonald SP, Brown FG, Boudville NC, Wiggins KJ, et al. Use of aminoglycosides for peritoneal dialysis-associated peritonitis does not affect residual renal function. Nephrol Dial Transplant. 2012 Jan; 27(1):381–7.

57 Michels WM, Verduijn M, Grootendorst DC, le Cessie S, Boeschoten EW, Dekker FW, et al.; NECOSAD study group. Decline in residual renal function in automated compared with continuous ambulatory peritoneal dialysis. Clin J Am Soc Nephrol. 2011 Mar;6(3):537–42.

58 Johnson DW, Mudge DW, Sturtevant JM, Hawley CM, Campbell SB, Isbel NM, et al. Predictors of decline of residual renal function in new peritoneal dialysis patients. Perit Dial Int. 2003 May-Jun;23(3):276–83.

59 Williams JD, Topley N, Craig KJ, Mackenzie RK, Pischetsrieder M, Lage C, et al.; Euro Balance Trial Group. The Euro-Balance Trial: the effect of a new biocompatible peritoneal dialysis fluid (balance) on the peritoneal membrane. Kidney Int. 2004 Jul;66(1):408–18.

60 Wang AY, Brimble KS, Brunier G, Holt SG, Jha V, Johnson DW, et al. ISPD cardiovascular and metabolic guidelines in adult peritoneal dialysis patients part I - assessment and management of various cardiovascular risk factors. Perit Dial Int. 2015 Jul-Aug;35(4): 379–87.

61 Chang TI, Ryu DR, Yoo TH, Kim HJ, Kang EW, Kim H, et al.; Yonsei Associate Network CHronic Kidney Disease Trial (YACHT) investigators. Effect of Icodextrin Solution on the Preservation of Residual Renal Function in Peritoneal Dialysis Patients: A Randomized Controlled Study. Medicine (Baltimore). 2016 Mar;95(13):e2991.

62 Cho Y, Johnson DW, Craig JC, Strippoli GF, Badve SV, Wiggins KJ. Biocompatible dialysis fluids for peritoneal dialysis. Cochrane Database Syst Rev. 2014 Mar;(3):CD007554.

63 Agar BU, Sloand JA. Single Daily Icodextrin Exchange as Initial and Solitary Therapy. Perit Dial Int. 2018 Mar-Apr;38(2):119–24.

64 Hartmann J, Fricke H, Schiffl H. Biocompatible membranes preserve residual renal function in patients undergoing regular hemodialysis. Am J Kidney Dis. 1997 Sep;30(3):366–73.

65 McKane W, Chandna SM, Tattersall JE, Greenwood RN, Farrington K. Identical decline of residual renal function in high-flux biocompatible hemodialysis and CAPD. Kidney Int. 2002 Jan;61(1):256–65.

66 Schiffl H. Choice of dialysis membrane does not influence the outcome of residual renal function in haemodialysis patients. Nephrol Dial Transplant. 1995;10(6):911–2.

67 Schiffl H, Lang SM, Fischer R. Ultrapure dialysis fluid slows loss of residual renal function in new dialysis patients. Nephrol Dial Transplant. 2002 Oct;17(10):1814–8.

68 Kalantar-Zadeh K, Crowley ST, Beddhu S, Chen JL, Daugirdas JT, Goldfarb DS, et al. Renal Replacement Therapy and Incremental Hemodialysis for Veterans with Advanced Chronic Kidney Disease. Semin Dial. 2017 May;30(3):251–61.

69 Basile C, Casino FG, Kalantar-Zadeh K. Is incremental hemodialysis ready to return on the scene? From empiricism to kinetic modelling. J Nephrol. 2017 Aug;30(4):521–9.

70 Bolasco P, Cupisti A, Locatelli F, Caria S, Kalantar-Zadeh K. Dietary Management of Incremental Transition to Dialysis Therapy: Once-Weekly Hemodialysis Combined With Low-Protein Diet. J Ren Nutr. 2016 Nov;26(6):352–9.

71 Chertow GM, Levin NW, Beck GJ, Depner TA, Eggers PW, Gassman JJ, et al.; FHN Trial Group. In-center hemodialysis six times per week versus three times per week. N Engl J Med. 2010 Dec;363(24):2287–300.

72 Daugirdas JT, Greene T, Rocco MV, Kaysen GA, Depner TA, Levin NW, et al.; FHN Trial Group. Effect of frequent hemodialysis on residual kidney function. Kidney Int. 2013 May; 83(5):949–58.