Having residual kidney function should lessen the requirement for hemodialysis. If the kidney still removes waste solutes to some extent, less dialysis is necessary to limit their accumulation in the body. A well-reasoned case has been made for reducing the intensity of dialysis in patients with residual function, particularly in those initiating dialysis. However, major barriers hinder reducing hemodialysis time, frequency, or both for patients with residual kidney function.

Current Guidelines for Incorporating Residual Function in the Dialysis Prescription

The first barrier to reducing dialysis time for patients with residual kidney function is encountered in determining an appropriate dialysis prescription. The 2015 Update of the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Hemodialysis Adequacy adopted weekly standard $K_t/V_{urea}$ (std$K_t/V$) as an index of adequacy and provided formulas for std$K_t/V$ that incorporate residual urea clearance (Kru). For hemodialysis schedules other than thrice weekly, it suggests targeting a std$K_t/V$ of 2.3 to achieve a minimum delivered std$K_t/V$ of 2.1. It also suggests the dialysis prescription can be reduced for patients with significant residual function.

The 2015 guideline update not only adopted std$K_t/V$ as a measure of adequacy, but changed the definition of this parameter. As originally defined by Gotch, std$K_t/V$ depended on the average peak urea concentration during the weekly dialysis cycle. If urea production and body size were held constant, different dialysis prescriptions provided the same std$K_t/V$ if the weekly average peak urea concentration was the same. However, when the 2015 update adopted std$K_t/V$ as an adequacy measure, it increased the weight given to residual kidney function and abandoned Gotch’s original definition of std$K_t/V$. Different prescriptions that provide the same std$K_t/V$ according to the 2015 update will no longer yield the same weekly peak urea concentrations.

The increased weight given to Kru appears in the formulas the 2015 update provides for calculating std$K_t/V$. Dau-Girdas et al. had developed formulas that allowed approximation of Gotch’s std$K_t/V$ from the single pool $K_t/V$ (sp$K_t/V$) for an individual treatment, the treatment frequency ($n$), the weekly ultrafiltration volume, and Kru. The update employs these formulas, but changes the factor by which Kru is multiplied. A value very close to the value for std$K_t/V$ the patient would have in the absence of residual function can then be calculated as follows:

$$stdK_t/V = stdK_t/V_{without residual function} + Kru$$

In this formula, $V$ is the volume of distribution of urea and $F$ is the number of treatments per week (also referred to as $N$). The contribution of residual function to std$K_t/V$ is then reflected by the addition of one more term. A value very close to std$K_t/V$ as defined by Gotch is given by the following:

$$stdK_t/V = \frac{0.974}{spK_t/V + 1.62} + 0.4 \times \frac{10,080}{V}$$

However, the 2015 update specifies that std$K_t/V$ should be calculated as follows:

$$stdK_t/V = \frac{0.974}{spK_t/V + 1.62} + 0.4 \times \frac{10,080}{V}$$

The removal of the multiplier $(0.974/\left( spK_t/V + 1.62 \right) + 0.4)$ increases the weight given to Kru. This change, which went largely unheralded, appears minor on examination of the formulas. It has, however, a large effect on the treatment time required to achieve a target std$K_t/V$ for patients with significant Kru, as illustrated in Figure 1. Although the 2015 update abandoned std$K_t/V$ as an adequacy measure, it maintained the previous guidelines’ recommendations to reduce the intensity...
of thrice-weekly dialysis only for Kru > 2 ml/min and reduce dialysis frequency only for Kru > 2 or 3 ml/min.

A Mobile Phone Application to Facilitate Calculation of stdKt/V
The increased weight given to Kru in the 2015 update has not stimulated much effort to reduce treatment time for hemodialysis patients with residual function. One barrier to reducing time is the difficulty of the required calculations. Monthly reports generated by dialysis providers generally do not include stdKt/V calculated as described in the 2015 update, and prescribing physicians who attempt to calculate stdKt/V for themselves face a daunting task. The web-based program Solute Solver What If simplifies this task, but requires entering multiple time values to estimate stdKt/V as a function of time.6 We created a mobile phone application (app) to simplify estimating the treatment time required to reach a target stdKt/V (Figure 2). The app first requires an estimate of the urea distribution volume. A physician can either enter a urea volume obtained from the provider’s monthly report or enter the patient’s age, sex, weight, and height to obtain the body water volume calculated by the Watson formula. The physician then enters the treatment time, spKt/V, Kru, estimated weekly fluid gain, and a target stdKt/V. The default target stdKt/V is 2.3, as recommended in the 2015 update, but different values can be entered. From these values, the app calculates the treatment times required to reach the target stdKt/V if thrice-weekly treatment frequency is maintained, and if treatment is reduced to twice weekly. The app provides an alert if suggested treatment times would result in fluid removal rates in excess of a commonly cited maximum of 13 ml/kg per hr. The Supplemental Materials describe the calculations used by the app (Supplement 1) and offer documentation that results obtained with the app are close to those obtained with a urea kinetic program over a wide range of modeled dialysis prescriptions (Supplement 2). The app is available as stdKt/V Calculator for iOS through the App Store and as stdKt/V Calculator for Android in the Play Store.

Administrative Barriers to Incorporating Residual Function in the Dialysis Prescription
In the United States, there are also administrative impediments to reducing treatment time and/or frequency for patients with residual kidney function. The End Stage Renal Disease Quality Incentive Program (QIP) and related policies of the Centers for Medicare & Medicaid Services pose a barrier to reducing treatment time.7 The QIP requires each dialysis facility to report the fraction of adult patients on hemodialysis achieving a threshold spKt/V ≥1.2. However, it specifically prohibits including residual function in this measure, despite its inclusion being recommended in reporting adequacy for patients on peritoneal dialysis. Excluding residual function from adequacy assessment likely lengthens treatment times. Most patients have Kru > 2 ml/min when they begin dialysis, and some maintain this for a considerable period. Dialysis prescriptions for these patients may be adequate by KDOQI standards and yet not meet the QIP threshold, as shown in Table 1. Because dialysis facilities must report the portion of their patients meeting the threshold, they are thus encouraged to maintain longer thrice-weekly treatment times than would be required to provide adequate dialysis by KDOQI standards in patients with residual function.
The QIP does not pose a barrier to reducing treatment frequency, because adequacy reporting is not required for patients dialyzed twice weekly. However, twice-weekly treatment may prove costly for facilities. It could leave gaps in standard Monday-Wednesday-Friday and Tuesday-Thursday-Saturday dialysis schedules. Decreasing the treatment frequency could also reduce revenue from commercial insurers, which pay as much as four times the Medicare rate for each hemodialysis treatment. The small share of patients with commercial insurance provides a disproportionate

Table 1. Thrice weekly treatment times required to reach stdKt/V = 2.3

<table>
<thead>
<tr>
<th>Kru (ml/min)</th>
<th>Larger Body Size (Vdurea 42 L)</th>
<th>Smaller Body Size (Vdurea 32 L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Required Time (Min)</td>
<td>spKt/V</td>
</tr>
<tr>
<td>0</td>
<td>225</td>
<td>1.35</td>
</tr>
<tr>
<td>1</td>
<td>189</td>
<td>1.17</td>
</tr>
<tr>
<td>2</td>
<td>158</td>
<td>0.98</td>
</tr>
<tr>
<td>3</td>
<td>131</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Treatment times required per session for a thrice-weekly hemodialysis regimen to provide a stdKt/V of 2.3 calculated as specified in the 2015 update. In patients with residual function treatments that provide adequate stdKt/V will often result in spKt/V values below the target value of 1.2 imposed by the End Stage Renal Disease QIP. Times were calculated using Solute Solver What If® for patients with the specified two pool urea distribution volumes (Vdurea) and assuming a dialytic clearance for urea of 250 ml/min. Kru values were multiplied by 0.93 to convert values, which are usually calculated in terms of ml of plasma per minute to ml of water per minute for entry into the urea kinetic modeling program.
share of facilities’ revenue. To the extent that commercial insurance coverage is, as with residual function, more commonly maintained early in the course of dialysis, placing patients with residual function on twice-weekly dialysis would reduce revenues. Together, governmental policies and financial constraints thus encourage at least thrice-weekly treatments, providing spKt/V ≥1.2 for all patients on in-center hemodialysis, regardless of residual function.

Other Barriers to Reducing Dialysis Time and Frequency
Reducing treatment requires more rapid ultrafiltration. In patients with residual function, however, urine output reduces the need for ultrafiltration, and can be increased by diuretics. Further studies are needed to ensure that diuretics do not impair residual clearance of uremic solutes or have other undesirable consequences. Limiting salt intake also reduces the need for ultrafiltration, and although difficult, might be achieved more often if patients were offered reduced treatment time in return.

Elevated plasma potassium and phosphate concentrations sometimes preclude reducing dialysis time and frequency. Residual function, however, helps remove both potassium and phosphate, and diuretics can increase residual excretion of potassium. In general, patients with residual function have been reported to have lower-than-average potassium and phosphate levels, and neither high potassium nor high phosphate has posed a notable barrier to initiating incremental hemodialysis.\(^9\)\(^10\)

Finally, maintaining dialysis times in patients with residual function might be presumed necessary to remove some unmeasured uremic toxin(s). However, our reliance on urea to assess solute removal by both dialysis and residual kidney function can be misleading. Urea has the highest dialytic clearance of any known solute, but the kidney, by contrast, clears many solutes more rapidly than urea, which is in part reabsorbed in the proximal tubule. Low molecular weight proteins such as \(\beta_2\) microglobulin are cleared at rates close to the GFR. Tubular secretion raises the clearances of many other solutes above the GFR, and their high clearances relative to urea are preserved at least to some extent in residual functioning kidneys of patients on dialysis. The increased weighting of residual function in the 2015 update can thus be scientifically defended. This is most apparent by comparing predicted levels of different solutes in patients with and without residual function who receive treatments that provide the same stdKt/V, as shown in Figure 3. As previously noted, although patients with residual function will have slightly higher average peak urea levels, levels of other solutes will tend to be lower. Thus, without a clinical study demonstrating benefit, extending treatment of patients with residual function beyond the 2015 update’s target stdKt/V seems hard to justify.

Future Directions
Reliance on urea kinetics prevents confident assessments of the relative values of different dialysis prescriptions.\(^11\) Some modification of the urea-based KDOQI Guidelines and of Centers for Medicare & Medicaid Services’ policies thus seem warranted.

One possible approach is the strategy advocated by the International Society of Peritoneal Dialysis,\(^12\) which still recommends routine assessment of toxin removal using urea and/or creatinine as surrogates, but does not obligate a patient on peritoneal dialysis who feels well to increase volume or frequency of exchanges to meet a numeric target. An analogous approach to hemodialysis would require continued measurement of stdKt/V. Low values would suggest that symptoms such as fatigue and poor appetite were due to inadequate toxin removal and alert physicians to poor vascular access function. In many patients,

Figure 3. The effect of residual function on the plasma levels of different uremic solutes. Predicted plasma solute levels in a patient with no residual function (red lines) and with a Kru of 2 ml/min (blue lines) dialyzed thrice weekly to provide a stdKt/V of 2.3 calculated using the KDOQI 2015 update. The treatment time is 210 minutes in the patient without residual function and 130 minutes in the patient with residual function. Peak (solid line) and time averaged (dashed line) concentrations of urea are slightly higher in the patient with residual function (left panel). At the same stdKt/V, however, the patient with residual function has lower plasma concentrations of \(\beta_2\) microglobulin (middle panel) and even more markedly lower concentrations of hippurate (right panel). Reviewing the figure, it is tempting to increase the weighting of residual function above the level assigned in the 2015 update as described by Casino and Basile.\(^2\) Modeled for a patient with characteristics described in Supplement 3.
treatment time and frequency would still be determined by the need to remove fluid and inorganic ions. Others might find by experimentation that they feel better with longer treatment, more frequent treatment, or both. However, individual patients who feel well and have adequate volume and inorganic ion control would not be obliged to spend more time on dialysis to achieve a target stdKt/V.

Trials have largely failed to show that solute removal beyond the level necessary to improve symptoms provides long-term benefit. When the burden of more intense treatment is additional time on dialysis, benefit should be better established. To proceed beyond treatment on the basis of symptom control, we will need better knowledge of uremic solutes and clinical trials assessing the benefit of controlling their levels.

DISCLOSURES

The results presented in this paper have not been published previously in whole or part, except in abstract form. T.L. Sirich and T. Meyer have served as consultants for Baxter. T. Meyer has a patent application pending for improved removal of protein-bound solutes by dialysis; reports receiving research funding from Outset Medical; and reports being a scientific advisor or member of the JASN Editorial Board, and Kidney International on the Editorial Board. J.K. Leyboldt reports serving as a consultant for Baxter International, Diality, Novaflux, and NxStage (Fresenius). All remaining authors have nothing to disclose.

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SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2021030361/-/DC Supplemental.

Supplement 1. How the stdKt/V calculator program works.

Supplement 2. Testing of the stdKt/V calculator app.

Supplement 3. Parameters used in modeling dialysis treatment times and plasma solute levels in patients with residual function.

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