

# Dialysis Dose as a Determinant of Adequacy

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The intent-to-treat analyses of all patients in the HEMO trial suggested that increases in dose of dialysis as measured by urea Kt/V were of marginal or no benefit when dialysis was provided in a 3 times/wk schedule. The as-treated analysis in the HEMO trial pointed to markedly increased mortality when the delivered dose decreased even slightly below the targeted dose, evidence of a dose-targeting bias. The intent-to-treat HEMO study results suggested a potential interaction between sex and the dose-mortality relationship, and this also has been found in some cross-sectional studies, the cause of which remains unexplained. Whether dialysis dose should continue to be targeted based on urea distribution volume (V), or targeted to a body size measure that is a lower power of body weight (such as body surface area), remains an open question. The lack of benefit of increasing the dialysis dose in a 3 times/wk setting is more understandable if one looks at measures of equivalent continuous solute removal, such as the standard Kt/V. Differences in standard Kt/V in the 2 dose arms of the HEMO trial, for example, were only about 15%. Without going into removal of very large solutes (eg, beta-2-microglobulin), which is discussed elsewhere in this issue, or protein-bound uremic solutes, the only way to provide significantly more dialysis dose may be to move to more frequent dialysis schedules and/or to very long session lengths. Here, benefit may be related as much to better control of salt and water balance as to better removal of uremic toxins.

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Interest in the question of hemodialysis dose or adequacy became acute in the United States about 15 years ago,<sup>1</sup> when investigators began looking for answers as to why mortality in US dialysis patients was so much higher than in their counterparts from Europe or Japan.<sup>2</sup> One of the possible explanations for a US patient disadvantage had to do with the fact that the dialysis session length tended to be longer in European and especially in Japanese dialysis patients.<sup>3</sup> Such concerns led to the design and implementation of the National Institutes of Health–sponsored, randomized HEMO trial in which patients were randomized to 2 levels of dialysis dose, equivalent to urea reduction ratios (URR) of approximately 75% and 66%, respectively (dose levels were targeted more formally as equilibrated urea Kt/V).<sup>4</sup> Overall, patients assigned to the higher-dose group in the HEMO trial had no significant survival benefit.<sup>5</sup> Also, further analysis of population survival statistics in the United States versus Japan, as

well as survival of Asian-origin US dialysis patients, suggested that the previously identified differences in survival between US and Japanese dialysis patients may not be related to their dialysis treatments at all.<sup>6</sup>

The lack of an overall survival benefit in the higher-dose group of patients in HEMO was a bit of a surprise, particularly in view of the expected 15% to 30% survival difference predicted based on results from a cross-sectional study of very large datasets, including the Japanese dialysis registry,<sup>7</sup> the US Fresenius Medical Care group,<sup>8</sup> and the US Renal Data System and Medicare information sets.<sup>9</sup> In the HEMO trial, the overall survival difference between the 2 randomly assigned dose groups was only 5%, with a 95% confidence limit range of 18% survival benefit to 10% survival disadvantage.<sup>5</sup> The lower confidence bound of an 18% survival benefit for dose in the HEMO study is not inconsistent with some of the cross-sectional study predictions; however, given the meager mean 5% survival benefit, even a study 2 to 3 times larger than the HEMO trial would not be able to prove a benefit of higher dose with an accepted level of statistical significance.

Analysis of mortality by achieved dose in the HEMO study, which is ongoing but has been reported in abstract form, suggests that dialysis patients who fail to achieve a given

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target dose have a very substantial increase in mortality, even when the shortfall in achieved dose is quite small. We have termed this a *dose-targeting bias*.<sup>10,11</sup> The causes of this still are being worked out, but appear to relate to increased mortality in dialysis patients in whom the modeled volume (urea distribution volume) increases, and in whom the delivered dialysis dose decreases as a result. The extent to which this dose-targeting bias is a product of the controlled conditions of the HEMO trial or may generalize to observational settings is not yet clear. However, the identification of the dose-targeting bias and the confounding role of modeled volume points out the trade-off between the types of evidence provided by randomized trials and large population-based observational studies. The large sample sizes of population-based observational studies provide more precise estimates of the dose-response relationship with mortality than obtained with the sample size attainable in a randomized trial. On the other hand, observational relationships may be subject to biases resulting from uncontrolled confounding factors such as modeled volume, and such bias may exist no matter how large the sample size.

The randomized dose comparison of survival in the HEMO trial found a gender-related disparity: assignment to the high-dose group was associated with a significantly higher survival rate in women.<sup>12</sup> In men, there was a trend in the opposite direction, nullifying the dose effect in the overall randomized comparison. The contrast between the genders was a prespecified outcome in the HEMO trial, although at the time the HEMO trial was designed there was no evidence for a dose-gender interaction, and the comparison between the genders was prespecified largely to conform to recent National Institutes of Health guidelines that gender should be examined in clinical trials whenever possible.<sup>13</sup> While the HEMO trial was in progress, Owen et al,<sup>14</sup> looking at dose (as URR) versus survival in the large US Fresenius Medical Care dataset, reported that dose seemed to affect mortality differently in men versus women, and also in Caucasians versus African Americans. In explaining their data, Owen et al<sup>14</sup> pointed out that women were smaller than men, given their relatively low amount of muscle mass and that approximately 50% of total body water in humans is thought to be caused by muscle. The concept of these investigators was that patients with smaller muscle mass, especially women, may be underdialyzed when solute clearance is factored by volume, as in  $Kt/V$ . One hypothesis might be that muscle tissue contributes little to the generation of uremic toxins. Lowrie et al<sup>15</sup> have proposed factoring the dialysis dose in other ways. For example, by giving a minimal dose of  $K$  times  $t$  to all adult patients regardless of body size or anthropometrically estimated volume.<sup>15</sup>

Glomerular filtration rate in humans often is normalized to body surface area ( $S$ ), and  $S$  varies to the 0.667 (two-thirds) power of body weight.<sup>16,17</sup> Urea distribution volume is a direct function of body weight, or, said another way, depends on weight to the 1.0 power.<sup>18</sup> Therefore, it may be reasonable to prescribe dialysis dose, or  $Kt$ , based on  $V^{0.667}$  power instead of volume alone. Such a strategy would give relatively more dialysis to patients with small values of volume, includ-

ing women, and at the same time would not require the very large  $Kt$  values and associated lengthy dialysis sessions for large male dialysis patients. Others have proposed that, in cross-species comparisons, glomerular filtration rate is tied closely to the metabolic rate, which is a function of  $V^{0.75}$  power.<sup>19</sup> Targeting  $Kt/V^{0.75}$  power would be intermediate between the current  $Kt/V$  approach versus using  $Kt/V^{0.667}$ .

Getting back to the HEMO trial, the possible modulation of gender on the observed dose-mortality relationship in the randomized analysis was examined while controlling for various measures of body size.<sup>12</sup> In the HEMO dataset, patients with smaller baseline values for anthropometrically estimated volume (computed using the Watson equation) did indeed have a higher mortality rate.<sup>12</sup> Also, anthropometric volume as well as other body size measures had an effect on the dose-mortality relationship,<sup>12</sup> as would be predicted by the hypothesis of Lowrie et al.<sup>15</sup> However, controlling for anthropometric volume or for a number of other body size measures did not efface the statistical relationship between gender and dose-mortality, although controlling for gender did remove most of the effect of body size on the dose-mortality relationship.<sup>12</sup> Hence, the HEMO results did not lend support for the need to re-express the denominator of  $Kt$  as some power of the body weight other than 1.0. Having said this, the HEMO patient-set was not optimally chosen to answer gender versus size questions because almost all of the women were considerably smaller than the men, with little overlap in body size between the 2 genders.<sup>12</sup> So this interesting question remains unresolved.

To make matters more interesting, after the HEMO study on the effect of gender on dose-mortality was released, further analysis of large United States Renal Data System (USRDS) and Medicare datasets were able to detect similar gender versus dose-mortality interactions.<sup>20</sup> In these analyses, which also controlled for body size, mortality decreased in women as the dose was increased, but much less so in men, results quite similar to HEMO findings. Whether this effect of gender on dose-mortality is real or just a statistical accident requires further investigation. In cross-sectional studies, the magnitude of the dose-targeting bias might conceivably be greater in women than in men. Another effect that requires confirmation is the trend found in the HEMO trial for mortality to increase at high URR levels in men. This trend was not statistically significant and therefore its importance should not be overstated. In the HEMO trial, this effect could not be explained by oversampling of patients with small values of anthropometric volume at high URR levels because this high-dose–high-mortality trend was present in the randomized dose comparison. In the HEMO study analysis, we could find no obvious explanation for this trend.

If an effect of gender on dose-mortality does exist, and if it is not caused by body size, it is intriguing to speculate that perhaps women might be more susceptible to uremia than men. Overall, mortality in women with end-stage renal disease (ESRD) is similar to that in men with ESRD after controlling for age and comorbidity.<sup>21</sup> Given the substantially higher life expectancy of nonuremic healthy women versus men,<sup>22</sup> a similar mortality rate between the 2 genders with

ESRD might be consistent with an increased susceptibility among women to ESRD or to some aspect of its treatment.

## Equivalent Measures of Solute Removal

In the HEMO trial, the separation between the 2 dose arms appears considerable if one considers the difference in mean delivered equilibrated  $Kt/V$  per treatment, 1.53 versus 1.16,<sup>5</sup> or a 32% increase. However, the amount of increase becomes less if one considers this in terms of a decrease in urea ratio in the 2 arms, about 75% versus 66%.<sup>5</sup>

For example, consider the analogy of a family with 4 children who continuously are disordering a family room. The homemaker in the family has been cleaning the family room so that it is 65% clean 3 times/wk. The mother-in-law has just paid a visit and disapproves of the level of disorder. After a family conference, it is decided to increase the cleaning efficiency to 75% on Monday, Wednesday, and Friday morning. It is doubtful that on a repeat visit the mother-in-law will be impressed with the improvement.

This sort of analysis has been quantified in terms of equivalent solute clearance by Casino and Lopez,<sup>23</sup> equal to the solute generation rate divided by the time-averaged solute concentration. Gotch<sup>24</sup> has modified this to divide the solute generation rate by the mean predialysis solute concentration, resulting, for urea, in an equivalent clearance that is approximately one-third lower than when the time-averaged concentration is used as the divisor. Gotch<sup>24</sup> then took this further by using an equivalent urea clearance in mL/min multiplied by the number of minutes in a week and divided by volume to derive the standard  $Kt/V$ .

When the mean dialysis doses delivered in the HEMO trial are expressed in terms of the Gotch<sup>24</sup>-derived standard  $Kt/V$ , the difference in therapy becomes less impressive, and more consonant with the family-room analogy (high-dose arm  $\sim$ 2.59 weekly standard  $Kt/V$  versus low-dose arm  $\sim$ 2.25; or a 15% difference). Further analysis of 3 times/wk dialysis dosing with 4- to 5-hour session lengths shows that it is very difficult to achieve standard  $Kt/V$  levels of greater than 3.0, even at high levels of dialysis efficiency.<sup>25</sup>

So one interpretation for the HEMO trial results is that inherent limitations of a conventional hemodialysis schedule cannot be overcome by increasing solute removal during 3 conventional treatments per week. Because of the accumulation of urea between dialysis sessions, increasing the URR or urea  $Kt/V$  for the individual treatments of a 3 times/wk schedule has relatively little effect on measures of equivalent renal clearance that relate the dose of intermittent HD to the dose that could be achieved with a uniform clearance, as occurs with the native kidney.

In our discussion so far, we have been focusing on urea, which most investigators agree is only a marker solute and not responsible for most uremic toxicity. Standard  $Kt/V$  analysis,<sup>24</sup> although originally proposed as a derivative of the peak-concentration hypothesis, alternatively can be thought of as measuring an intermediate molecular weight (MW) sol-

ute that is removable during dialysis, but that is highly sequestered in tissues, as discussed in detail by Depner.<sup>26</sup> Such a solute would have an intercompartmental mass transfer coefficient of approximately 100 mL/m (eg, instead of 500 mL/min for urea), and its time-averaged concentration would be close to its mean peak-concentration level (unpublished data). Candidates for such a marker solute are numerous. One possibility is uric acid, which as summarized by Feig, Johnson et al,<sup>27</sup> can be both vasculotoxic and nephrotoxic. High predialysis serum uric acid levels have been associated with poor outcome in dialysis patients.<sup>28</sup> However, the intercompartmental mass transfer coefficient for uric acid, although substantially lower than that for urea, is considerably higher than 100 mL/min.<sup>29</sup> Various other low molecular weight, water-soluble, and non-protein-bound toxins have been proposed as contributing to the uremic syndrome<sup>30</sup>; any of these might have a low intercompartmental mass transfer coefficient and act similar to sequestered solutes.

Hyperphosphatemia is also an important contributor to uremic toxicity, and high calcium  $\times$  phosphorus (Ca-P) products in the serum are associated with very high levels of mortality risk.<sup>31</sup> Conventional 3 times/wk hemodialysis is capable of removing only about 2.4 g of phosphorus per week, far less than the 5 g/wk typically absorbed in the diet, so that phosphorus-binding drugs are required.<sup>32</sup> Ingestion of calcium-containing phosphorus-binding drugs in the setting of ESRD may be associated with progression of coronary and aortic vascular calcification<sup>33</sup> and vascular stiffening.<sup>34</sup> A more comprehensive view of dialysis adequacy certainly should encompass phosphate removal. Discussion of phosphate removal with more frequent dialysis schedules, and especially with 6 times/wk nocturnal hemodialysis, is beyond the scope of the present article, but large increases in phosphorus removal, and even freedom from phosphate binders, certainly is possible with such newer forms of therapy.<sup>35</sup>

A comprehensive approach to dialysis adequacy also would require some concern about removal of very large solutes, such as beta-2-microglobulin. After 7 or more years of dialysis, beta-2-microglobulin amyloidosis, with its attendant clinical complications, becomes overt, even in otherwise well-dialyzed patients such as those treated for 24 h/wk in Tassin, France.<sup>36</sup> The issue of beta-2-microglobulin and flux is discussed in article by Chelamcharla, et al on pages 81-89 in this issue of *Seminars in Nephrology*, and therefore is not discussed here.

A conventional hemodialysis schedule typically exposes patients to fluid gains of 2 to 4.5 L during the interdialytic intervals. The resulting hypertension and volume overload further stress a cardiovascular system often already damaged by hypertension and volume overload before ESRD. Rapid removal of this large amount of accumulated fluid during the relatively short hemodialysis session often causes hypotension, potentially injuring heart, brain, and residual kidney tissue. Most hemodialysis patients are hypertensive and require multiple antihypertensive drugs. Left ventricular hypertrophy is found in 75% of patients initiating hemodialysis,<sup>37</sup> and left ventricular hypertrophy often progresses once ESRD is established, so a system of dialysis permitting better control of excess salt and water would be de-

sirable. In the early years of dialysis, 8- to 10-hour treatment sessions were not unusual. As technology improved, comparable decreases in serum urea levels were obtainable with session lengths of 3 to 4 hours. However, one center in Tassin, France, maintained a 3 times/wk schedule of 8-hour treatments, and subsequently has reported high survival, good blood pressure control, low antihypertensive medication requirements, and long-term increases in dry weight.<sup>38,39</sup> Analysis of fluid status by bioimpedance and inferior vena cava ultrasonography suggested that the 8-hour treatments provided better control of extracellular fluid volume than standard shorter treatment times.<sup>40</sup> Owing in part to the Tassin results, the concept that extended hemodialysis sessions of 8 or more hours may decrease mortality and morbidity has continued to intrigue the dialysis community. Again, more frequent dialysis schedules as well as nocturnal dialysis have been reported in preliminary communications to greatly improve salt and water balance and blood pressure control.

In summary, recent hopes that outcomes in hemodialysis patients being dialyzed 3 times/wk might be improved by increasing urea reduction ratios (and  $Kt/V$ ) by only modestly increasing the dialysis session length have not been supported by results of the large randomized HEMO study data. As-treated analysis in the HEMO trial also identified markedly increased mortality when the delivered dose was decreased just slightly below the targeted dose, evidence of a dose-targeting bias that potentially might complicate analysis of dose-mortality relationships derived from cross-sectional studies. Within the limits of 3 times/wk dialysis sessions, there is evidence from the HEMO trial as well as cross-sectional studies that women may be more sensitive to the dose of dialysis in the  $Kt/V$  ranges commonly being delivered. Whether  $Kt$  should be factored by  $V^{0.667}$  power versus by volume remains to be determined. When looking at the delivered dose with newer adequacy measures, it is apparent that meaningful increases in clearances of many other solutes, such as uric acid, the guanidine compounds, or phosphorus, for example, only will be achievable by much longer session lengths given 3 times/wk, and/or by sessions given more frequently than 3 times/wk. Definitive (eg, based on randomized controlled trials) benefits of the newer, more frequent dialysis schedules remain to be shown.

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