

patients with CKD, trading greater weight loss for increased risk may be the best option. Weight loss after bariatric surgery is associated with a number of improvements that can help resolve kidney disease—even ESRD, eliminating the need for transplantation.<sup>14</sup>

Bariatric surgery improves underlying causes of CKD (dyslipidemia, hypertension, urinary albumin excretion, atherosclerosis, and metabolic syndrome). It can also improve measures linked to kidney function (insulin resistance, adiponectin, TNF- $\alpha$ , IL-18, and C-reactive protein).<sup>16,17</sup> For patients attempting to meet kidney transplant requirements through surgical weight loss, RYGB may provide the quickest and best weight loss outcomes. It is the most commonly performed procedure in patients with obesity and CKD; it enables them to undergo transplantation.<sup>18</sup>

Bariatric surgery in CKD patients requires a careful balance of risks and benefits.<sup>19,20</sup> High-quality controlled trials are needed to identify and quantify those risks and benefits. To improve options for predicting surgical risk on a case-by-case basis in patients with obesity and diabetes, studies of GFR estimation techniques are necessary.

## DISCLOSURES

None.

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See related article, "The Impact of Renal Function on Outcomes of Bariatric Surgery," on pages 885–894.

## New Observational Data Demonstrate that Mortality Is Lower in Patients Receiving More Frequent Dialysis

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Despite improvements in medical care and technology, the life expectancy of patients with ESRD receiving hemodialysis in the United States remains high, with an annual mortality rate of around 20%/yr.<sup>1</sup> Conventional dialysis regimens based on three times weekly treatment sessions are reasonably acceptable to patients and are cost effective, but may not deliver optimum therapy. The obvious question is whether delivery of more dialysis improves survival among these patients.<sup>2</sup> Observational studies dating back to the 1990s predicted this may be the case, with better survival reported among patients on a three times weekly regimen who received a larger delivered dose, as assessed by solute clearance.<sup>3,4</sup>

The first randomized controlled trial designed to test the hypothesis that delivering more dialysis would improve outcomes, the Hemodialysis (HEMO) study, was negative.<sup>5</sup> In this study, a modest increase in delivered dialysis dose, which was assessed in terms of solute clearance as measured by KT/V and achieved in the context of a three times weekly regimen, showed no clear benefits in terms of patient survival.

Increasing the frequency of dialysis sessions will enhance solute clearance and salt and water removal. Observational studies again indicate this strategy is associated with better outcomes.<sup>6,7</sup> Three recent randomized controlled trials have tested the hypothesis that delivering more frequent treatment improves outcomes in hemodialysis patients. Using standard thrice weekly dialysis as the comparator, these trials have assessed short daily regimens<sup>8</sup> or long nocturnal regimens delivered six times weekly.<sup>9,10</sup> The trials were not powered to determine effects on mortality, although mortality was part of a composite end point in two studies,<sup>8,9</sup> but did show benefits on surrogate end points including BP,<sup>8-10</sup> hyperphosphatemia,<sup>8-10</sup> and left ventricular hypertrophy,<sup>8,9</sup> as well as improvements in physical health scores.<sup>8</sup> The frequency of vascular access-related events increased in more frequently dialyzed patients in two of the studies,<sup>8,9</sup> although there was no difference in access survival.

In these trials, random allocation to the two interventions (standard versus more frequent dialysis regimens) reduces the chances of there being any systematic differences between the two groups, making the controls an appropriate substitute for the treated group in all ways except for the intervention of interest. However, such randomized trials not only require substantial resources, but are also difficult to conduct, particularly when one or both of the interventions require major changes to patient lifestyle. From a patient's perspective, allowing the play of chance to determine allocation to a treatment regimen that will have major lifestyle implications may not be appealing and may limit willingness to enroll. It is therefore not surprising that it has been difficult to conduct trials of different dialysis regimens powered to assess hard clinical end points.

Accepting these difficulties, what more can we learn from the observational data? In this issue of *JASN*, Weinhandl *et al.*<sup>11</sup> present a large observational study in which they compare outcomes in 1873 home hemodialysis patients receiving daily treatment to outcomes in 9365 in-center controls receiving a standard

thrice weekly regimen. The authors use a complex algorithm, which includes up to 17 different patient factors, in an attempt to ensure that the two groups were as precisely matched as possible. In an intention-to-treat analysis, they demonstrate a lower hazard ratio for all-cause mortality (0.87; 95% confidence interval, 0.78–0.97) among those patients receiving home dialysis. The authors reasonably conclude that daily dialysis, delivered at home, is associated with a modest survival benefit.

The paper provides the largest and most robust observational data to date addressing this question. However, as the authors concede, the study has limitations. A significant proportion of patients discontinued home dialysis, suggesting that this therapy was not acceptable in the longer term. All home patients, and presumably none of the in-center subjects, used a specific machine, the Nx stage system. Thus, the improvement in outcome could have resulted from a technical difference in the equipment rather than the frequency of dialysis. In addition, as the authors discussed, because no data on compliance are available, they can only assume that those patients assigned to a daily home regimen actually received more dialysis. Furthermore, as in any retrospective study, potential bias in data collection is an important consideration. For example, the completeness of comorbidity data may systematically differ between the two groups.

The key question in interpreting this study, however, is whether the control group receiving in-center treatment represents an appropriate comparator population for the home dialysis group. In other words, were the two groups comparable in all ways other than exposure to the different dialysis regimens? The authors identified five control subjects for each home dialysis case, but even with data from a quarter of a million dialysis patients available from the US Renal Data Systems data set, only about one third of cases were matched on all factors and almost 9% were matched on less than half. This means that despite matching, the home dialysis group was not only a year younger but also less deprived socioeconomically, as demonstrated by the lower number dually eligible for both Medicare and Medicaid. Although the authors report that adjustment for matching factors did not alter the relative hazard ratio for death, these observations highlight the challenge of identifying appropriate controls in this type of study.

As acknowledged by the authors and in common with all observational studies, a further limitation is the extent of unmeasured confounding. No statistical method can deal with the possibility that unquantified factors associated with both the exposure (home hemodialysis) and the outcome (death) account for the differences in mortality observed between the two groups. In an effort to address this possibility, the authors attempt to quantify the magnitude of effect at various levels of differential prevalence that such an unmeasured factor would need to exert to account for the differences in outcome. Although the authors should be commended for their attempts to illustrate what is effectively a shortcoming in all observational studies, the

situation may be more complex because several small confounders, particularly when combined with measurement error, can substantially alter the estimate of effects due to the exposure.<sup>12</sup>

The hazard ratio in the study by Weinhandl *et al.* is closer to unity than that reported in previous observational studies, as referenced in the paper, which had less rigorous control for confounding factors. Therefore, do we now have an accurate estimate of the beneficial effect of daily home versus in-center thrice weekly dialysis or would further adjustment for multiple small causes of confounding shift the hazard ratio even closer to 1? Can we ever assume that estimates of effects from observational studies would be reproduced in prospective randomized controlled trials? We should remember that there are well known examples in the literature where this has not been the case.<sup>13</sup> Such disparity has been attributed to a failure to adequately adjust for multiple (time dependent, socioeconomic) confounders in the observational studies.<sup>13</sup> Indeed it has been suggested that “. . . useful observational studies on the effects of therapy will be the exception. . .”<sup>14</sup> as the selection of intervention by patient characteristics will play such an overwhelming part in determining exposure and it is almost impossible to control for. In reality, systematic comparison of observational versus randomized controlled evidence has not identified large differences in the effect estimates reached using the two techniques.<sup>15–17</sup> However, there have been no comparisons of observational and randomized evidence in the context of dialysis. Of all the clinical scenarios in which confounding may influence the interpretation of evidence collected in the context of observational versus randomized trials, those involving invasive procedures or lifestyle disruption might be most prone.<sup>16</sup>

We should perhaps accept that we will never get a randomized controlled trial comparing daily home hemodialysis versus thrice weekly center-based treatment powered to assess differences in mortality. The observational study by Weinhandl *et al.* is informative and provides the best data to date on the subject, despite the above limitations. Although meta-analysis of independent randomized trials will remain the gold standard for assessing the effectiveness of dialysis interventions, the accompanying study is consistent with the hypothesis that daily dialysis therapy is of benefit to patients. Unless data from clinical trials become available in the future, decisions regarding the provision of daily dialysis delivered at home are likely to be based on these observational data.

## DISCLOSURES

D.C.W. has received honoraria from Fresenius.

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See related article, "Survival in Daily Home Hemodialysis and Matched Thrice-Weekly In-Center Hemodialysis Patients," on pages 895–904.