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See related article, "Mitochondria-Targeted Peptide Accelerates ATP Recovery and Reduces Ischemic Kidney Injury," on pages 1041–1052.

Differential Outcomes Between Dialysis Modalities: Purely a Reflection of Selection Bias?

Jula K. Inrig and Robert D. Toto
University of Texas Southwestern Medical Center, Dallas, Texas

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Cardiovascular morbidity and mortality among patients receiving lifesaving dialysis far exceeds that of the age-adjusted general population. Over the last several decades, there have been ongoing debates and numerous investigations seeking to identify the ideal dialysis modality for individual end-stage renal disease (ESRD) patients. Despite a paucity of evidence to support the use of one modality over another, the prevalence rates of peritoneal dialysis (PD) have declined in the United States to a current level of 7%.[1] In the era of bundled dialysis payments, health care reform, and pay-for-performance, there is a heightened interest in identifying the most cost-effective interventions associated with the best clinical outcomes. Home dialysis modalities are cost-effective, but do they improve clinical outcomes?

While the annual payer costs for patients treated with peritoneal dialysis are lower compared with hemodialysis, it remains unknown which modality is associated with the best clinical outcomes. Several recent studies have identified an early survival advantage associated with the use of PD *versus* hemodialysis (HD) among incident ESRD cohorts, while others have either failed to identify a survival difference or have identified poorer outcomes associated with PD *versus* HD.[2–6] However, considering the known selection bias introduced by patients and physicians in choosing the appropriate dialysis modality, comparisons of outcomes between dialysis modalities inevitably is limited by unmeasured prognostic differences between groups at baseline. While a randomized controlled trial is necessary to solve the differential findings in observational studies, an initial attempt at a trial was not successful.[7] Thus, observational studies with robust statistical methods are the only feasible alternative.

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Correspondence: Dr. Jula K. Inrig, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8523. Phone: 214-645-8263, Fax: 214-645-8903; E-mail: jula.inrig@utsouthwestern.edu

In this issue of *JASN*, Perl *et al.* compare outcomes between PD and HD among a Canadian cohort of incident ESRD patients, with the HD patients stratified by dialysis access.[8] The authors speculate that patients initiating HD with an arteriovenous fistula or graft (AVF/AVG) *versus* a catheter would be more similar to patients starting dialysis with a PD catheter, thus minimizing selection bias. They also hypothesize that the previously identified early survival advantage associated with PD *versus* HD would be attenuated in a comparison that controlled for vascular access. This study included 38,512 patients incident to dialysis between 2001 and 2008 who were registered in the Canadian Organ Replacement Register. Approximately 19% of patients started PD, and, of those who started on HD, only 21.4% initiated dialysis with an AVF or AVG. Similar to prior studies, PD patients in this cohort had lower overall comorbidity compared with HD patients, including a lower prevalence of diabetes mellitus, coronary artery disease, peripheral vascular disease, malignancy, and pulmonary disease.

Overall, 1-yr adjusted mortality was higher with HD compared with PD; however, when patients were stratified by dialysis access type, the increased mortality was limited to HD patients with a catheter. Among patients who started HD with an AVF/AVG *versus* PD, 1-yr adjusted mortality was equivalent between HD and PD (hazard ratio 0.9, 95% CI 0.8 to 1.1). However, 5-yr adjusted mortality was lower among HD patients with an AVF/AVG relative to PD patients (HR 0.80, 95% CI 0.80 to 0.90). Among patients who started HD with a catheter *versus* PD, 1-yr and 5-yr adjusted mortality was higher among HD-catheter patients *versus* PD patients. However, after the first year, HD-catheter patients had similar mortality risk to PD patients.

In further sensitivity analyses including the use of marginal structures models, which adjusted for propensity scores for selection of dialysis modality and probability of renal transplantation, the results were robust. In prespecified subgroup analyses, nearly all subgroups had improved 5-yr survival associated with HD with an AVG/AVF *versus* PD, while there was decreased survival among those with HD with a catheter *versus* PD.

These findings provide new insights into outcomes associated with different dialysis modalities. Only patients who have been under the care of a nephrologist and have planned for dialysis initiation will have dialysis access in place (whether a PD catheter or AVG/AVF), which makes comparisons between these groups reasonable. Furthermore, the use of a catheter *versus* AVF/AVG is known to be associated with higher infectious complications and higher mortality, and may bias toward worse early outcomes with HD, as suggested by prior observational studies. Thus, the analysis by Perl *et al.* appears to be a reasonable approach to compare outcomes between dialysis modalities while minimizing the inherent selection bias between groups.

However, cautious interpretation and application of these findings should be considered. This is a secondary analysis in which patients were allocated to one dialysis modality for a reason, whether it was patient or physician selection or other possibly unmeasured risk factors. While this study attempts to minimize these differences by minimizing pre-ESRD care as a confounder, residual unmeasured confounding likely exists. Despite over 50 years of

renal replacement therapy being federally funded in the United States, the ideal way to deliver dialysis and the best modality to use for individual patients remains uncertain. However, in the era of bundled payments, it has been proposed that the prevalence rates of PD will rise, as it remains a lower-cost therapeutic option. This study by Perl *et al.* supports the individualized use of PD as an equivalent dialysis modality to HD and as a preferred modality if the alternative is to start hemodialysis with a catheter.

DISCLOSURES

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See related article, "Hemodialysis Vascular Access Modifies the Association between Dialysis Modality and Survival," on pages 1113–1121.

REIN on Obesity, Proteinuria and CKD

Mary E. Choi
Renal Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115

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Chronic Kidney Disease (CKD) is a major public health concern worldwide[1] and obesity is increasingly recognized as an independent risk factor for development of CKD.[2] There has been a global epidemic of obesity and a parallel rise in the prevalence of metabolic syndrome that likely have contributed to the increasing incidence of CKD.[3] Culprits implicated in this epidemic include the development of a general tendency toward sedentary lifestyles together with a diet with excessive caloric intake linked to junk food and high fructose consumption, largely in the form of high-fructose corn syrup in sugary sodas.[4–6] Epidemiologic and experimental studies have linked high fructose intake with the development of obesity and metabolic syndrome, insulin-resistant diabetes, and albuminuria.[3,7]

Obesity is associated with proteinuria and a more rapid progression of CKD[8] and the reversal of obesity can improve proteinuria[9,10] and GFR.[11] Moreover, there is evidence that obesity causes glomerular hypertrophy and impaired glomerular function, even in the absence of a primary kidney disease. An obesity-related glomerulopathy akin to focal segmental glomerulosclerosis has been observed in morbidly obese patients, often accompanied by massive proteinuria and rapid loss of kidney function.[10,11] Based on the high prevalence, associated complications, and rising cost, obesity that parallels an increase in the prevalence of CKD has become a global burden.

There is now convincing evidence for proteinuria as a marker of kidney injury and a surrogate outcome in CKD, and that reducing proteinuria can prevent or delay cardiovascular events and the progression of kidney disease.[12] Blockers of the renin-angiotensin system (RAS) have emerged as the mainstay of therapy in large part due to their antiproteinuric effects in preventing the progression of kidney disease. Randomized trials assessing the efficacy of angiotensin-converting-enzyme (ACE) inhibitors with respect to kidney-protection have been studied in diabetic[13,14] as well as nondiabetic nephropathies.[15,16] Notably, the Ramipril Efficacy In Nephropathy (REIN) study-1 was the first to demonstrate that an ACE inhibitor, ramipril, had a kidney-protective effect in slowing the decline of GFR in nondiabetic CKD patients with a proteinuria of 3 g or more per day.[16]

In this issue, Mallamaci and colleagues,[17] through a *post hoc* analysis of the REIN study cohort, asked two critical questions, whether body mass index (BMI) influences the incidence rate of renal events, defined as either doubling of serum creatinine or end-stage renal disease (ESRD), and whether obesity modifies the effect of ramipril on these outcomes. The latter question was not addressed previously. In the placebo-treated group, the incidence rate of renal outcomes was higher in obese patients than those with normal BMI. Importantly, treatment with ramipril not only reduced the incidence rate of renal

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Correspondence: Mary E. Choi, M.D., Renal Division, Brigham and Women's Hospital, Department of Medicine, Harvard Medical School, 4 Blackfan Circle, HIM-5, Boston, Massachusetts 02115, Phone: 617-525-5977; Fax: 617-525-5923, E-mail: mchoi@rics.bwh.harvard.edu