

Relative Survival With Peritoneal Dialysis: The Hunt for a Comparator Continues

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Few topics have captured the imagination of end-stage kidney disease (ESKD) outcomes researchers more than survival with peritoneal dialysis (PD) versus hemodialysis. A recent meta-analysis of studies that used pro-

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ensity score matching to estimate relative survival with PD in adult patients with incident ESKD uncovered 17 studies published between 2010 and 2018.¹ It concluded that survival with PD and hemodialysis was “equivalent” (mortality hazard ratio, 1.06; 95% CI, 0.99-1.14) and that >90% of variation among studies could be attributed to differences in study era, country of origin, and cohort design (prospective or retrospective). However, an earlier systematic review of evidence from patients with incident ESKD due to diabetic nephropathy simply concluded that estimates of relative survival with PD were “inconsistent.”² Considering that studies comparing PD and hemodialysis continue to be performed, perhaps variation among studies is more memorable than meta-analytic effect estimates. In any case, each new study comparing PD and hemodialysis ought to be interpreted against the backdrop of the dozens that preceded it. From that perspective, the newest study appears to be anomalous.

Analyzing data from the US Renal Data System (USRDS), in this issue of *Kidney Medicine*, Mukhopadhyay et al³ report that the adjusted hazard ratio of death with PD versus hemodialysis was approximately 1.2 during the 360 days after dialysis initiation. During the first 90 days of dialysis, PD was associated with a modest and nonsignificant survival advantage. However, during the rest of follow-up, PD was associated with a significant disadvantage, punctuated by an adjusted hazard ratio of death approximately equal to 1.35 between 180 and 360 days after dialysis initiation. This trajectory of relative survival might inspire incredulity but the study design checks all the requisite boxes. The cohort was well defined, with initial dialysis modality ascertained from the End-Stage Renal Disease Medical Evidence Report. Follow-up was straightforward; application of the intention-to-treat principle essentially resulted in follow-up until the earlier of death or kidney transplantation—events that are readily identifiable in the USRDS registry.⁴ Cox regression models of mortality risk were adjusted for demography, comorbid conditions, and geography and were stratified by calendar year of dialysis initiation. Confounding by indication, including residual kidney function and care partner status, likely persists but adjustment for age alone is powerful.

What therefore gives rise to a seemingly atypical result? The answer is not in the cohort of PD patients because the study excluded only slightly more than 1% of all incident patients with ESKD who selected PD during the study era. Instead, the answer is in the comparator of hemodialysis patients. There are many approaches to specifying a comparator. One approach is to include all incident patients with ESKD who select hemodialysis during a fixed interval. Many early studies used this approach⁵ but it requires risk adjustment in multiple domains, including socioeconomic status, comorbid conditions, and pre-ESKD care. The limitation of this approach is a technical concept, the positivity assumption,⁶ which requires—in the context of dialysis modalities—that every patient carry nonzero probabilities of selecting each of PD and hemodialysis. Empirically, this assumption is dubious because incident patients with ESKD who are very elderly, are in poverty, or have substantial comorbidity are unlikely to select PD. Violation of the positivity assumption can induce bias.

Another approach is propensity score matching, whereby for each PD patient who carries a certain probability (ie, propensity) of PD selection, a matched hemodialysis patient with a similar probability of PD selection is identified.⁷ This approach also requires thorough risk adjustment—in the propensity score, which is an estimated function of patient characteristics—but admittedly provides an escape from the positivity assumption. A third approach is restriction of incident patients with ESKD who select hemodialysis. In practice, most studies that have compared PD and hemodialysis and used restriction have focused on aspects of pre-ESKD care, or alternatively, the evident consequences of pre-ESKD care.

Several Canadian studies of relative survival with PD exemplify restriction. In a study of Ontario residents, Quinn et al⁸ restricted incident patients with ESKD, regardless of initial modality, to those who visited a nephrologist 4 or more months before dialysis initiation and who electively began dialysis treatment in an outpatient setting. Even in the subset of all incident patients with ESKD who initiated dialysis treatment in an outpatient setting—a subset comprising more than half of all incident patients with ESKD in Ontario in 1998 to 2006—the restriction was more likely to exclude hemodialysis patients than PD patients. Later, Wong et al⁹ restricted incident patients with ESKD to those who completed a multidisciplinary modality assessment (after dialysis initiation) and were deemed by staff to be eligible for both PD and hemodialysis.⁹ In a novel twist, Mukhopadhyay et al restricted the comparator of hemodialysis patients to those with a functioning arteriovenous fistula (AVF) at the first

outpatient dialysis session, according to the Medical Evidence Report.

The rationale for restricting to hemodialysis patients with a functioning AVF at dialysis initiation is reasonable. These patients must have visited a nephrologist before initiation, been referred to a vascular surgeon, and had a fistula mature. The hallmarks of dialysis preparation are apparent, just as they are apparent for PD patients who, in the absence of an urgent-start program, must have visited a nephrologist before dialysis initiation and been referred to a surgeon who placed a PD catheter. (Curiously, 14% of PD patients and 11% of hemodialysis patients in the study indicated no nephrology care before ESKD diagnosis.) Nevertheless, the inclusion criteria for hemodialysis patients implicitly require a pair of events: an AVF was placed and that AVF matured.

What is the prognostic significance of this sequence? In an analysis of 2,300 patients who initiated hemodialysis at 5 Canadian sites in 2004 to 2012, Quinn et al¹⁰ found 487 (21%) who underwent a pre-ESKD AVF creation attempt. For nonelderly patients, an AVF creation attempt was associated with 51% lower adjusted risk for death after dialysis initiation; for elderly patients, an attempt was associated with 40% lower adjusted risk for death during the first 2 years after dialysis initiation. For patients with a pre-ESKD AVF creation attempt, fistula versus catheter use at dialysis initiation was associated with 74% and 8% lower adjusted risks for subsequent death among nonelderly and elderly patients, respectively. Clearly, the combination of AVF placement and maturation before dialysis initiation is predictive of sharply lower risk for death after initiation, especially in the nonelderly. This raises the question of whether a comparator of hemodialysis patients with a functioning AVF “flips” the usual confounding of survival with PD versus hemodialysis. Possible mechanisms for the failure of AVF maturation are numerous.¹¹

Of course, another possibility is that PD is simply inferior to conventional hemodialysis with an AVF. The current study has precedent. Perl et al¹² reported neutral survival with PD versus hemodialysis but inferior survival with PD versus hemodialysis with an arteriovenous access. One contemporary meta-analysis estimated that the hazard ratio of death with PD versus hemodialysis is 1.2 in patients with ESKD with diabetes.¹³ In the United States, there is considerable enthusiasm for home dialysis on the heels of the Executive Order on Advancing American Kidney Health.¹⁴ Medicare payment models may directly incentivize great use.¹⁵ However, it is notable that home dialysis use is a process outcome, not a clinical outcome. Paths to good clinical outcomes exist both at home and in the facility. Considering this study, Medicare should consider incentivizing optimal starts¹⁶: pre-emptive transplantation, home dialysis, or in-facility hemodialysis with an arteriovenous access.

One last point merits discussion. Patient priorities vary. Life expectancy with dialysis is important. In a survey of more than 4,500 in-facility hemodialysis patients in

Germany, 80% rated life expectancy as “very important.”¹⁷ However, life expectancy was most important for patients aged 21 to 60 years. For older patients, other factors may be more important. For patients 60 years or older with chronic kidney disease stage 4 or 5, maintaining independence outranked survival; nearly half the patients ranked survival as a third or fourth priority.¹⁸ Urquhart-Secord et al¹⁹ reported that energy (or fatigue), ability to travel, and dialysis-free time all outranked survival as priorities for 58 hemodialysis patients. Researchers are understandably attracted to study designs with positive attributes, including validated outcome data. However, it is unclear that in-facility hemodialysis with the best vascular access could possibly outperform PD in the domains of lifestyle independence and ease of travel. The study by Mukhopadhyay et al adds a potentially valuable observation that patients with chronic kidney disease and their families can consider when selecting a modality, but the study should not be used by nephrologists and nurses to discourage PD selection.

The future will surely include more comparisons of PD and hemodialysis. Comparisons are good because modality education necessarily ends with a decision to select PD, home hemodialysis, or in-facility hemodialysis—hopefully with the benefit of accurate information. Whether comparing PD to hemodialysis with pre-ESKD AVF placement and maturation is “accurate” remains unclear considering the social factors involved in pre-ESKD nephrology care and the biology of AVF maturation. What is clear is that both PD and hemodialysis with an arteriovenous access are good starts to ESKD treatment.

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Support: None.

Financial Disclosure: Dr Weinhandl is a consultant (epidemiologic research) to Fresenius Medical Care North America. Dr Gilbertson declares that he has no relevant financial interests.

Acknowledgments: The authors thank Chronic Disease Research Group colleague Nan Booth, MSW, MPH, ELS, for manuscript editing.

Peer Review: Received August 4, 2020, in response to an invitation from the journal. Accepted August 18, 2020, after editorial review by the Editor-in-Chief.

Publication Information: © 2020 Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). Published online November 4, 2020 with doi [10.1016/j.xkme.2020.11.001](https://doi.org/10.1016/j.xkme.2020.11.001)

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