Timing of Dialysis Initiation: When to Start? Which Treatment?

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During the late 1990s early initiation of dialysis was introduced on a large scale and between 1996 and 2008, the percentage of patients with an estimated glomerular filtration rate (eGFR) above 10 mL/minute starting dialysis rose from 25% to 54% in the United States. However, several subsequent studies showed no survival benefit for patients commencing dialysis earlier. One possible explanation for the negative results could be that eGFR may be a flawed index; s-creatinine is lower in patients with muscle wasting or fluid overload and these vulnerable patients with high comorbidity burden often start "early", i.e., at higher eGFR. Another explanation could be that dialysis is in fact harmful; dialysis initiation with conventional thrice weekly in-center hemodialysis clearly associates with increased initial mortality risk especially when using temporary dialysis catheters. Interestingly, patients starting on peritoneal dialysis (PD) appear to have better initial outcomes. More attention should be given to finding new objective mortality-predictive markers of uremia, reducing the use of temporary hemodialysis catheters, and increasing the use of PD as initial dialysis modality. PD may not only provide better initial dialysis outcomes but may also preserve renal function and vessels for vascular access for the benefit of better long-term outcomes.

IN PATIENTS WITH chronic kidney disease (CKD), the risk of all-cause and cardiovascular mortality increases with decline in renal function, especially when the glomerular filtration rate (GFR) decreases below 60 mL/minute.[1] As patients with CKD are more likely to die than progress to renal replacement therapy,[2] one may ask whether the high mortality risk in patients with CKD stages 4 to 5 can be reduced by earlier dialysis initiation. On the other hand, if the dialysis procedure is associated with factors leading to increased risk of morbidity and mortality,[3] what is the added risk by starting dialysis earlier rather than later and would in fact earlier dialysis initiation instead increase the mortality risk? In this review, we briefly discuss these questions and some of the factors that could influence the decision on when to start dialysis and the choice of dialysis treatment modality.

Early Dialysis Initiation: Not as Good as Previously Thought

In the past, and still during the 1980s, resources for dialysis therapy were lacking, and dialysis was in general initiated only when patients demonstrated clear signs of life-threatening uremic complications. In 1985, Bonomini et al[4] from Bologna, Italy, reported that earlier initiation of dialysis could convey survival benefits; patients, who started dialysis early at a mean creatinine clearance rate of 11 mL/minute, had a higher survival rate than those who started late at a clearance rate of less than 5 mL/minute. Although this report did not appear to influence dialysis initiation practices much, the publication of the Canada–USA study[5] in 1996, which reported that survival was greater in patients starting peritoneal dialysis (PD) with a higher residual renal function (RRF) resulted in major changes. Based on the observation in the Canada–USA study that a total (peritoneal plus renal) removal of urea corresponding to Kt/V >2.0 per week associated with improved survival, the US National Kidney Foundation-Dialysis Outcomes Quality Initiative working group on the initiation of dialysis therapy in 1997 proposed that the adequacy target for dialysis patients not yet on dialysis should not fall below this threshold.[6] Predialysis patients should have RRF equal to a GFR of 10.5 mL/minute or more (corresponding to weekly Kt/V >2.0); if this cut-off point was not achieved, the patients should be started on dialysis[6] This policy led to a major change in the timing of dialysis initiation practices in the United States and—although to a lesser extent—also in other countries. Thus, in the United States, between 1996 and 2008, the percentage of patients starting dialysis with an estimated GFR (eGFR) above 10 mL/minute rose from 25% to 54%, and the percentage of patients initiating dialysis at an eGFR above 15 mL/minute increased from 4% to 17%.[7]

After these dramatic changes in the timing of dialysis initiation practices, several large observational studies were performed comparing outcomes in patients starting dialysis at

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various levels of eGFR. These studies included large numbers of patients; in some cases, more than 800,000, in registry-type data sets, including the United States Renal Data System (USRDS), Bureau of National Health Insurance in Taiwan, European Registry, the French Renal Epidemiology and Information Network Registry, and the Canadian Organ Replacement Registry as well as one randomized study, the Initiating Dialysis Early and Late (IDEAL) study.[7,8] However, perhaps unexpectedly, these studies showed that an early start of dialysis had no beneficial effect[7-10] or even resulted in a worse outcome[11-13]; starting dialysis at lower levels of eGFR (= "late start") thus appeared to be associated with lower mortality. Altogether, these studies indicated that early start of dialysis especially when using in center-hemodialysis (HD) as initial therapy could be harmful and questioned the trend to early dialysis initiation based primarily on eGFR; the clinical status of the patients, besides eGFR levels, should also be taken into account in the decision making process. Furthermore, a meta-analysis concluded that the outcome after dialysis initiation was not only affected by GFR and patient characteristics but also appeared to associate with the type of dialysis modality used; interestingly, although early dialysis initiation using in-center HD associated with worse outcomes, this was not a consistent finding when PD was used as initial therapy.[13]

Possible Factors That May Explain Lack of Favorable Effect of Early Dialysis Initiation

When analyzing factors explaining why starting dialysis early appear to be harmful, first of all, it should be noted that observational studies do not–and cannot—prove that starting dialysis with higher eGFR is indeed causing the observed worse outcomes. One important confounder is that patients are only included in studies if they actually started dialysis; only the fittest patients survive long enough to be included in the late start groups; this is the survivor bias. Furthermore, among patients who survived long enough to take part in these studies, those with symptoms or comorbidities are more likely to be started on dialysis early. In addition, eGFR based on s-creatinine may overestimate true GFR in the latter patients who may have a low s-creatinine concentration because of low muscle mass or fluid overload, or both; these patients who have an increased high mortality risk due to frailty and comorbidities are likely to be started "earlier" at a higher eGFR level. In a study based on the Nederlands Co-operative Study Adequacy of Dialysis treatment cohort, it was reported that although patients with lower eGFR had worse survival than those with higher eGFR at start of dialysis, such a survival difference was not seen when comparing the same patients according to their levels of renal function based on measured GFR; muscle mass was found to associate with eGFR but not with measured GFR.[14]

Another reason is that eGFR–or any index based on creatinine (or urea)—may be a poor predictor of the concentrations for a broad range of uremic toxins. Thus, because eGFR is poorly associated with concentrations of uremic toxins in patients with different degrees of CKD and correlates differently with each individual solute, eGFR cannot be considered representative for evaluating the accumulation of solutes in the course of CKD.[15] Furthermore, although eGFR (or measured GFR) is not a good predictor of the concentrations of uremic solutes or their biological action, other factors may be more important such as tubular secretion of toxins, generation of toxins by the intestinal flora, and the metabolism of toxins.[15] Because of the association between nutritional status and eGFR and the other reasons mentioned previously, there is now consensus that renal function estimated by s-creatinine (eGFR) may be useless or even misleading as a sole guide on when to start dialysis.

Harmful Effects of Dialysis

Another reason why early dialysis initiation could associate with worse outcomes could be that the dialysis procedure is harmful. Dialysis, and especially conventional intermittent thrice-weekly HD, leads to an accelerated loss of RRF, a powerful predictor of mortality in CKD patients. The rate of RRF loss should therefore be an important consideration for the timing of the dialysis initiation decision and the choice of initial dialysis modality; several studies have shown that RRF is better preserved in terms of slower rate of decline in GFR and a longer time to loss of RRF in patients treated with PD compared with those treated with conventional thrice weekly HD. Furthermore, dialysis introduces the risk of access-related infections, a powerful predictor of worse outcomes, induces an inflammatory response and—especially when using intermittent dialysis—leads to unphysiological fluctuations in solutes and fluid that increase the risk for sudden cardiac death, the most common cause of death in dialysis patients according to USRDS data. In fact, mortality increases markedly during the first month after initiation of HD suggesting possible harmful effect of the dialysis procedure as such or complications caused by dialysis.[12] Potential biological factors contributing to poor outcomes on early dialysis initiation in HD and PD may be more often associated with HD than with PD.[9] Furthermore, mortality during the initial years after start of dialysis was found to be similar or better with PD than with in-center HD.[16] A propensity-matched mortality comparison of 6,337 incident HD–PD patient pairs showed that survival from the first day on dialysis was 8% higher for PD patients than for HD patients (hazard ratio 0.92; 95% confidence interval 0.86-1.00; $P = .04$).[17] Furthermore, the latest USRDS report shows that the first year mortality rate (in year 2010) was much lower in patients initiating dialysis with PD than with HD even when adjusting for age, gender, race, and primary diagnosis;