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Starting dialysis is dangerous: how do we balance the risk?

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Recent studies of timing of dialysis initiation have challenged the recent trend to earlier initiation of therapy. The observed outcomes though are a consequence of the balance between the risks of advanced uremia versus the inherent dangers relating to dialysis therapy itself. Many of these risks are inherent in how dialysis treatment is currently carried out, and may indeed be amenable to mitigation, through refinement of clinical practice (and potentially modality choice). This article aims to lay out a discussion relating to patient outcomes being the composite result of this balance, pivoting on the vulnerability of a particular patient to these attendant risks.

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Dialysis treatment has long been accepted as a life-saving treatment in the setting of terminal uremia, and now offers life-sustaining treatment to approximately two million people around the world, in a wide variety of health-care systems. Despite the widespread adoption of this life-saving therapy, dialysis treatment (and in particular the initiation phase) is redolent with dangers, many of which are only recently starting to be fully appreciated. This inherent tension between benefit and harm has, up to this point, been explored mainly through a focus on timing of dialysis initiation. This area of interest has been twinned with further consideration of conservative nondialytic care in chronic kidney disease (CKD) stage 5 patients; detailed discussion of this literature, however, is beyond the scope of this particular article.

Conventional wisdoms have evolved concerning the expected benefits of early dialysis initiation. These have largely led to very similar national and international guidelines regarding the best time to start dialytic treatment.[1] These guidelines have been associated with a marked increase over the past decade in patients to commencing dialysis at an ever earlier stage.[2] The core question as to when the best time to commence treatment, in both populations and individuals, has received remarkably little systematic study. There has been only a single randomized controlled trial examining the issue of early- versus late-start dialysis initiation.[3] The other investigations have almost entirely relied on retrospective interrogations of registry or other observational data sets. These studies have relied on statistical manipulations to adjust for case mix and comorbidity burden. More recent iterations of this approach have consistently identified earlier initiation as being associated with poorer outcomes in both general populations and subsets of younger patients without significant comorbidity.

Since 2001, 11 observational studies have examined the issue of comorbidity-adjusted survival versus the estimated glomerular filtration rate (eGFR) level (as assessed by the serum creatinine-based Modification of Diet in Renal Disease equation) at dialysis initiation. All but two of these studies found a comorbidity-adjusted survival disadvantage of early dialysis initiation, possibly underestimated by 'lead time bias', and recently a variety of observational studies have reported a graded survival benefit associated with lower eGFR.[4–6]

Comorbidity has been considered a crucial factor in many of the previous studies. LaSalle and co-workers[7] found early-start disadvantage only in patients with the highest level of pre-dialysis comorbidity. Adjustment of survival for measured comorbidity, however, still seems to suggest no advantage in early start. However, comorbidity data collected at the registry level has not been well validated, with only one published study that found high specificity but low sensitivity of comorbidity data from the US Renal Data System. Although comorbidity is strongly associated with dialysis mortality, one study of patients with a low comorbid burden has also confirmed this trend to reduced survival in patients with higher starting eGFR.[4]

The question of dialysis start has been the subject of a recently published randomized controlled trial.[3] Cooper and colleagues[3] randomly assigned 828 patients 18 years of age or older to early dialysis start estimated GFR by surface area corrected Cockcroft–Gault equation of 10–14 ml/min or late start estimated GFR of 5–7 ml/min. During a follow-up period of about 3.5 years, 152 of 404 patients in the early-start group (37.6%) and 155 of 424 in the late-start group (36.6%) died (hazard ratio with early initiation, 1.04; 95% confidence interval, 0.83 to 1.30; $P = 0.75$). There was no significant difference between the groups in the frequency of adverse events (cardiovascular events, infections, or complications of dialysis) or in quality-of-life measures. There appeared to be no health economic benefit of an earlier start. However, it should be noted that a significant proportion of patients randomized to later start did in fact commence earlier, because of clinician assessment of need (and indeed the majority commenced peritoneal dialysis (PD), rather than hemodialysis (HD)). These data are consistent with the proposition that exposure to the harm associated with dialysis initiation overwhelms the survival advantage related to attempted correction of uremia in the setting of relatively less advanced CKD.

This article introduces the concept that outcomes in dialysis are the composite result of negative effects of advanced CKD, balanced by the attendant risks of dialysis therapy, underpinned by the denominator of individual vulnerability of the patient to both of the above. This dynamic may be further influenced by attempts to mitigate many of those risks.

POTENTIAL BENEFITS OF DIALYSIS INITIATION

Although advanced CKD is associated with a plethora of metabolic, structural, and functional abnormalities, there is still very little certainty in mapping the individual abnormalities to specifics of patient symptoms or subsequent adverse events. This has strengthened (by default) the focus on nutrition, owing to the inability to robustly identify other surrogates for outcome that might be manipulated by the dialysis process.

Malnutrition has been cited as the most common reason for clinicians choosing an earlier start (other than absolutes such as life-threatening hyperkalemia or oliguria-associated fluid overload),[8] and is contained in many guideline recommendations. This is largely driven by abundant observational data identifying low serum albumin as being the strongest determinant of mortality in dialysis patients. The NECOSAD study group suggested that increasing small-solute clearance (based on urea) might affect the observed pattern of developing malnutrition after dialysis start.[9] However, there are currently no studies that directly support the ability of conventional three-times-weekly dialysis to improve nutritional parameters, especially without enhanced nutritional supplements. No improvements were seen over 3 years of follow-up in the HEMO study of prevalent HD patients in either serum albumin or anthropomorphic measures of nutrition.[10] This study highlighted the importance of inflammation and its associated effects on serum albumin (rather than lower serum albumin being an exclusive or even primary marker of malnutrition). In a recent study by Rosansky and co-workers[4], the increase in mortality risk propensity with earlier dialysis initiation was preserved throughout the range of serum albumin.

Advanced CKD leads to a wide variety of subjective patient effects including pain, dyspnea, increasing fatigue, dependency, and depression. There are no prospective studies suggesting that initiation of current intermittent dialytic therapies consistently address this symptom burden. The application of more intensive dialysis regimes has been associated with an increase in many measures of nutrition and well-being.[11] However, at present only a small fraction of patients are undergoing this form of therapy, which is still at the early stages of rigorous scientific assessment.

RISKS OF DIALYSIS

Conventional dialysis treatment has many inherent risks for patients. This appears true in older frailer patients, and in those with minimal comorbidity. Some of these risks are fundamental to the dialytic therapy and some relate to management of the patient during the period of transition from nondialytic to dialytic management of end-stage renal disease. These risks may potentially be mitigated.

The period of dialysis initiation is associated with a particular increase in patient dependency (with similar increment in mortality).[12] In studies looking at longer-term dialysis outcomes, the effects of these risks are not evenly distributed over the entire dialysis vintage, with an excess of mortality condensed into the first 6–12 months of therapy.[4] Survival in the first year of dialysis (in the United States) has decreased despite evidence of overall improvement in dialysis patient survival overall.[13] The window of opportunity for a number of these risks is often in the dialysis preparation period, with a reduced period for specialist care/preparation being associated with increased mortality in the dialytic phase of patient care.[14]

Specific areas of risks that must be considered when initiating dialysis include the following:

Infection and dialysis access–related issues

Risks of all forms of infection are many times higher once the patient is started on dialysis. This relates partially to