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## Transition to Dialysis: Controversies in its Timing and Modality

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Currently over 400,000 people in the US receive maintenance dialysis treatment for end-stage renal disease (ESRD), each of whom incurs an average expenditure of \$60,000 to \$80,000 per year (i.e., approximately 8% of total Medicare spending is consumed by the ESRD program who represent only 1% of the Medicare population).<sup>1</sup> Approximately 115,000 patients annually *transition* from advanced non-dialysis dependent chronic kidney disease (NDD-CKD) to maintenance dialysis treatment, mostly in the form of conventional or thrice-weekly in-center hemodialysis. Despite a decline in the prevalent dialysis death rate over the past two decades, the proportion of patients who are alive three years after dialysis initiation remains abysmally low at 51%. It is also well-known that the highest mortality rates for ESRD occur within the first year of dialysis initiation.<sup>1,2</sup> This has led to an intense quest to identify modifiable risk factors and interventions that may ameliorate the exceptionally high mortality risk characterizing this vulnerable transition period. Consequently, the optimal approach to dialysis initiation among incident dialysis patients remains widely uncertain.

One of the most highly debated topics relating to the transition of care from NDD-CKD to ESRD has been centered on the *optimal timing* of dialysis initiation. Over the past 15 years, there has been a movement towards commencing dialysis at incrementally higher estimated glomerular filtration rates (eGFRs), such that the percentage of patients initiating dialysis early (eGFR >10 ml/min/1.73m<sup>2</sup>) has increased from 19% to over 45% from 1996 to 2010, respectively.<sup>1,3,4</sup> However, existing data that have examined the impact of timing of dialysis initiation on mortality provide weak support for this secular trend. Observational studies comparing an early vs. late approach for the transition to dialysis (dialysis initiation at higher vs. lower levels of kidney function, respectively) have been mixed, and are beset by biases that include confounding-by-indication, selection, and lead-time bias.<sup>5,6</sup> To date, the Initiating Dialysis Early and Late (IDEAL) study has been the only multi-center randomized controlled trial to compare early-start vs. late-start dialysis (defined as 10 to 14 ml/min/1.73m<sup>2</sup> vs. 5 to 7 ml/min/1.73m<sup>2</sup>, respectively). Although no differences in mortality or adverse events were found, interpretation of these data are limited by the large amount of cross-over between the early-start and late-start groups (i.e., 76% of late-start patients initiated dialysis at an eGFR of >7 ml/min/1.73m<sup>2</sup> due to occurrence of uremic symptoms).<sup>5</sup> Even though this study did not per se conclude that the transition to dialysis should be deferred to an eGFR of 5 to 7 ml/min/1.73m<sup>2</sup>, these findings suggest that delaying dialysis initiation until uremic symptoms develop may not necessarily confer greater mortality risk.<sup>7</sup>

Until very recently, clinical practice guidelines have tended to recommend earlier rather than later dialysis initiation, but there has also been greater emphasis on using clinical signs and symptoms as the primary indication for dialysis initiation as opposed to an arbitrary pre-

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defined eGFR. Whereas the 1997 Kidney Disease Outcomes Quality Initiative (KDOQI) Hemodialysis Adequacy Group supported dialysis initiation at an eGFR of 10ml/min/1.73m<sup>2</sup>, more recent 2006 KDOQI guidelines advised that dialysis initiation may be warranted at higher levels (i.e., earlier start at an eGFR > 15ml/min/1.73m<sup>2</sup>) in the context of symptoms or declining health related to loss of kidney function.<sup>8,9</sup> The 2012 Kidney Disease Improving Global Outcomes guidelines suggest that dialysis be initiated when there are signs or symptoms of uremia, an inability to medically control volume status or blood pressure, a progressive deterioration in nutritional status refractory to dietary interventions, or cognitive impairment.<sup>10</sup> Notwithstanding the ongoing debate about the timing of dialysis initiation, there are additional emerging fronts that are even more globally related to the transition of care from NDD-CKD to ESRD such as the optimal type of renal replacement therapy (RRT) (e.g., dialysis vs. transplantation), or in terms of dialysis, the most appropriate modality (e.g., hemodialysis vs. peritoneal dialysis) or frequency of treatment (e.g., daily vs. conventional vs. infrequent). The rise of India and China as world-dominating economies and the urgent need to prioritize RRT allocation in these and other fast growing nations have led to many new questions such as revisiting more conservative or incremental dialysis therapy (i.e., twice-weekly dialysis) and the need for individualized or personalized dialysis treatment.<sup>11</sup>

In this issue of *Seminars in Dialysis*, opinion leaders in dialysis and RRT investigation have congregated to address several important yet controversial topics related to the optimal transition from advanced NDD-CKD to dialysis, namely: 1) Do existing data justify an early vs. late approach for the transition of dialysis?; 2) Are these data broadly generalizable to populations with acute kidney injury (AKI), failing kidney transplants, and diverse socio-demographics who may experience a differential decline in residual kidney function and development of uremic symptoms, or should an individualized approach be applied?; 3) How does timing of dialysis initiation impact other patient-centered outcomes beyond survival?; 4) In addition to timing of dialysis initiation, do other factors such as modality and frequency during the transition to dialysis have a meaningful impact on outcomes?; and 4) Can pre-dialysis interventions such as dietary adjustments and multidisciplinary medical management effectively forestall the need for dialysis and/or promote survival once dialysis treatment is initiated?

Mehrotra *et al.* commence this discussion by providing a critical review of studies comparing dialysis initiation at high vs. low eGFR on mortality, as well as their respective methodological limitations and biases, and conclude that eGFR should not be the sole consideration when assessing indications for dialysis. Rosansky *et al.* expand upon this discourse by describing the conventional wisdoms that have driven a trend towards early dialysis initiation, maintaining that these previously-held beliefs are poorly justified by contemporary evidence, and that in most scenarios a late transition to dialysis should be the default approach. Norris *et al.* then introduce us to the concept of an individualized approach to dialysis initiation that not only incorporates clinical criteria, but also key demographic characteristics (e.g., age, sex, race/ethnicity and socioeconomic) as modifying factors in the decision to initiate dialysis. Molnar *et al.* specifically elaborate on data examining timing of dialysis re-initiation and outcomes among kidney transplant patients with failing allografts. Macedo *et al.* then summarize evidence evaluating RRT initiation in AKI, highlighting the various parameters used to define optimal timing of RRT initiation in this context. O'Hare *et al.* uncover the paucity of data examining timing of dialysis initiation in geriatric NDD-CKD patients among whom harms of dialysis might outweigh benefits, and introduce us to conservative care as an alternative approach that optimizes patient-centered outcomes as opposed to disease-based outcomes in caring for this complex population.

The issue continues with Johansen *et al.* describing the intricate inter-relationship between frailty, functional status, uremic states, and the transition to dialysis, and underscore the importance of examining frailty as both as a predictor and mediator of adverse outcomes as well as an outcome in and of itself in studies of dialysis initiation. Cohen *et al.* review literature examining the association between dialysis timing, frequency, and dose with the outcomes of quality of life and depression. Watnick presents a historical narrative of the evolution of financial, political, societal, and patient-level factors that have led to the inception and growth of the Medicare dialysis program, and that have shaped decisions regarding dialysis initiation, and makes a cogent argument for a more fully integrated health care system providing unified care to patients pre- and post-dialysis initiation in order to optimize outcomes and contain costs. Ghaffari *et al.* then discuss peritoneal dialysis as an initial modality that can improve clinical outcomes and confer cost savings, and outline the essential infrastructural requirements for a “PD First” model. Aparicio *et al.* provide guidance on the utilization of very-low protein diets supplemented with essential amino acids and ketoanalogues to safely delay development of uremic symptoms, progression of kidney disease, and dialysis initiation while preserving nutritional status among selected patients. Lastly, Rhee *et al.* draw upon historical precedents as they re-visit the concept of incremental hemodialysis (i.e., twice-weekly hemodialysis) as one approach to the transition from NDD-CKD to ESRD as a means to optimize survival through better preservation of native kidney function.

We feel that there is an urgent need to answer these critical and time-sensitive questions related to the optimal transition from advanced NDD-CKD to dialysis, given the vast changes occurring in our health care system, the disproportionately high costs to Medicare incurred by dialysis patients, and the poor survival of this population.<sup>1</sup> We believe that the unique compilation of articles in this issue of *Seminars in Dialysis*, composed by leading experts in the field, will serve as an invaluable resource for providers caring for NDD-CKD and dialysis patients, and will lay the groundwork for future studies and evidence-based guidelines centered on the optimal transition to dialysis.

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