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Timing of initiation of dialysis: time for a new direction?

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Abstract

Purpose of review—The past 15 years have seen tremendous growth in the initiation of dialysis at higher levels of kidney function in the setting of mixed evidence and at great societal economic cost. We review recent data on the early dialysis initiation trend, the clinical and economic impact of early dialysis initiation and the future implications for the management of advanced chronic kidney disease (CKD).

Recent findings—The percentage of patients who initiate dialysis with an estimated glomerular filtration rate (eGFR) above 10 ml/min/1.73m² is now greater than 50%, including 20% who initiate with an eGFR above 15 ml/min/1.73m². The drivers behind these findings are probably diverse but recent literature does not seem to support a higher symptom burden among the ageing CKD population as the major cause. The Initiating Dialysis Early And Late (IDEAL) trial provides guidance on the safety of waiting for symptoms or lower levels of estimated glomerular filtration rate prior to beginning dialysis. In addition, economic analyses based on the IDEAL and US Renal Data System findings suggest that significant cost savings could be achieved by reversing the early initiation trend.

Summary—These findings should help clinicians and policy makers looking to rein in costs while maintaining the quality of CKD care.

Keywords

dialysis; end-stage renal disease; initiation

INTRODUCTION

Value in healthcare is defined as the quality of care relative to cost. Maintenance dialysis therapy is associated with substantial morbidity and expense, so it is not surprising that policy-makers are interested in finding value in the delivery of dialysis care. The timing of initiation of dialysis in patients with progressive chronic kidney disease (CKD) is one area that could be targeted to improve value. Over the past decade, there has been a trend towards initiation of dialysis at progressively higher levels of estimated glomerular filtration rate (eGFR), generally assumed to represent an intervention earlier in the course of kidney disease [1,2]. The landmark Initiating Dialysis Early And Late (IDEAL) trial demonstrated that this practice did not improve patient outcomes and increased costs [3,4]. This article critically reviews recent literature surrounding the timing of dialysis initiation and its implications for improving the value of dialysis care.

FACTORS DRIVING THE GROWTH OF EARLY DIALYSIS INITIATION

In 1996 19% of individuals starting maintenance dialysis had an eGFR above 10 ml/min/1.73m² at the start of dialysis, but by 2009 this percentage had grown to 53.8% (Fig. 1). Furthermore, by 2009 20% of patients were initiating dialysis with an eGFR above 15 ml/min/1.73m² [5]. Guidelines from professional societies are widely seen as promoting this strategy. As an example, the 1997 National Kidney Foundation Kidney Disease Quality Outcomes Initiative (KDOQI) clinical practice guidelines suggested that initiation of dialysis be considered when the arithmetic mean of the urea and creatinine clearances fell below approximately 10.5 ml/min/1.73m² except in well nourished, asymptomatic patients [6]. These were updated in 2006 to suggest that when the eGFR fell below 15 ml/min/1.73m² the 'nephrologist should evaluate the benefits, risks and disadvantages of beginning kidney replacement therapy.' They went on to say that certain signs and symptoms might justify the initiation of dialysis when the eGFR was above 15 ml/min/1.73 m² [7].

These recommendations were based on several assumptions that now appear questionable. For example, one line of reasoning postulated that dialytic clearance of low-molecular-weight solutes was comparable to endogenous kidney function, and that higher levels of small solute removal could improve nutritional status and survival [2■]. Subsequent clinical trials showed that residual kidney function, and not dialytic clearance, was associated with improved nutritional status and survival [8–10]. A second line of reasoning was that at very low levels of kidney function, kidney disease progressed inexorably to kidney failure. However, recent studies suggest that progression of kidney disease may be slow in certain subgroups of patients, most notably the elderly, even when eGFR is markedly reduced [11,12].

Clinical practice guidelines may have also unintentionally conflated the CKD staging system with appropriate timing of initiation of dialysis, and minimized the role of uremic signs or symptoms. In a study of 2402 nursing home residents initiating dialysis, Kurella Tamura *et al.* [13■] assessed the extent to which early initiation of dialysis could be explained by symptom burden and symptom trajectories. The authors found that seven signs and symptoms commonly associated with declining kidney function, such as volume overload and cognitive or functional decline, accounted for less than one-third of all cases of early dialysis initiation including less than half of all cases of early out-patient dialysis initiation, suggesting that dialysis initiation may be primarily prompted by laboratory values in a significant fraction of patients.

RECENT OBSERVATIONAL STUDIES OF EARLY DIALYSIS INITIATION AND OUTCOMES

Early observational studies examining outcomes in relation to kidney function at dialysis start suggested the possibility of a survival advantage with earlier initiation [14–16]. These early studies were limited by lead time and selection biases, and did not account for differences in age or comorbidity.

Since 2001, at least 10 observational studies have examined the issue of survival in relation to eGFR at initiation of dialysis using a variety of methods to account for confounding and other potential biases. In all but two of these studies, earlier initiation was associated with a poorer outcome [17–25,26■]. For example, in a study using data from the US Renal Data System (USRDS), Wright *et al.* [24] examined 896 546 patients who initiated dialysis between 1995 and 2006. They found a dose-dependent increase in mortality associated with earlier dialysis initiation. Those initiating dialysis with an eGFR higher than 15 ml/min/1.73

m² had a 66% higher risk of death when compared to individuals who started dialysis when the eGFR fell below 5 ml/min/1.73 m² [24].

Similar results were seen in studies from Canadian and Taiwanese cohorts. In the Canadian study, a 48% higher risk of death was seen with initiation of dialysis at an eGFR above 10.5 ml/min/1.73 m² when compared to individuals who initiated at a level below this [25]. This increase in mortality was attenuated to 18% after adjustment for demographics, comorbidity and a variety of other factors but still remained statistically significant. In the Taiwanese cohort, the median eGFR at the start of dialysis was lower (4.7 ml/min/1.73 m²) compared to other cohorts, but a similar relationship between higher eGFR and higher risk of 1-year mortality independent of comorbid conditions was observed in this study [23]. In contrast, a French cohort study found that age and comorbidity explained almost all of the excess mortality risk associated with higher eGFR at dialysis initiation [22].

Given the concerns that eGFR may not accurately reflect kidney function in patients with low muscle mass, Rosansky *et al.* [26] recently examined patients between the ages of 20 and 64 who initiated dialysis with no reported comorbidities other than hypertension. Once again, a dose-dependent increase in mortality was found with higher eGFR at dialysis initiation. Even among the presumably most healthy subgroup with a serum albumin concentration above 3.5 g/dl, those who initiated dialysis with an eGFR of above 15 ml/min/1.73 m² had more than a three-fold increased risk for death during the initial 6 months of dialysis when compared to individuals who started dialysis with an eGFR of below 5 ml/min/1.73 m². Thus, the most recent observational studies suggest that early initiation of dialysis is not beneficial and may be harmful.

IDEAL TRIAL

The IDEAL trial randomized 828 patients with advanced CKD from 32 centers in Australia and New Zealand to either early or late start dialysis, which were defined as a Cockcroft–Gault estimated creatinine clearance of 10–14 ml/min/1.73m² and 5 to 7 ml/min/1.73m², respectively. Cockcroft–Gault equation based values corrected for body surface area were selected as the triggers for dialysis initiation as the authors wanted to develop criteria with broad clinical utility, while avoiding reliance on potentially inaccurate timed urine collections [27]. The four-variable Modification of Diet in Renal Disease (MDRD) equation to estimate GFR was not used to determine eligibility or timing of initiation, but was reported in the study results [3].

Patients were eligible for inclusion if they were over 18 years of age and had progressive CKD and an estimated creatinine clearance of 10–20 ml/min/1.73m², including those with failing kidney transplants. Individuals with anticipated kidney transplantation within a year of enrollment, a recent diagnosis of cancer likely to affect survival or an inability to provide informed consent were excluded. Patients randomized to the late start arm of the trial were able to start dialysis earlier (i.e. with an estimated creatinine clearance >7 ml/min/1.73m²) based on the recommendation of their treating physician.

Patients were followed for a median 3.6 years. The primary outcome was all-cause mortality. Secondary outcomes included cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, or new-onset angina), infectious events (death or hospitalization due to any infection-related cause), and complications of dialysis (temporary placement of an access catheter, need for access revision, infection at the access site, or fluid and electrolyte disorders requiring hospitalization, additional dialysis, or both). In addition, cost and quality-of-life data were recorded.

The mean estimated creatinine clearance at dialysis initiation was 12.0 ml/min/1.73m² in the early start group and 9.8 ml/min/1.73m² in the late start group (9.0 and 7.2 ml/min/1.73m² in the early and late start groups, respectively, using MDRD eGFR). More than 75% of patients randomized to the late start group initiated dialysis before reaching the target eGFR, primarily due to the development of uremic symptoms (Fig. 2). Nevertheless, the late start strategy resulted in a median 5.6 month delay in the time from randomization to dialysis start.

In the intention-to-treat analysis there was no difference between the groups in the primary outcome of all-cause mortality or in the secondary outcome of quality of life. Subgroup analysis by age, sex, body mass index, serum albumin concentration and the presence of diabetes or cardiovascular disease did not demonstrate material differences compared to the primary analysis.

It should be noted that the study cohort was predominantly white and had a lower comorbidity burden than the average US patient initiating dialysis. Among patients who initiated dialysis, the use of peritoneal dialysis was higher than in the US. Perhaps most importantly, individuals participating in the trial were receiving regular nephrology care for 3 years on average, prior to randomization, and they received very close follow-up subsequently. Thus, the results are not generalizable to patients who do not have reliable access to care, and may not be generalizable to patients with acute on chronic kidney failure. Nevertheless, IDEAL demonstrates that among patients with advanced CKD and reliable access to care, early initiation of dialysis in the absence of symptoms is not beneficial.

IMPLICATIONS OF EARLY INITIATION OF DIALYSIS

In the economic analysis of the trial, resource utilization data collected during the study period were used to estimate differences in quality of life and costs from a societal perspective. The late or symptom-based strategy of dialysis initiation was associated with more quality-adjusted life years for lower cost than early start dialysis. Total costs were nearly \$15 720 (US dollars) higher for patients in the early start group [4■■■]. It should be noted that these figures may underestimate cost differences in the US, since the proportion of patients utilizing peritoneal dialysis is lower in the US. In the accompanying editorial, Manns and Quinn [28] estimate the adoption of a late or symptom-based strategy of dialysis initiation could lead to over \$1 billion in savings for the US healthcare system each year.

O'Hare *et al.* [29■■■] used a modeling approach to estimate the magnitude of change in the timing of dialysis initiation over the past decade. They used information from a large integrated healthcare system to model the rate of eGFR decline prior to the onset of dialysis in order to predict how many additional days on dialysis patients spent in 2007 versus 1997. Over the past decade, they estimated dialysis was initiated an average of 5 months earlier in 2007 compared to 1997. Most strikingly, in patients 75 years and older dialysis was begun almost 8 months earlier in 2007 versus 1997. They estimate these changes translate to an increase in cost of more than \$1.5 billion if extrapolated to all US patients who initiated dialysis in 2007.

The results of IDEAL and other recent studies suggest that early initiation of dialysis has not improved the value of care for patients or the healthcare system. How might we modify the current approach to improve value? As a first step, we should delay initiation of dialysis among patients with a creatinine clearance above 10 ml/min/1.73m² and no uremic symptoms or other indications for dialysis initiation. In other words, we should avoid 'preemptive' or 'healthy start' dialysis initiation among patients who have reliable access to follow-up care. Such a strategy could also provide additional time for a permanent vascular access to mature. How long dialysis initiation can be safely delayed is currently unclear, but

a reasonable approach is to delay initiation until symptoms interfere with quality of life, traditional indications for dialysis initiation develop (i.e. fluid overload not responsive to diuretics, electrolyte disturbances), or creatinine clearance is 5–7 ml/min/1.73m². More data are needed to guide the next steps. For example, uremic symptoms were cited as the primary reason for earlier initiation of dialysis in the late start arm of IDEAL (Fig. 2). Additional information about the character of these symptoms and their course after initiation of dialysis could help to refine decision-making. Related to this idea, clinical trials of delayed initiation are needed in older patients, the population most likely to experience early initiation of dialysis. Many symptoms used as indications for dialysis are nonspecific for uremia, and may contribute to earlier initiation especially in older and chronically ill patients. Small pilot studies suggest delayed initiation of dialysis is safe in selected older patients, but larger studies are needed [30]. Could an incremental approach to dialysis initiation balance the risks and benefits with reduced cost? Finally, what role should residual kidney function play in these decisions, and what is the optimal measure?

CONCLUSION

Early initiation of dialysis does not improve patient outcomes or quality of life and increases costs. Strategies to safely delay initiation of dialysis in patients with CKD are beginning to emerge, and hold promise for improving the value of dialysis care for patients and the healthcare system.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1. Rosansky SJ, Clark WF, Eggers P, Glasscock RJ. Initiation of dialysis at higher GFRs: is the apparent rising tide of early dialysis harmful or helpful? *Kidney Int.* 2009; 76:257–261. [PubMed: 19455195]
2. Rosansky S, Glasscock RJ, Clark WF. Early start of dialysis: a critical review. *Clin J Am Soc Nephrol.* 2011; 6:1222–1228. [PubMed: 21555505] ■ A review of the ‘conventional wisdoms’ that supported the strategy of early initiation of dialysis.
3. Cooper BA, Branley P, Bulfone L, et al. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med.* 2010; 363:609–619. [PubMed: 20581422] ■■ A large multicenter prospective trial comparing early versus late dialysis initiation strategies. The late start strategy was associated with an average 6 month delay in dialysis initiation and no difference in mortality or any of the secondary outcomes.
4. Harris A, Cooper BA, Li JJ, et al. Cost-effectiveness of initiating dialysis early: a randomized controlled trial. *Am J Kidney Dis.* 2011; 57:707–715. [PubMed: 21349618] ■■ This is an economic analysis of the IDEAL trial that compares the cost per quality-adjusted life year of early and late start dialysis initiation strategies. The analysis found that early initiation was associated with higher costs and no difference in quality of life compared to the late initiation strategy.
5. US Renal Data System. *USRDS 2009 Annual Data Report.* National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2009.

6. NKF-DOQI clinical practice guidelines for peritoneal dialysis adequacy. National Kidney Foundation. *Am J Kidney Dis.* 1997; 30:S67–S136.
7. Foundation NK. KDOQI Clinical practice guidelines and clinical practice recommendations for 2006 updates: hemodialysis adequacy, peritoneal dialysis adequacy and vascular access. *Am J Kidney Dis.* 2006; 48:S1–S322. [PubMed: 17045862]
8. Paniagua R, Amato D, Vonesh E, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol.* 2002; 13:1307–1320. [PubMed: 11961019]
9. Termorshuizen F, Korevaar JC, Dekker FW, et al. The relative importance of residual renal function compared with peritoneal clearance for patient survival and quality of life: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *Am J Kidney Dis.* 2003; 41:1293–1302. [PubMed: 12776283]
10. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. *J Am Soc Nephrol.* 1996; 7:198–207. [PubMed: 8785388]
11. Hemmelgarn BR, Zhang J, Manns BJ, et al. Progression of kidney dysfunction in the community-dwelling elderly. *Kidney Int.* 2006; 69:2155–2161. [PubMed: 16531986]
12. O'Hare AM, Choi AI, Bertenthal D, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol.* 2007; 18:2758–2765. [PubMed: 17855638]
13. Tamura, M Kurella; O'Hare, AM.; McCulloch, CE.; Johansen, KL. Signs and symptoms associated with earlier dialysis initiation in nursing home residents. *Am J Kidney Dis.* 2010; 56:1117–1126. [PubMed: 20974509] ■ This study examines commonly assessed signs and symptoms in a cohort of nursing home residents and their relationship to early initiation of dialysis. Symptom burden explained less than one third of cases of early dialysis initiation in this elderly cohort.
14. Bonomini V, Vangelista A, Stefoni S. Early dialysis in renal substitutive programs. *Kidney Int Suppl.* 1978:S112–S116. [PubMed: 357813]
15. Bonomini V, Feletti C, Stefoni S, Vangelista A. Early dialysis and renal transplantation. *Nephron.* 1986; 44:267–271. [PubMed: 3540689]
16. Tattersall J, Greenwood R, Farrington K. Urea kinetics and when to commence dialysis. *Am J Nephrol.* 1995; 15:283–289. [PubMed: 7573184]
17. Korevaar JC, Jansen MA, Dekker FW, et al. When to initiate dialysis: effect of proposed US guidelines on survival. *Lancet.* 2001; 358:1046–1050. [PubMed: 11589934]
18. Traynor JP, Simpson K, Geddes CC, et al. Early initiation of dialysis fails to prolong survival in patients with end-stage renal failure. *J Am Soc Nephrol.* 2002; 13:2125–2132. [PubMed: 12138145]
19. Beddhu S, Samore MH, Roberts MS, et al. Impact of timing of initiation of dialysis on mortality. *J Am Soc Nephrol.* 2003; 14:2305–2312. [PubMed: 12937307]
20. Sawhney S, Djurdjev O, Simpson K, et al. Survival and dialysis initiation: comparing British Columbia and Scotland registries. *Nephrol Dial Transplant.* 2009; 24:3186–3192. [PubMed: 19390120]
21. Stel VS, Dekker FW, Ansell D, et al. Residual renal function at the start of dialysis and clinical outcomes. *Nephrol Dial Transplant.* 2009; 24:3175–3182. [PubMed: 19515803]
22. Lassalle M, Labeeuw M, Frimat L, et al. Age and comorbidity may explain the paradoxical association of an early dialysis start with poor survival. *Kidney Int.* 2010; 77:700–707. [PubMed: 20147886]
23. Hwang SJ, Yang WC, Lin MY, et al. Impact of the clinical conditions at dialysis initiation on mortality in incident haemodialysis patients: a national cohort study in Taiwan. *Nephrol Dial Transplant.* 2010; 25:2616–2624. [PubMed: 20519231]
24. Wright S, Klausner D, Baird B, et al. Timing of dialysis initiation and survival in ESRD. *Clin J Am Soc Nephrol.* 2010; 5:1828–1835. [PubMed: 20634325]
25. Clark WF, Na Y, Rosansky SJ, et al. Association between estimated glomerular filtration rate at initiation of dialysis and mortality. *CMAJ.* 2011; 183:47–53. [PubMed: 21135082]

26. Rosansky SJ, Eggers P, Jackson K, et al. Early start of hemodialysis may be harmful. *Arch Intern Med.* 2011; 171:396–403. [PubMed: 21059968] ■■ This observational study examines a relatively healthy cohort of US patients and shows an increase in mortality associated with initiating dialysis at higher levels of kidney function, particularly among the ‘healthiest’ subset of patients, as indicated by those with preserved serum albumin concentrations.
27. Cooper BA, Branley P, Bulfone L, et al. The Initiating Dialysis Early and Late (IDEAL) study: study rationale and design. *Perit Dial Int.* 2004; 24:176–181. [PubMed: 15119639]
28. Manns BJ, Quinn RR. Early dialysis of no benefit to the patient or the healthcare system. *Am J Kidney Dis.* 2011; 57:649–650. [PubMed: 21496724]
29. O’Hare AM, Choi AI, Boscardin WJ, et al. Trends in timing of initiation of chronic dialysis in the United States. *Arch Intern Med.* 2011; 171:1663–1669. [PubMed: 21987197] ■■ This study estimated the magnitude of changes in the timing of dialysis initiation over the last decade in terms of additional days spent on dialysis. The authors found that US patients are initiating dialysis an average of five months earlier in 2007 versus 1997.
30. Brunori G, Viola BF, Parrinello G, et al. Efficacy and safety of a very-low-protein diet when postponing dialysis in the elderly: a prospective randomized multicenter controlled study. *Am J Kidney Dis.* 2007; 49:569–580. [PubMed: 17472838]

KEY POINTS

- Over the past decade, there has been a striking shift in dialysis initiation practices towards earlier initiation (i.e. with a higher eGFR).
- By some estimates, this shift in practice has resulted in five additional months on dialysis for the average patient.
- The IDEAL trial demonstrated that early initiation of dialysis does not improve survival or quality of life and increases costs.
- The practice of 'healthy start' dialysis should be discouraged.

FIGURE 1. Percentage of incident ESRD patients initiating dialysis with an estimated glomerular filtration rate at or above 10 ml/min/1.73m². ESRD, end-stage renal disease.

FIGURE 2. Reasons for initiating dialysis early in the late start group of the IDEAL trial. Data from [3■■■].