Initiation of dialysis at higher GFRs: is the apparent rising tide of early dialysis harmful or helpful?

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Over the past decade a trend of increasing estimated glomerular filtration rate (eGFR) at the initiation of dialysis for treatment of end-stage renal disease (ESRD) has been noted in the United States. In 1996, only 19% of patients began dialysis therapy with an eGFR of greater than 10 ml/min/1.73m² (denoted as ‘early start’), but by 2005 the fraction of early start dialysis patients had risen to 45%. This review examines US dialysis data, national guidelines, and publications relevant to the early start phenomenon. It is not known whether early start of dialysis is beneficial, harmful or neutral with respect to the outcome of dialysis treatment for ESRD. Available data indicate that mortality while on dialysis therapy may be higher in those subjects with early start. Comorbidities present at the time of dialysis initiation do not appear to be a major driving force for early start patients. As well, residual kidney function in these patients is a major contributor to total urea or creatinine clearance. This can be a positive factor for patient outcomes and might be compromised by early start. Finally, we estimate the dollar cost of early start to the US Medicare-supported ESRD program. Properly designed, prospective and randomized studies may help to clarify the benefit or harm of early start of dialysis for ESRD.

The purpose of this Mini-Review is to describe and analyze a recent phenomenon; namely, the decline in average serum creatinine levels (which translates to an increase in the calculated estimated glomerular filtration rate (eGFR)) at the initiation of dialysis in the USA in the preceding decade. Using standard analysis files from the United States Renal Data System (USRDS), we examined trends in eGFR at initiation of dialysis and found a dramatic increase in the frequency of patients initiating dialysis (both hemodialysis and peritoneal dialysis) with estimated eGFRs above 10 ml/min per 1.73 m², herein denoted as ‘early start’ of dialysis¹ (see Figure 1). In 1996 15% of patients initiated dialysis with an eGFR of 10–14.9 ml/min per 1.73 m² and only 4% started dialysis with eGFR greater than 15 ml/min per 1.73 m². Ten years later, in 2005, 30% of patients started dialysis at eGFR values of 10–14.9 ml/min and 15% started dialysis with eGFR values greater than 15 ml/min per 1.73 m². The frequency of eGFR ≥10 ml/min per 1.73 m² rose to 54% in 2005 from 25% in 1996 in those patients over the age of 75 years at the time of initiation of dialysis. In both 1996 and 2005, there was a gradual increasing trend to initiate dialysis at higher levels of eGFR with age, in adults ages 20 to over 75 years of age (Figure 2), but this relationship became steeper in 2005. Similar observations have been reported by Kurella et al.², in 2007 in octogenarians and nonagenarians. A very large fraction of the rise in the incident dialysis frequency over the period 1996–2005 can be attributed to an early start (see Figure 1).

These observations generate several important questions: (1) what are the potential impacts of this change in practice on the subsequent mortality and/or morbidity of dialysis therapy? (2) What factors have driven the change in the frequency of early start of dialysis and (3) what are the implications of these observations on the reported incidence of patients newly treated with dialysis and the attendant expense to the Medicare-ESRD program?

WHAT ARE THE IMPACTS OF ‘EARLY START’ ON DIALYSIS OUTCOMES?

The timing of initiation of dialysis for ESRD is a matter of clinical judgment guided by values of residual kidney...
function (RKF) and symptoms and signs present in the patients, including those related to comorbidity. In 1999 Obrador et al., observed that 23% of the US ESRD population, between 1995 and 1997, started dialysis at an eGFR less than 5 ml/min per 1.73 m². They opined that this 'late start' of dialysis needed further examination, including studies of the impact on outcomes and cost of ESRD treatment. In 1997 the National Kidney Foundation (NKF) workgroup, after a comprehensive review of the published literature, recommended that initiation of dialysis be considered when the arithmetic mean of the urea and creatinine clearances fell below approximately 10.5 ml/min per 1.73 m² except in well-nourished, asymptomatic patients. One of the early studies used to support this recommendation was the CANUSA study of continuous ambulatory peritoneal dialysis, an observational study that suggested a potential benefit on renal survival of a weekly peritoneal creatinine clearance of >70l/1.73 m². This would correspond to an RKF measured by creatinine clearance of about 9–14 ml/min per 1.73 m². Subsequent studies, including the ADEMEX randomized control trial, led to doubt regarding the appropriateness of using of peritoneal clearances of creatinine for guiding the timing of initiation of dialysis. Similar conclusions were reached in the HEMO trial of hemodialysis therapy. Both the ADEMEX and HEMO trials demonstrated that higher levels of removal of urea or creatinine by dialysis do not necessarily translate into better outcomes. In addition, although the CANUSA study supported a relationship between the level of peritoneal clearance and survival, one can argue that the RKF in these continuous ambulatory peritoneal dialysis patients was primarily responsible for the survival advantage. Furthermore, it is difficult to understand why, in patients with a RKF roughly equivalent to a weekly peritoneal urea clearance of 701 per min, thus double the minimal peritoneal clearance suggested by CANUSA, the NKF guideline for RKF at the start of dialysis was promulgated.

In 2006, the NKF work group updated the guidelines for initiation of hemodialysis and stated that 'at CKD Stage 5, when the eGFR is <15 ml/min per 1.73 m², that nephrologists should evaluate the benefits, risks and disadvantages of beginning renal replacement therapy.' They also suggested that initiation of dialysis therapy before CKD Stage 5 (an eGFR of >15 ml/min per 1.73 m²) may be appropriate in patients who have symptoms believed to be related to both their comorbidities and their level of RKF. The NKF workgroup also opined that the outcome data relating the intensity of dialysis therapy (measured as Kt/V urea or creatinine clearance) to improved outcomes, provided a justification for the use of similar values of eGFR as guidelines for the initiation of dialysis therapy despite results to the contrary of the two available randomized controlled trials addressing this issue. Nevertheless it should be pointed out that existing guidelines do not advocate a dialysis start point at a specific eGFR or serum creatinine level, which some nephrologists may be undertaking due to a misinterpretation of the NKF guidelines.

Additional published studies have not been able to demonstrate any clear-cut benefits for early start of dialysis. Studies by Bonomini, et al., led to a recommendation for early start but did not account for 'lead-time bias' (that is, not basing survival analysis on the same starting point of RKF in patients who started early or late on dialysis) or comorbidity. Churchill et al., in 1997, examined the available studies to date dealing with the issue of dialysis start time. These authors acknowledged the confounding factors, including referral time bias, comorbidity, patient compliance, and recommended a randomized controlled trial to produce a definitive answer. Nevertheless, these authors supported the initiation of dialysis at a creatinine clearance of...
EARLY START?
WHAT ARE THE DRIVERS OF THE INCREASED FREQUENCY OF EARLY START?

Kurella et al.², when comparing octogenarian and nonagenarians, starting dialysis in 1996 versus 2003 noted the latter group had a higher eGFR at initiation and less comorbidity, but no difference in 1 year survival. Murtagh et al.¹⁷, in a retrospective survival analysis of CKD 5 patients over 75 years of age, found no difference in comorbidity between patients treated with dialysis versus non-dialytic, nephrologist care. These data tend to suggest that early start is not being driven by a rise in the fraction of patients starting dialysis with extensive comorbidities, as will be discussed below.

WHAT ARE THE DRIVERS OF THE INCREASED FREQUENCY OF EARLY START?

As the available data are largely observational; they are not conclusive as to mechanisms underlying the early start of dialysis and subsequent outcomes. Several non-mutually exclusive hypotheses may be offered as possible explanations for the secular trend in early start (as defined herein). These include: (1) Too heavy reliance on eGFR values instead of symptoms and signs of uremia for determining the optimal time for initiation of dialysis; (2) a general lack of understanding by Nephrologists concerning the guidelines for the use of eGFR or creatinine clearance values as one part of the process for determining the ‘best’ time to initiate dialysis; (3) Relative ease of management of renal failure related issues (fluid overload, hypertension, uremic bone disease, anemia) with dialysis therapy compared with customary conservative outpatient care; (4) preemptive dialysis, especially in patients with perceived uremia-related weight loss, anorexia and manifestations of possible malnutrition (for example, hypoalbuminemia); (5) financial motives to initiate dialysis early. With respect to the latter hypothesis, similar secular trends in eGFR at initiation of dialysis between 1997 and 2006 (43% increase in mean eGFR at dialysis initiation) have been noted in the United Kingdom, a country where financial incentives favoring early start would seem to be lacking due to the low penetrance of for-profit dialysis units and the lack of financial benefit to the treating physician (UK Renal Registry Report 2006: http://www.renalreg.com/downloads/publications/). In addition, financial incentives for early start of dialysis were not different in the USA during the 10-year interval of our study. Finally, according to our analysis of the USRDS data, for-profit outpatient dialysis facilities have very similar eGFR at start of dialysis versus not-for-profit outpatient dialysis facilities during the 1995–2006 interval. A small rise in the fraction of incident ESRD due to diabetes (43% in 1996 and 44.2% in 2005), does not account for the rise in the frequency of early start over the time periods examined. At the present time, it is not possible to determine, with any degree of certainty the most likely mechanisms underlying the observed secular trends in eGFR at the time of starting dialysis. In addition, to date, no randomized controlled trials of the impact of timing of initiation of dialysis on subsequent outcome have been published. The IDEAL randomized controlled trials, which is in progress, may help clarify this
uncertainty and provide useful data on the relationship of timing of initiation of dialysis and survival, morbidity, quality of life and costs of dialysis therapy.\textsuperscript{18}

**CAN EARLY START BE HARMFUL?**

Collectively, the observations concerning a rise in the frequency of early start prompts the need to consider the potential harms of early start of dialysis because conclusive evidence of a clear benefit is lacking. The NKF workgroup in their 2006 update emphasized the importance of preservation of RKF as prospective randomized trials and observational studies have confirmed the importance of RKF in patients undergoing dialysis therapy.\textsuperscript{7} The dose of dialysis received may affect the outcome in patients without any RKF, but may have less of an impact on outcome in those with substantial RKF. The CANUSA study showed a strong association between RKF at the start of dialysis and better nutritional status.\textsuperscript{5} O’Hare et al.\textsuperscript{19}, in a study of the US Veterans patients with CKD class 3–5, 47% of whom were over 75, found that RKF declined more slowly in the elderly versus younger cohort. In addition, these authors demonstrated the important point that patients over 75 with CKD 4 (eGFR 15–29 ml/min per 1.73 m\textsuperscript{2}) were far more likely to die than to develop ESRD. Thus, preemptive start of hemodialysis, especially in the elderly with significant levels of RKF, may be detrimental because loss of eGFR may accelerate after initiation of dialysis.\textsuperscript{20} In addition, according to current guidelines, many of these elderly patients with stable CKD 4 may be subject to inappropriate vascular access procedures, often repeated, with their accompanying post operative complications, including serious infection. Hemodialysis therapy is not innocuous and patients with adequate urine output, often associated with higher levels of RKF may be prone to intra-dialytic hypotension. For example, Termorshuizen, et al.\textsuperscript{21}, in the Netherlands Cooperative Study on the adequacy of dialysis, a large prospective, observational multi-center cohort study demonstrated, as did others, that RKF had a direct and strong relationship to a decreased expected mortality. On the other hand, excess ultrafiltration relative to interdialytic weight gain, which they postulated was more likely in those patients with high RKF, was an important predictor of mortality, independent of dialysis clearance.

The forces driving the changes in the frequency of early start of dialysis remain to be elucidated. It is possible that KDOQI guideline development and promulgation and the unrealized but postulated benefits of early start have contributed to the trends favoring earlier start of dialysis between 1996 and 2005. Based on the consideration detailed above, it does not appear that an overall increase in comorbidities present at the time dialysis is initiated can fully explain these trends.

**WHAT ARE THE POTENTIAL EFFECTS OF EARLY START ON INCIDENCE AND COST OF DIALYSIS THERAPY?**

The phenomenon of a ‘rising tide’ of early start of dialysis (herein defined as an eGFR > 10 ml/min per 1.73 m\textsuperscript{2} at initiation of dialysis) may have influenced the incidence of newly treated patients and the cost of the Medicare-ESRD program as well. Figure 1 demonstrates that most of the increase in USRDS treatment incidence counts over the period 1996–2005 occurred in early start dialysis patients. According to an analysis of the 2006 USRDS annual data report, the average costs per year for treating dialysis patients over the age of 65 years was $71,000. Comparing 1996–2005 dialysis treatment incidence counts, for the over 65-year cohort, with starting eGFR greater than 10 ml/min per 1.73 m\textsuperscript{2}, there were 18,076 more patients started in 2005 versus 1996. If one assumes that half these new starts could have been safely delayed, the annual additional costs could be estimated to be approximately $641 million in 2006 alone.

It is not clear how many or indeed if any nephrologists use a specific eGFR level as an arbitrary threshold as a sole indication to start dialysis. Additional studies are needed to evaluate this possibility. Patients with a higher eGFR at dialysis initiation may well also have some of the other accepted clinical indications for starting the dialysis. The presence of uremic encephalopathy, uremic pericarditis, diuretic-resistant volume overload with congestive heart failure and perhaps progressive malnutrition (due to anorexia) may be indications for starting dialysis, even if eGFR is > 10 or even > 15 ml/min per 1.73 m\textsuperscript{2}. However, conservative management, especially in the elderly with multiple comorbidities and at most 1–2 year life expectancies, may be a better choice especially when considering quality of life issues. Murtagh, et al.\textsuperscript{17}, suggested that in patients with significant comorbidity (ischemic heart disease, in particular), non-dialytic therapy provided by a nephrologist might offer a comparable survival without the risks and quality of life effects of dialysis treatment. The regular monitoring and careful management of blood pressure, nutrition and psychosocial well-being that attends dialysis therapy should also be offered to these patients.

Regardless of its underlying mechanisms or effects, the ‘rising tide’ of an early start of dialysis is viewed with concern, as it may not be justified on the basis of the risk/benefit relationship. Efforts should be undertaken now to study the phenomenon further with particular emphasis on the stability of eGFR in CKD Stages 4 and 5. Specifically, a US study of the impact of early versus late start of dialysis (using eGFR as the discriminating variable) on morbidity, mortality, and quality of life in the pre-and post-dialysis periods could be undertaken. This study would differ from the IDEAL protocol in that all subjects would be randomized at the early start (relative to RKF) to thrice weekly dialysis or to thrice weekly assessments and non-dialytic medical interventions to balance the benefits of a thrice weekly health assessment in a dialysis program.

**SUMMARY AND CONCLUSIONS**

A clear trend of initiating dialysis at higher levels of estimated residual kidney function has been evident between 1996 and 2005. The reasons underlying this trend require further study.
However, if this trend continues it will likely have adverse financial implications. The basis for starting dialysis early (eGFR over 10 ml/min/1.73 m²) may be fundamentally flawed, because recent studies do not support a positive relationship between dialysis clearance as an additive contributor to a patient’s overall renal function and to outcomes on dialysis treatment. Starting dialysis early might result in a more rapid decline of a patient’s residual kidney function. Residual kidney function has been shown to have a positive relation to outcome.9,19 Until randomized controlled trials are completed and with the possibility that, in some cases, early start of dialysis therapy may be harmful, the nephrology community needs to ‘first do no harm’, and only offer early dialysis when a clear indication for such a strategy exists.

**DISCLOSURE**

All the authors declared no competing interests.

**ACKNOWLEDGMENTS**

The authors thank Ms Ginardi and Ms Bird, William Jennings Bryan Dorn VA Hospital, Columbia, SC, for their librarian assistance, and Ms Alice Griffin, for assistance with the article.

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