When should we commence dialysis? The story of a lingering problem and today’s scene after the IDEAL study

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Abstract
Over the last 15–20 years, there has been an increasing trend for dialysis to be commenced earlier in the development of chronic kidney disease (CKD). The drivers for initiation of dialysis at higher levels of renal function are complex but were primarily based on the assumption that by improving solute and water clearances with earlier dialysis, morbidity, mortality and quality of life would be improved. The Initiating Dialysis Early and Late (IDEAL) trial definitively demonstrated that elective earlier initiation of dialysis was not associated with improved clinical outcomes or quality of life. Indeed, no subset of patients was found to benefit from earlier dialysis. Observational data suggests that patients who commence dialysis with higher levels of renal function are more likely to have significant comorbidity that results in higher mortality rates compared to patients who remain clinically well and biochemically stable and are able to defer the initiation of dialysis till later in the course of CKD. However, patients who are able to defer dialysis should have appropriate access created so as to avoid the use of temporary catheters and to facilitate initiation using the preferred dialysis modality. Estimates of glomerular filtration rates in Stage 5 CKD have been poorly validated and should not be used as the key determinant influencing the commencement of dialysis. The results of the IDEAL trial have influenced guidelines internationally and provide clinicians, patients and health care providers with important information to drive clinical decision making and rational service planning.

Keywords: dialysis initiation; optimal dialysis outcomes

Background and purpose of this commentary
Dialysis has been initiated at higher levels of renal function increasingly over the last 15–20 years [1, 2]. Although the validity of the estimated glomerular filtration rate (eGFR) in people with Stage 5 chronic kidney disease (CKD) is lacking, available data would suggest that in the USA, over 50% of patients start dialysis with an eGFR of >10 mL/min/1.73m² and ~20% of people start dialysis with an eGFR of >15 mL/min/1.73m² [2]. This increase is equally evident across all age groups and, to date, shows no sign of abatement with time (Figure 1). Although the level of kidney function at which glomerular filtration rate (GFR) is commenced varies internationally [4], guidelines around the globe suggest a level of kidney function at which dialysis should be considered. Clearly, if evidence were available to support improved clinical or economic outcomes with the initiation of dialysis earlier in the course of CKD, there would be justification for the use of ‘early’ dialysis. Prior to the results of the Initiating Dialysis Early and Late (IDEAL) trial, recommendations to start dialysis early were based on the opinion that dialysis should be initiated once endogenous clearances fell below the target clearances proposed in various international guidelines for continuous ambulatory peritoneal dialysis [5]. Retrospective data, predominantly from the 1980s and early 1990s, suggested an improvement in survival [6], nutritional parameters [7], fluid management, social and economic productivity and quality of life [8] with early start. Conversely, it was argued that many complications of CKD leading to increased hospitalization, including those related to dialysis access, were amplified by early dialysis. However, those studies were confounded by referral bias, lead time bias and the comorbidity of the patients. Since the 1980s when the initial studies were reported, the demographic of the dialysis population has changed. Many more patients with diabetic nephropathy and of an older age group are accepted into dialysis programmes. Much of the comorbidity of ‘end-stage’ diabetes and old age is similar to ‘end-stage’ CKD, e.g. neuropathy and cardiovascular disease. Hence, invalid assumptions were made that improving renal clearances by dialysis would afford benefit with respect to dialysis complications. This has contributed to the increasing number of patients on dialysis, in particular with diabetes mellitus and of an older age group [9]. Furthermore, several jurisdictions have had funding arrangements that incentivize the providers to start dialysis earlier in the development of progressive kidney disease [10]. Many studies currently reporting the benefits (or lack thereof) of starting dialysis early or later are similarly confounded by these issues.

The IDEAL study was undertaken to demonstrate definitely in a clinical trial, whether the timing of dialysis influenced mortality, cardiovascular or nutritional outcomes and quality of life and costs incurred. The study was
undertaken in an environment sceptical of success of the trial. Indeed, in 2002, Tatterstall in this journal suggested ‘There is a need for a prospective randomized controlled study to clarify this issue. It is recognized that such a study would be difficult to perform, as it would be almost impossible to enforce an unbiased subject allocation bias’ [11]. Similarly, Traynor et al. [12] stated that ‘Against this background, it may be such that a randomized prospective trial will never be performed, placing a greater emphasis on the results of retrospective and cohort studies’.

Summary of results of IDEAL

The study design and rationale were published in 2004 [13]. The key issues of relevance were that the patients were randomized to start dialysis at a GFR, estimated by the Cockcroft and Gault formula, of either 10–14 or 5–7 mL/min/1.73m², with stratification for dialysis modality (haemodialysis or peritoneal dialysis), study centre and the presence or not of diabetes. The pragmatic approach to the study design was taken in that the study protocol permitted patients allocated to the late–start arm to commence dialysis with an eGFR >7 mL/min/1.73m², based on the recommendation of the treating physician. There was no requirement for the physician to discuss this decision with the trial coordinating centre. The dialysis modality and prescription remained the choice of the patient and the treating physician. Each study centre was advised to consider timely placement of access for dialysis, but the timing was not specified in the protocol. It was assumed that a 10% difference in 3-year survival would be clinically important. Based on the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), a minimal sample size of 800 patients with 3-year follow-up was required and a final sample size of 828 was achieved. The demographics and characteristics of the patients enrolled in the IDEAL study were not statistically different from the patients recorded in the ANZDATA registry [14]. The major results of the IDEAL trial were reported in 2010 [15] and the economic analysis in 2011 [16]. In summary, there was no advantage in the early commencement of dialysis on the primary end point of all-cause mortality or the secondary end points of cardiovascular events, infectious complications, structural cardiac disease or nutritional parameters. Importantly, no subgroup, including those considered previously to have perhaps benefited from the earlier start of dialysis, such as the diabetic or the elderly, demonstrated any advantage in early versus late dialysis. In patients randomized to commence dialysis late, there was paradoxically an increased use of temporary dialysis catheters, suggesting an inappropriate complacency regarding vascular access when dialysis is electively deferred. The economic analyses not unexpectedly demonstrated an increase in dialysis costs when dialysis was commenced early and an increase in transport costs. Although the overall costs were greater in the early dialysis group, this was not statistically significant due to the large confidence intervals. Surprisingly, quality of life was not different in patients who started dialysis early versus late. Clearly, the results did not demonstrate any significant clinical or economic benefit in commencing dialysis at higher levels of endogenous renal function. Hence, policy decisions and drivers influencing the timing of initiation of dialysis should be reviewed. Indeed, as a result of the IDEAL trial, guidelines have been revised [17]. The European Renal Best Practice Guidelines have more strongly advocated that creatinine-based estimates of GFR should not be used to guide the start of dialysis. The recommendation to defer dialysis in asymptomatic patients with advanced renal disease is supported by the IDEAL results and allows appropriate medical, nursing and allied health input into planning treatment and future options.

Commentary on the IDEAL trial has been extensive. The difference in the eGFR at the start of dialysis between the early and late start groups (2.2 mL/min/1.73m²) has been suggested as a shortcoming of the trial. However, despite this apparently small difference, patients allocated to late-start group started dialysis almost 6 months later than those allocated to the earlier start group. This time interval is similar to that by which patients initiated dialysis earlier in 2007 compared with 1997, with the group starting dialysis by the greatest interval over this period being the patients over the age of 75 years [18]. The generalizability of our data has been questioned. However, the patients are representative of the Australian and New Zealand dialysis population. Furthermore, no differences in subgroup analyses were observed. The high rate of peritoneal dialysis has been considered to be different from common practice in Europe and the USA. However, no effect on primary or secondary outcomes of early versus late start dialysis was observed in the subgroup of patients electing to commence haemodialysis [19].

Changing clinical environments and practice: the swinging pendulum

The IDEAL trial was conceived in an environment where ‘more’ dialysis and ‘earlier’ dialysis were considered clinically beneficial. During the course of subject recruitment, and indeed, since the publication of IDEAL, these hypotheses have not been upheld. Indeed, despite the evidence that dialysis is being commenced earlier, more studies are emerging that suggest that patients who commence dialysis with higher degrees of endogenous renal function fare worse than those who start dialysis late [20–24]. The results are consistent
across most populations including those initially considered likely to benefit most from early-start dialysis, that is, the older [9] and diabetic [24] cohorts. These studies suffer from the same weaknesses as do all observational and cohort studies and despite survival modelling to correct mathematically for age and comorbidity, the evidence that elective early-start dialysis is harmful at best. However, the data are consistent across all cohorts in suggesting that patients who are able to defer dialysis till a later stage in the history of CKD do better than those who have clinical indications or comorbid conditions that require initiation of dialysis at higher levels of endogenous renal function (Table 1). Reanalysis of the survival of subjects in the IDEAL trial, based on Modification of Diet in Renal Disease (MDRD) estimation of GFR at the time of start of dialysis, confirms that those who were able to defer dialysis until eGFR was <6 mL/min/1.73m² had a greater probability of survival compared to those who started dialysis with higher levels of renal function (Pollock, Cooper, Harris et al., unpublished data). Clearly, such data do not suggest that dialysis is of itself harmful nor that dialysis ‘should’ be commenced at lower levels of eGFR. Indeed, observational data from the Taiwanese and Canadian haemodialysis cohorts suggest that comorbidity present in patients who commence dialysis at higher levels of eGFR accounts for excess mortality risk [2, 29]. These data support the conclusions of the IDEAL trial that the decision to initiate dialysis should be primarily independent of eGFR. Hence, the question of the value in measuring eGFR in Stage 5 CKD is raised.

Validity of using eGFR in patients with Stage 5 CKD

The IDEAL study was designed prior to the widespread use of eGFR based on the MDRD equation. The eGFR at randomization in the early versus late group was 13.0 and 13.1 mL/min/1.73m² when determined by the Cockcroft and Gault formula. However, the eGFR was considerably lower when estimated by the MDRD formula, being 9.8 and 9.9 mL/min/1.73m², respectively. At the time of dialysis start, the eGFR using the Cockcroft and Gault formula was 12 versus 9.8 and 9.0 versus 7.2 mL/min/1.73m² using the MDRD equation in the early versus late start groups, respectively. This difference in eGFR estimated by the two formulae is of considerable significance when one considers that the majority of studies report ‘early’ dialysis as being >10 mL/min/1.73m² based on the MDRD formula and the large and increasing numbers of patients who are starting dialysis with an MDRD eGFR of >15 mL/min/1.73m². Based on such MDRD criteria, the mean eGFR values at randomization for subjects in the IDEAL trial were in the ‘late’-start range, and, indeed, in excess of two-thirds of subjects actually started dialysis with an MDRD estimate of a GFR of <10 mL/min/1.73m². This amplifies the significance of the trial findings in that many people are able to delay dialysis safely provided nephrological oversight is provided and suggests that many asymptomatic people could safely defer dialysis.

These analyses led us to consider the validity of the various estimates of eGFR in patients with Stage 5 CKD. Validity and reproducibility of estimates based on serum Cr measures are lacking. Indeed, the Cockcroft and Gault equation was derived from 249 patients aged 18–92 years [30]. The lowest GFR was reported in the 80–92 year old group with a mean of 37 mL/min/1.73m². The MDRD study included 1628 patients, 1070 in development sample and 558 in the validation sample with a mean eGFR 39.8 mL/min/1.73m² [31]. Similarly, in the largest cohort to date used to estimate eGFR in the general population, i.e. for the CKD-EPI formula, there were 8254 patients in the development sample and 3896 in validation sample. However, only 2.6% in the validation sample had a GFR <15 mL/min/1.73m² [32]. Hence, using creatinine-based eGFR in patients with Stage 5 CKD has limited validity, an issue raised recently by other investigators [33]. The results of the IDEAL trial add weight to the view that initiation of dialysis based primarily on a creatinine-based estimation of GFR has no place.

Late start versus late referral

Late referral of patients with CKD has been shown to result in inferior control of CKD and cardiovascular risk factors and an overall inferior survival [34, 35]. Prior studies addressing early versus late dialysis have been confounded systematically by the fact that many ‘late’ starters were ‘late’ referrals, with a lack of optimal pre-dialysis care. The IDEAL trial is unable to address this issue as all patients enrolled in the trial were by definition referred ‘early’ to allow randomization to either arm of the study. We are currently comparing the study participants who commenced dialysis with an eGFR <7 mL/min/1.73m² with a cohort from ANDATA, who were referred late to a renal physician and who started dialysis with a similar GFR. This will provide evidence as to the impact of late start versus late referral. Dialysis, Outcomes and Practice Patterns data in 8500 incident haemodialysis patients suggests that the adjusted hazard ratio of death falls progressively with up to five nephrological consultations prior to the start of dialysis [36]. Furthermore, there was a graded benefit in referral >3 months versus 3–12 months versus >12 months prior to the start of dialysis, independent of the presence of diabetes and the age of the patient [37]. Patients who have a functioning
arteriovenous fistula, a haemoglobin >11 g/dL and a normal serum albumin at the time of dialysis initiation, reflecting both optimal pre-dialysis care and lack of co-morbidity, have been determined in retrospective analyses to have a lower risk of death in the first year on dialysis [38]. Pre-dialysis care by a nephrologist is only one facet in the care of the patient with Stage 5 CKD as it is clear that additional support from the allied health sector is required and hence that multiple factors intersect to predict positive dialysis outcomes [39].

The majority of patients in the IDEAL trial opted for home-based therapies, predominantly peritoneal dialysis as the treatment modality of choice. It has clearly been demonstrated that late presentation of patients with CKD results in an increased use of temporary catheters and reduced likelihood of home-based therapies. Interestingly, 92% of patients allocated to the early start group commenced dialysis on their nominated preferred therapy, with the majority being initiated on home-based therapies, with 86% of patients allocated to the late start group commencing dialysis on their preferred modality and the majority being in centre or satellite facilities (Pollock, Cooper, Harris et al., unpublished data). This in conjunction with the increased use of catheter-based access in patients allocated to ‘late start’ suggests the clinicians and patients need to be prepared for dialysis even if dialysis can be deferred to maintain optimal care and personal independence.

Impact of the IDEAL study

The optimal time to commence dialysis has occupied the minds of clinicians, health providers and patients for decades. The key drivers for decision making for individuals, clinicians and health care providers are morbidity and mortality risk, quality of life and cost, among other considerations. Hence, it is incumbent upon the nephrological community to provide high-quality evidence to each of these groups so as to inform personal and population-based decisions. It is clear that there is no level of kidney function defined by an estimation of GFR based on serum creatinine that should direct the initiation of dialysis. The results of the IDEAL study do not support initiation of dialysis above an eGFR of 10 mL/min in otherwise stable patients, under the care of a nephrologist. In this regard, the international community is becoming increasingly united [40].

Clearly, there is a need for the nephrological community to lead investigator initiated clinical trials that will ultimately change clinical practice. The IDEAL trial has demonstrated that clinical questions, of importance to patients, families, employers, service providers and government, can be answered with appropriate engagement from the nephrological community. Further studies should be directed to determining the characteristics of patients who start useful versus futile dialysis so as to better inform patients, families and health care providers.

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