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Original Investigation

Cost-Effectiveness of Initiating Dialysis Early: A Randomized Controlled Trial

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Background: Planned early initiation of dialysis therapy based on estimated kidney function does not influence mortality and major comorbid conditions, but amelioration of symptoms may improve quality of life and decrease costs.

Study Design: Patients with progressive chronic kidney disease and a Cockcroft-Gault estimated glomerular filtration rate of 10-15 mL/min/1.73 m^2 were randomly assigned to start dialysis therapy at a glomerular filtration rate of either 10-14 (early start) or 5-7 mL/min/1.73 m^2 (late start).

Setting & Population: Of the original 828 patients in the IDEAL (Initiation of Dialysis Early or Late) Trial in renal units in Australia and New Zealand, 642 agreed to participate in this cost-effectiveness study.

Study Perspective & Timeframe: A societal perspective was taken for costs. Patients were enrolled between July 1, 2000, and November 14, 2008, and followed up until November 14, 2009.

Intervention: Planned earlier start of maintenance dialysis therapy.

Outcomes: Difference in quality of life and costs.

Results: Median follow-up of patients (307 early start, 335 late start) was 4.15 years, with a 6-month difference in median duration of dialysis therapy. Mean direct dialysis costs were significantly higher in the early-start group ($10,777; 95% CI, $313 to $22,801). Total costs, including costs for resources used to manage adverse events, were higher in the early-start group ($18,715; 95% CI, −$3,162 to $43,021), although not statistically different. Adjusted for differences in baseline quality of life, the difference in quality-adjusted survival between groups over the time horizon of the trial was not statistically different (0.02 full health equivalent years; 95% CI, −0.09 to 0.14).

Limitations: Missing quality-of-life questionnaires and skewed cost data, although similar in each group, decrease the precision of results.

Conclusion: Planned early initiation of dialysis therapy in patients with progressive chronic kidney disease has higher dialysis costs and is not associated with improved quality of life.

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INDEX WORDS: Chronic kidney disease; cost; cost-effectiveness; dialysis; economic evaluation; quality of life; randomized.

Editorial, p. 649

It has been suggested that earlier start of dialysis therapy may improve overall survival, improve quality of life due to amelioration of symptoms of end-stage kidney disease, and decrease costs through a favorable trade-off of excess short-term adverse events and costs against decreased medium- to long-term adverse events and costs.[1-3] The IDEAL (Initiation of Dialysis Early or Late) trial reported that early start of dialysis therapy in patients with stage 5 chronic kidney disease had no

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significant effect on either all-cause mortality or the secondary outcome measures of cardiovascular events, infection, or dialysis complications compared with patients in whom dialysis therapy initiation was delayed by a mean of almost 6 months.[4] This article reports outcomes from the companion economic study of IDEAL, which compared total costs of treatment and quality-of-life outcomes in the early- and late-start groups.

METHODS

Patients

The IDEAL trial was a multicenter randomized controlled trial in which 828 patients with stage 5 chronic kidney disease in 32 renal units in Australia and New Zealand were randomly assigned to start dialysis therapy at an estimated glomerular filtration rate (calculated using the Cockcroft-Gault formula) of 10-14 (early) or 5-7 mL/min/1.73 m^2 (late) during July 1, 2000, to November 14, 2008. Full details of the protocol and procedures for clinical data collection in the IDEAL trial have been described previously.[4,5] Enrollment in the economic substudy followed approval by local ethics committees at each center from March 2002 until November 14, 2008, and follow-up continued until November 14, 2009. All patients provided written consent, and the trial protocol and procedures followed those of the IDEAL trial.

Costs

Health care–related resource use was collected during the 8 years of the trial. For resources provided at each study center, the extent of resource use was determined by completion of a quarterly questionnaire by the study nurse with access to patient records. For resources delivered in the community setting, resource use was determined using patient responses to a monthly questionnaire.

A societal perspective was taken that included total health care–related costs during the trial irrespective of who paid, but excluded any impact on patient incomes. The direct cost of dialysis therapy, by facility type and modality, was estimated from disaggregated cost items, including staff costs, consumables, and building and capital data provided by a representative sample of 6 study centers in Australia and 3 in New Zealand. Each center provided data for number of treatments by modality, expenditure on staff, cost of specific dialysis-related consumables, and water treatment associated with each modality in the previous year. Costs were discounted at an annual equivalent rate of 5% and reported in 2008 Australian dollars (US $1 = AU $1.478 at 2008 purchasing power parity[6]). Resources used in establishing access for dialysis in the first instance were not included in the analysis because use of this resource was common to both groups. However, resources used in revision of dialysis access were included because of capture of data for hospitalization episodes. There were no differences between the 2 groups with respect to use of temporary dialysis access. Costs of travel to and from dialysis were estimated by applying unit costs for each mode of transportation from publicly available sources to actual distance travelled. Costs associated with episodes of hospitalization at the study center were estimated by applying a unit cost for the relevant Australian Refined Diagnosis Related Groups (version 5.1, round 12) to recorded episodes of hospitalization at the study center. Unit costs for visits to outpatient and emergency departments were sourced from national average costs reported for such services. Unit costs for visits to general practitioners, medical investigations, and pharmaceuticals were derived from public insurance reimbursement rates. Unit costs for visits to allied health practitioners were based on most common fees. Further details of methods and sources of unit costs are given in Item S1, available as online supplementary material.

Sensitivity analyses were conducted on the cost of dialysis treatment by excluding cost outliers without imputation using complete cases only and using discount rates of 3% and zero.

Health Outcomes

The primary outcome was survival weighted by health-related quality of life or what is known as quality-adjusted life-years (QALYs). The quality-of-life component was measured using the Assessment of Quality of Life (AQoL)[7] at baseline and every 3 months. The AQoL is a general quality-of-life instrument for health interventions that has been validated as a quality-of-life instrument in the general population[7] and used across a wide range of conditions.[7-9] It measures health-related quality of life across 5 dimensions (illness, independent living, social relationships, physical senses, and psychological well-being) and generates patient preference–based indexes on a scale of 0.00 (death) to 1.00 (perfect health), using the time-trade-off method.

QALYs were calculated as the sum of years of survival weighted by average AQoL score for each patient during each year and discounted at 5% per annum.

Quality of life also was measured using the 36-Item Short Form Health Survey (SF-36)[10] at baseline and every 12 months, summarized into 2 standardized scores; one for mental and one for physical health. A 10-point difference corresponded to a 1–standard deviation change in score for the Australian population.[11]

Statistical Analysis

Results are expressed as percentages for discrete variables, medians and interquartile ranges for non–normally distributed continuous variables, and mean ± standard deviation for normally distributed continuous variables. All analyses were performed on an intention-to-treat basis. To adjust for censoring, each cost and QALY observation was weighted by the inverse probability of individual Kaplan-Meier estimates of predicted censoring during the period, quarterly for costs in years 1-3 and annually thereafter, and annually for QALYs.[12] Missing quarterly data for the AQoL for each patient were imputed by applying the average of that individual's observations within the year for annual analyses or adjacent periods for quarterly analyses. The likelihood of bias from missing quality-of-life data was tested using a log-rank test of the difference in Kaplan-Meier survival curves of those who completed a questionnaire and those who did not at baseline and in each year after randomization. When patient-cost logs were not returned, no cost was attributed for that period. Only recorded data were used for other quality-of-life and cost items.

Quality-of-life scores were compared between groups using a generalized estimating equation regression analysis of unweighted AQoL values and treatment, allowing for repeated observations with an exchangeable correlation structure. Baseline values were included as a covariate. Differences in total QALYs over the trial were tested using linear regression with treatment allocation and AQoL score as a covariate. The 95% confidence intervals (CIs) for non–normally distributed differences in average cost per patient between treatment groups were estimated using nonparametric bias-corrected bootstrapping.[13] Outlying observations for each cost category were defined as those that were more than 3 times the interquartile range above the 75th percentile.

The trial was powered to detect an incremental cost per QALY (difference in mean cost divided by the difference in mean number of QALYs between the early- and late-start groups) of less than a nominated critical threshold ($30,000 based on gross domestic product per capita[14]). It was calculated that a total sample size of 554 would be sufficient to detect a 10% absolute increase in

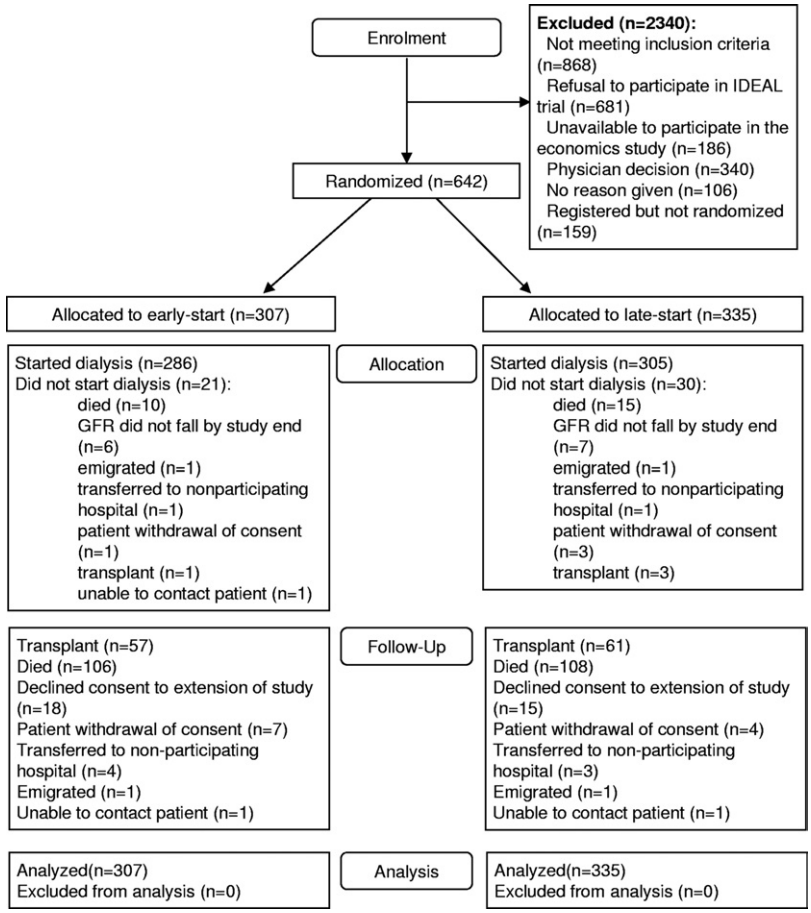

Figure 1. Enrollment and analysis. Abbreviations: GFR, glomerular filtration rate; IDEAL, Initiation of Dialysis Early or Late.

QALYs and a 20% decrease in total costs associated with early compared with late dialysis (assuming a coefficient of variation of 1 for costs and correlation of 0.1 between costs and quality of life) with 80% power at $P = 0.05$.[15]

RESULTS

Study Population

Of 828 patients randomly assigned in the IDEAL trial, 642 (78%) participated in the economics study (Fig 1). The main reason for the lower number of patients was a delay in ethics approval for the economics study. Baseline demographic and clinical characteristics were similar between groups (Table 1) and similar to those participating in the main IDEAL trial.[5] Median times to dialysis therapy initiation after randomization were 1.90 months in the early-start group and 7.30 months in the late-start group (hazard ratio, 1.96; 95% CI, 1.67 to 2.30; $P < 0.001$). Median duration of follow-up was 4.15 years in each group. Consistent with results of the IDEAL trial, no significant difference in survival was found between intervention groups (hazard ratio for early-start group, 1.10; 95% CI, 0.84 to 1.45; $P = 0.5$).

Costs

The key elements of cost data (dialysis and hospital costs) were complete for all patients, whereas investigation costs were 91% complete. As anticipated, completion of the patient log for out-of-hospital medical services and transport costs decreased during the trial. In year 1, the completion rate was 69% in the early-start group and 71% in the late-start group. During the course of the trial, there was only a small and statistically insignificant difference in rates of completion between the early and late groups (45% in the early-start and 47% in the late-start group; $P = 0.06$) and the same percentage in each group completed at least 1 patient log (76%). These elements of cost were expected to be relatively small and to vary less between groups.

Average annual direct dialysis treatment costs per patient were $60,051 for hospital hemodialysis, $38,513 for satellite hemodialysis, $30,815 for home hemodialysis, and $31,063 for peritoneal dialysis. Costs per randomly assigned patient by category for each group and associated resource use are listed in Table 2. Direct dialysis costs were significantly higher in the early-start group by $10,777

Table 1. Baseline Characteristics

Variable	Early-Start Group	Late-Start Group
No.	307	335
Women	104 (34)	115 (34)
Age (y)	60.0 ± 13.2	60.5 ± 12.1
Time since first seen by nephrologist (mo)	33.6 (11.0, 86.0)	30.0 (10.0, 77.7)
Race (%)		
White	72.3	74.0
Asian	9.1	8.7
Maori	7.1	5.1
Pacific Islander	5.2	6.6
Aboriginal/Torres Strait Islander	2.9	1.5
Other	3.3	4.2
Primary cause of ESKD (%)		
Diabetes	33.2	34.6
Glomerulonephritis	14.3	16.4
Polycystic kidney disease	12.1	11.6
Hypertension	8.8	8.1
Analgesic nephropathy	4.6	3.3
Reflux nephropathy	3.9	3.3
Renovascular disease	3.3	5.7
Interstitial nephritis	2.3	0.6
Obstructive nephropathy	1.6	0.3
Other	16.0	16.1
Failing kidney transplant	3.9	4.2
Comorbid conditions (%)		
Hyperlipidemia	60.6	62.4
Diabetes	42.0	43.6
Cardiovascular disease	37.8	38.2
Ischemic heart disease	27.7	28.1
Peripheral vascular disease	16.6	17.3
Congestive cardiac failure	3.6	4.8
Stroke	3.3	1.8
Smoking (%)		
Current	12.1	11.0
Past	50.2	45.7
Never	37.8	43.3
Medications (% used)		
ACE inhibitor	47.6	46.6
Angiotensin II blocker	24.8	24.5
Statin	59.6	56.7
Erythropoiesis-stimulating agent	40.1	43.0
Planned dialysis modality (%)		
CAPD	59.0	55.8
HD	41.0	44.2
Clinical parameters		
BMI (kg/m^2)	28.8 ± 5.8	29.0 ± 6.3
Systolic blood pressure (mm Hg)	142.4 ± 20.9	141.8 ± 20.1
Diastolic blood pressure (mm Hg)	78.9 ± 11.2	78.2 ± 11.7
Laboratory results		
Creatinine (mg/dL)	6.0 ± 1.5	6.0 ± 1.4
$eGFR_{CG}$ (mL/min/1.73 m^2)	13.1 ± 1.4	13.1 ± 1.4
$eGFR_{MDRD}$ (mL/min/1.73 m^2)	9.9 ± 2.3	9.8 ± 2.2
Albumin (g/dL)	3.9 ± 0.5	3.9 ± 0.5
Phosphate (mg/dL)	5.6 ± 1.3	5.6 ± 1.5
Hemoglobin (g/dL)	11.4 ± 1.6	11.4 ± 1.7

Note: Unless otherwise indicated, values are given as number (percentage), mean ± standard deviation, or median (25th, 75th percentile). Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; serum albumin in g/dL to g/L, ×10; serum phosphate in mg/dL to mmol/L, ×0.3229; serum hemoglobin in g/dL to g/L, ×10. Full definitions of variables used are given in the Initiation of Dialysis Early or Late trial report.[5]

Abbreviations and definitions: ACE, angiotensin-converting enzyme; BMI, body mass index; CAPD, continuous ambulatory peritoneal dialysis; $eGFR_{CG}$, estimated glomerular filtration rate calculated using the Cockcroft-Gault formula ([140 − age] × weight in kg × 1.73 × [0.85 if female] × serum creatinine in mg/dL × 72); $eGFR_{MDRD}$, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease Study equation ($186 \times [\text{serum creatinine in mg/dL}]^{-1.154} \times \text{age}^{-0.203} \times$ [0.742 if female] × [1.210 if of African descent]); ESKD, end-stage kidney disease; HD, hemodialysis.

(95% CI, $313 to $22,801). These costs were exclusive of the additional costs listed in Table 2 and did not include indirect costs related to loss of productivity.

The early-start group had substantially higher mean costs of transport for dialysis ($3,610; 95% CI, $1,111 to $9,959). Costs associated with hospital admissions also were higher for the early-start group, although the difference was not statistically significant ($5,112; 95% CI, −$3,662 to $12,247). The cost of tests and investigations, although high, showed a small and nonsignificant difference between the early- and late-start groups. Other component costs for most patients were small and did not differ significantly between the early- and late-start groups. Overall, mean cost per patient discounted over the time horizon of the trial and adjusted for censoring was $18,715 (95% CI, −$3,162 to $43,021) higher in the early-start group than in the late-start group (Table 2).

Figure 2 shows the distribution of dialysis and total costs during the first 3 years. In the first year, direct costs of dialysis and hospital inpatient costs were

Table 2. Use of Resources and Total Cost Per Patient Over the Duration of the Trial

	Early-Start Group (n = 307)	Late-Start Group (n = 335)	Difference (early − late)
Use of Resources by Group Over Duration of Trial			
Dialysis (mo)	36.7 ± 23.0	32.9 ± 22.2	3.8 (0.3 to 7.3)
Hospitalizations (d)	48 ± 64	40 ± 54	8 (−2 to 17)
Admissions	8 ± 6	8 ± 6	0 (−1 to 2)
Nonadmitted hospital visits	15 ± 19	15 ± 16	0 (−3 to 3)
Visits to community GPs and allied health care professionals	29 ± 36	29 ± 36	0 (−6 to 5)
Investigations	93 ± 79	89 ± 72	3 (−10 to 17)
Cost per Patient by Resource Category for Each Group During the Trial, $AU (2008)[a]			
Dialysis	117,163 (54,844, 168,307)	96,763 (45,012, 155,662)	10,777 (313 to 22,801)
Transportation for dialysis	4,459 (2,166, 9,406)	4,132 (1,989, 8,624)	3,610 (1,111 to 9,959)
Hospital admissions	33,135 (7,526, 71,574)	32,515 (7,744, 63,916)	5,112 (−3,662 to 13,247)
Nonadmitted hospital treatment	2,897 (0, 6,820)	3,823 (587, 8,230)	−129 (−1,155 to 1,070)
Out-of-hospital visits to physicians and other health professionals	1,005 (160, 2,392)	1,284 (329, 3,104)	−259 (−722 to 242)
Investigations	11,610 (0, 24,174)	12,362 (2,374, 27,732)	88 (−2,955 to 3,155)
Pharmaceutical	25,379 (10,949, 43,099)	25,597 (14,072, 40,906)	−484 (−4,175 to 3,371)
Total	215,354 (114,777, 311,713)	202,124 (114,636, 288,704)	18,715 (−3,162 to 43,021)

Note: Values shown as mean ± standard deviation, mean (95% confidence interval), or median (25th, 75th percentile).
Abbreviation: GP, general practitioner.
[a]Data are skewed and median (25th, 75th percentile) values are presented for each group. However, because mean costs are the relevant policy variable, inferences are made on differences in mean values using bias-corrected bootstrap confidence intervals. All costs are discounted quarterly at 5% per annum equivalent and adjusted for censoring using inverse-weighted survival at the beginning of each period. Note that the cost of dialysis accounts for only direct treatment costs. Erythropoiesis-stimulating agents are included in pharmaceutical costs, all pathology and imaging services are included in investigations, and costs incurred for revision of dialysis access is included in hospital admissions.

higher in the early-start group (difference of $8,961 and $2,469), with significantly higher total costs in the early-start group compared with those in the late-start group (difference of $11,814; 95% CI, $6,318 to $17,311).

Quality-of-Life Scores

AQoL scores and SF-36 summary scores are shown in Fig 3. Quality of life was low, but relatively stable during the trial. A *t* test of AQoL scores at 6 months showed no significant difference between the early- and late-start groups ($P = 0.3$). Regression analysis adjusting for baseline quality of life confirmed a significant but small decrease in average quality of life over the duration of the trial, but no significant difference between the early- and late-start groups (−0.00; 95% CI, −0.03 to 0.03). SF-36 physical and mental summary scores confirmed the AQoL findings. Physical health was particularly low relative to the general population.

Seventy-one percent of patients completed the quality-of-life questionnaire in the first year, but attrition increased over time so that by the fourth year, 54% completed the questionnaires. However, there was no significant difference in survival of those who completed an AQoL questionnaire and those who did not at any time.

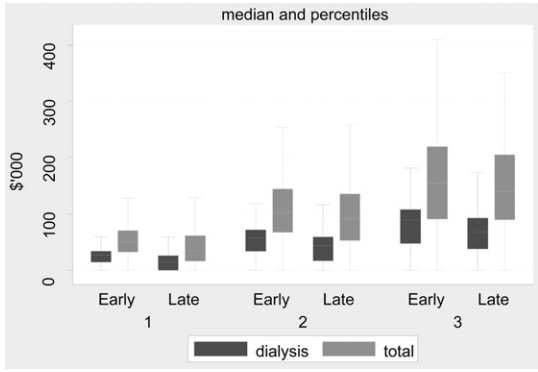

Figure 2. Box plot of cumulative dialysis and total costs per randomly assigned patient by group in the first 3 years. Plot shows median quality-of-life scores as a line within the interquartile range box. Whiskers show 5th and 95th percentiles. Outliers are not shown.

Figure 3. Quality-of-life scores (Assessment of Quality of Life [AQoL] and 36-Item Short Form Health Survey [SF-36] physical and mental health summary scores). Plots show median quality-of-life scores as a line within the interquartile range box. Whiskers show 5th and 95th percentiles with outliers plotted as diamonds. Scores are shown annually from time 0 (baseline) to 4 years from baseline. After 4 years, the response was too low to be reliable.

Quality-Adjusted Life-Years

There were 1.97 (95% CI, 1.81 to 2.14) discounted QALYs per patient in the early-start group and 2.07 (95% CI, 1.92 to 2.21) in the late-start group. Adjusted for AQoL baseline quality-of-life score, QALYs were not statistically different between groups (−0.09; 95% CI, −0.12 to 0.31).

Cost-Effectiveness

The point estimate of the incremental total cost per QALY of early compared with late dialysis was negative because early-start dialysis was associated with both higher costs and fewer QALYs on average. Figure 4 shows a plot of the bootstrap replicates of per-patient incremental costs and incremental QALYs and shows that 72% of replicates had both higher costs and lower QALYs in the early- compared with the late-start group.

Sensitivity Analyses

When outliers were removed, patients in the early-start group had on average a higher total cost of $13,989 (95% CI, −$6,399 to $34,295) compared with those in the late-start group. Using published public unit dialysis costs from the state of Victoria as an alternative estimate of direct dialysis costs; the difference in direct cost of dialysis increased to $14,395 (95% CI, $565 to $30,998) and the total cost difference was $22,277 (95% CI, −$2,809 to $49,773). Although the exact magnitude of the cost difference between the early- and late-start dialysis groups was somewhat sensitive to prices and variation within the population, the cost difference was robust to outliers and a higher cost of dialysis in terms of direction and order of magnitude. Discounting at 3% rather than 5% increased the extra mean cost of the early-dialysis group to $19,151 and the difference in QALYs in the early dialysis group to −0.10; discounting at zero led

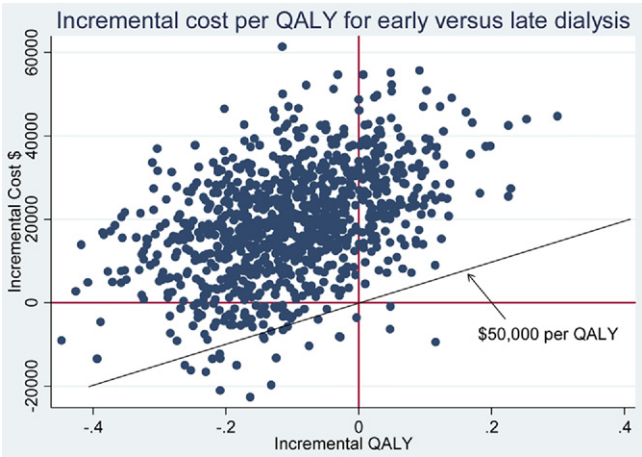

Figure 4. Bootstrap replicates of incremental cost per quality-adjusted life-year (QALY) for early- versus late-start dialysis. Of 1,000 replicated mean cost-per-QALY samples, there were 229 in the northeast quadrant (greater cost, but more QALYs in the early-start group), 719 in the northwest (greater cost and less QALYs in the early-start group), and 49 in the southwest (less cost and fewer QALYs), of which 8 were <$50,000. There were only 3 in the southeast quadrant, with less cost and more QALYs in the early-start group.

to values of $19,853 and −0.10, respectively. Removing the weightings for censoring did not substantially affect the mean difference in cost or QALYs. Analysis of cost data for only patients who completed at least some information in the patient diary (n = 489) increased the mean difference in cost for dialysis to $17,083 (95% CI, $4,802 to $29,664) and for total costs to $34,160 (95% CI, $8,749 to $60,023). There was only a small statistically insignificant difference in AQoL scores in this subsample. Regression analysis for complete cases of AQoL scores showed little difference in mean AQoL score between groups after adjusting for baseline score (0.01; 95% CI, −0.03 to 0.05).

DISCUSSION

Results of our study indicate that planned early initiation of dialysis therapy in patients with progressive CKD is associated with similar quality of life, increased dialysis costs, increased transport costs, and a trend to higher total treatment costs in comparison to those in whom dialysis has been electively delayed. Results do not provide evidence that planned early-start dialysis is cost-effective compared with planned late-start dialysis.

These results confirm a recent small study that showed significant economic benefit of deferring dialysis by optimizing conservative therapies in the elderly population with no net negative consequences in terms of morbidity or mortality.[16] Patients in that study were somewhat older, although cost savings amortized over time were similar to those observed in our own study. The IDEAL trial had higher mean costs of hospital admissions in patients randomly assigned to early- versus late-start dialysis, as in other studies,[16] but this was not large or statistically significant, in part because relatively few temporary dialysis access catheters were required in either early- or late-start patients[5] and costs seemed to have been driven by a small number of high-cost longer stay patients. Distributions of some individual cost items were highly skewed. This was not unexpected with clinical cost data, for which a few individuals can have disproportionate health care needs and transport costs. This could have affected the robustness of the conclusions, but sensitivity analyses excluding outliers did not substantially influence results, and although bootstrapped CIs were wider, they did not differ substantially from normal distribution–based intervals. It is interesting to note that although patient demography in the trial was similar to that of dialysis patients in other developed countries, the absolute cost of dialysis per patient apparently was lower than many estimates for countries with similarly developed health care systems.[17-19] The present study attributed costs to patients randomly assigned to early- versus late dialysis rather than to only dialysis treatment. As a consequence, many costs that were attributed to investigations, medical and hospital services, or pharmaceuticals in this study were attributed directly to dialysis in other studies. Thus, our results are not easily compared with studies of patient cost by dialysis modality. However, compared with many countries in which most patients are managed using hemodialysis, use of peritoneal dialysis as the initial dialysis mode was relatively high in this study (50% in early start, 45% in late start). Because use of long-term peritoneal dialysis therapy was least costly, this suggests that the cost advantage of late-start dialysis found in this study may be even greater in countries in which dialysis costs are higher and initiation on hemodialysis therapy is more common.[16-18]

The high incremental cost per QALY for planned early-start dialysis and the wide distribution within the population is similar to that simulated for the US dialysis population[20] and beyond what usually is considered "reasonable" value. In the United States, cost-effectiveness ratios <$50-$100,000 per incremen-

tal QALY are considered reasonable, and one review suggested that in-center hemodialysis was cost-effective based on a lower boundary of society's willingness to pay for an additional life-year of US $55,000.[21] In the United Kingdom, apart from end-of-life treatments, a figure of £30,000 is accepted.[22] In Australia, a range of values has been shown to be acceptable for public funding, with a ratio of $50,000/QALY more likely than not to be accepted in a treatment for a non–immediately life-threatening disease.[20,21,23] This raises the broader implication of society's valuation of a year of life, which is beyond the scope of the study. However, importantly, differences in QALYs were small and not statistically significant between patients allocated to early- and late-start dialysis, whereas costs were greater in the early-start group, driven largely by the increase in time and cost of dialysis. This implies that early-start dialysis is not cost-effective at any social value of a year of life.

The trial shows that quality of life is low compared with the general population, but does not alter significantly over time after initiation of dialysis therapy. This contrasts with the common view that quality of life decreases for those on dialysis therapy. To our knowledge, there are few longitudinal studies of quality of life on dialysis therapy, but our results confirm those of one large observational study.[24]

There are limitations to the analysis. Patient resource-use log and quality-of-life questionnaire response rates decreased during the course of the trial. It is possible that nonresponse may have led to an underestimate of the size and variance of some elements of the cost and quality-of-life differences between groups. However, there was no significant difference in either response rates between groups or survival between responders and nonresponders. Furthermore, the self-reported log elements of costs were a relatively small component of total costs. Attrition is inevitable in this patient group during such a long trial, but the data suggest that this may have decreased the precision of our estimates rather than the estimated size of the treatment effect. The study provided good and timely access for all patients before starting dialysis therapy, and the rate of temporary dialysis access catheter provision was low for both early- and late-start patients. Our results therefore need to be understood in the context of local clinical practice, for which other studies have found that a delay in dialysis therapy may lead to less than optimal insertion of access for dialysis and an increased cost of access revision.[16]

In conclusion, this study indicates that in a closely managed setting, dialysis can be delayed safely without worsening quality of life or increasing total treatment costs until either glomerular filtration rate decreases to <7 mL/min/1.73 m^2 or more traditional clinical indicators for dialysis therapy initiation arise. Planned initiation of dialysis therapy before this is likely to increase the cost of dialysis without an offsetting decrease in use or cost of hospital or medical services in later periods. There is no evidence that quality of life on average would be decreased if there was a planned delay in dialysis therapy initiation until more traditional clinical indicators for the initiation of dialysis therapy are present. Together with the absence of a survival advantage for early-start dialysis shown in the IDEAL trial, these results further support the need for changes in clinical practice and health policy.

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SUPPLEMENTARY MATERIAL

Item S1: Resource data collection methods and unit cost sources

Note: The supplementary material accompanying this article (doi:10.1053/j.ajkd.2010.12.018) is available at www.ajkd.org.

REFERENCES

1. Bonomini V, Vangelista A, Stefoni S. Early dialysis in renal substitutive programs. *Kidney Int Suppl*. 1978;8:S112-S116.

2. Jungers P, Zingraff J, Albouze G, Chauveau P, Page B, Hannedouche T. Late referral to maintenance dialysis: detrimental consequences. *Nephrol Dial Transplant*. 1993;8:1089-1093.

3. Tattersall J, Greenwood R, Farrington K. Urea kinetics and when to commence dialysis. *Am J Nephrol*. 1995;15:283-289.

4. 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.

5. 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.

6. Organisation for Economic Co-operation and Development (OECD). OECD StatExtracts. http://stats.oecd.org/Index.aspx?datasetcode=SNA_TABLE4. Accessed December 9, 2010.

7. Hawthorne G, Richardson J, Osborne R. The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life. *Qual Life Res*. 1999;8:209-224.

8. Richardson J, Day N, Peacock S, Iezzi A. Measurement of the quality of life for economic evaluation and the Assessment of Quality of Life (AQoL) Mark 2 Instrument. *Aust Econ Rev*. 2004;37(1):62-88.

9. Chua R, Keogh AM, Byth K, O'Loughlin A. Comparison and validation of three measures of quality of life in patients with pulmonary hypertension. *Int Med J*. 2006;36:705-710.

10. Ware J, Sherbourne C. The MOS 36-Item Short-Form Health Survey (SF-36). *Med Care*. 1992;30:473-483.

11. Australian Bureau of Statistics. 1995 National Health Survey—SF-36 Population Norms. ABS Catalogue No. 43990; Canberra 1997.

12. Bang H, Tsiatis AA. Estimating medical costs with censored data. *Biometrika*. 2000;87:329-343.

13. Efron B, Tibshirani R. *An Introduction to the Bootstrap*. New York, NY: Chapman & Hall; 1993.

14. World Health Organisation. Cost effectiveness thresholds. http://wwwwhoint/choice/costs/CER_thresholds/en/printhtml. Accessed April 22, 2010.

15. Willan AR. Analysis, sample size, and power for estimating incremental net health benefit from clinical trial data. *Control Clin Trials*. 2001;22:228-237.

16. Scalone L, Borghetti F, Brunori G, et al. Cost-benefit analysis of supplemented very low-protein diet versus dialysis in elderly CKD5 patients. *Nephrol Dial Transplant*. 2010;25:907-913.

17. Baboolal K, McEwan P, Sondhi S, Spiewanowski P, Wechowski J, Wilson K. The cost of renal dialysis in a UK setting—a multicentre study. *Nephrol Dial Transplant*. 2008;23:1982-1989.

18. Neil N, Guest S, Wong L, et al. The financial implications for Medicare of greater use of peritoneal dialysis. *Clin Ther*. 2009;31:880-888.

19. Zelmer JL. The economic burden of end-stage renal disease in Canada. *Kidney Int*. 2007;9:1045-1047.

20. Lee CP, Chertow GM, Zenios SA. An empiric estimate of the value of life: updating the renal dialysis cost-effectiveness standard. *Value Health*. 2009;12:80-87.

21. Winkelmayer WC, Weinstein MC, Mittleman MA, Glynn RJ, Pliskin JS. Health economic evaluations: the special case of end-stage renal disease treatment. *Med Decis Making*. 2002;22:417-430.

22. National Institute for Health and Clinical Excellence. Appraising life-extending, end of life treatments. http://wwwniceorguk/media/88A/F2/SupplementaryAdviceTACEoLpdf 2009. Accessed December 2, 2010.

23. Harris AH, Hill SR, Chin G, Li JJ, Walkom E. The role of value for money in public insurance coverage decisions for drugs in Australia: a retrospective analysis 1994-2004. *Med Decis Making*. 2008;28:713-722.

24. Wu AW, Fink NE, Marsh-Manzi JV, et al. Changes in quality of life during hemodialysis and peritoneal dialysis treatment: generic and disease specific measures. *J Am Soc Nephrol*. 2004;15:743-753.