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## A Randomized, Controlled Trial of Early versus Late Initiation of Dialysis

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### ABSTRACT

#### BACKGROUND

In clinical practice, there is considerable variation in the timing of the initiation of maintenance dialysis for patients with stage V chronic kidney disease, with a worldwide trend toward early initiation. In this study, conducted at 32 centers in Australia and New Zealand, we examined whether the timing of the initiation of maintenance dialysis influenced survival among patients with chronic kidney disease.

#### METHODS

We randomly assigned patients 18 years of age or older with progressive chronic kidney disease and an estimated glomerular filtration rate (GFR) between 10.0 and 15.0 ml per minute per 1.73 m<sup>2</sup> of body-surface area (calculated with the use of the Cockcroft–Gault equation) to planned initiation of dialysis when the estimated GFR was 10.0 to 14.0 ml per minute (early start) or when the estimated GFR was 5.0 to 7.0 ml per minute (late start). The primary outcome was death from any cause.

#### RESULTS

Between July 2000 and November 2008, a total of 828 adults (mean age, 60.4 years; 542 men and 286 women; 355 with diabetes) underwent randomization, with a median time to the initiation of dialysis of 1.80 months (95% confidence interval [CI], 1.60 to 2.23) in the early-start group and 7.40 months (95% CI, 6.23 to 8.27) in the late-start group. A total of 75.9% of the patients in the late-start group initiated dialysis when the estimated GFR was above the target of 7.0 ml per minute, owing to the development of symptoms. During a median follow-up period of 3.59 years, 152 of 404 patients in the early-start group (37.6%) and 155 of 424 in the late-start group (36.6%) died (hazard ratio with early initiation, 1.04; 95% CI, 0.83 to 1.30; *P*=0.75). There was no significant difference between the groups in the frequency of adverse events (cardiovascular events, infections, or complications of dialysis).

#### CONCLUSIONS

In this study, planned early initiation of dialysis in patients with stage V chronic kidney disease was not associated with an improvement in survival or clinical outcomes. (Funded by the National Health and Medical Research Council of Australia and others; Australian New Zealand Clinical Trials Registry number, 12609000266268.)

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\*Participants in the Initiating Dialysis Early and Late (IDEAL) Study are listed in the Appendix.

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**T**HE WORLDWIDE PREVALENCE OF LONG-term dialysis continues to rise,<sup>1,2</sup> driven in part by strong trends toward the initiation of dialysis earlier in the natural history of chronic kidney disease than was the practice previously.<sup>3-5</sup> Traditionally, the indicators for starting dialysis were the presence of signs and symptoms of uremia in combination with the results of biochemical measurements in serum and plasma.<sup>6</sup> However, a number of observational cohort and case-control studies have suggested that starting dialysis early may improve patients' survival, quality of life, and capacity for employment and decrease complications.<sup>7-9</sup> Although such studies were potentially limited by biases related to lead time, patient selection, and referral time, the clinical practice guidelines that were in use at the time our study was conceived<sup>10</sup> recommended the commencement of dialysis when the directly measured or calculated (estimated) glomerular filtration rate (GFR) was higher than the values previously targeted for the initiation of dialysis. However, more recent observational data have suggested that starting dialysis early may, in fact, be harmful.<sup>11-15</sup> Data from randomized, controlled trials that establish the optimal timing for the initiation of dialysis are lacking. The Initiating Dialysis Early and Late (IDEAL) study was designed to determine whether initiating dialysis early in people with stage V chronic kidney disease reduces the rate of death from any cause. The secondary aims were to determine whether early initiation of dialysis is associated with a reduction in cardiovascular and infectious events and in complications of dialysis.

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## METHODS

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### STUDY OVERSIGHT

The study design has been described previously.<sup>16</sup> We conducted the study in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonisation, and local regulatory requirements. The study was approved by the ethics committee at each participating center.

The authors (who made up the study's steering committee) designed and supervised the trial and the statistical analysis plan in collaboration with the staff of the coordinating center and Clinical Trials Research Unit at the University of Auckland, New Zealand. Site investigators and their locally

employed study nurses collected the patient data at each site. The staff of the regional coordinating centers regularly visited the sites and checked source data to confirm adherence to the protocol and the veracity of the data obtained. The first author wrote the first draft of the manuscript; subsequent drafts were prepared by the steering committee. The members of the steering committee attest that the study was performed in accordance with the protocol and the statistical analysis plan and vouch for the accuracy and completeness of the reported analyses. The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org.

### PATIENTS

Patients were recruited at 32 centers in Australia and New Zealand. Patients were eligible for inclusion in the study if they had progressive chronic kidney disease (patients with a failing kidney transplant were eligible) and an estimated GFR between 10.0 and 15.0 ml per minute per 1.73 m<sup>2</sup> of body-surface area. The estimated GFR was determined with the use of the Cockcroft-Gault equation,<sup>17</sup> corrected for body-surface area,<sup>18</sup> on the basis of the serum creatinine concentration measured at a local laboratory. For comparison, we also calculated the estimated GFR at baseline and at the start of dialysis with the use of the Modification of Diet in Renal Disease (MDRD) equation (see the Supplementary Appendix, available at NEJM.org, for a description of these equations). All patients provided written informed consent.

Patients could not be included in the study if they were younger than 18 years of age, had an estimated GFR of less than 10.0 ml per minute, had plans to receive a kidney transplant from a live donor within the next 12 months, had a recently diagnosed cancer that was likely to affect survival, or were unable to provide written informed consent.

### STUDY TREATMENT

Patients were randomly assigned either to commence dialysis when the estimated GFR was 10.0 to 14.0 ml per minute (early-start group) or to continue to receive routine medical care and commence dialysis when the estimated GFR was 5.0 to 7.0 ml per minute (late-start group). The study protocol permitted patients who were assigned to the late-start group to commence dialysis when the estimated GFR was more than 7.0 ml per min-

ute if the treating physician recommended that they do so. There was no requirement for the physician to discuss this decision with the trial coordinating center. Randomization was performed centrally by a computer-based randomization service (Clinical Trials Research Unit, University of Auckland, New Zealand) with the use of a permuted-block design stratified according to center, planned method of dialysis (hemodialysis or peritoneal dialysis), and the presence or absence of diabetes mellitus. Although the planned method of dialysis was specified before randomization, the method of dialysis and regimen that were ultimately prescribed remained the choice of the patient and the treating physician.

Physicians at each study center were advised to consider the timely placement of an access for dialysis in each trial participant. There was no requirement for temporary placement of a catheter to avoid a delay in the assigned start time, and decisions about temporary placement were based on clinical judgment. The following dialysis clearance targets were recommended in accordance with evidence on adequate dialysis clearance from trials at the time the protocol was written<sup>19,20</sup>: a total weekly Kt/V value (a measure of clearance in which K is the urea clearance of the dialyzer, t is the duration of dialysis, and V is the volume of distribution of urea in the patient) greater than 2.0 in the case of patients receiving peritoneal dialysis (2.2 if they were undergoing automated peritoneal dialysis) and greater than 3.6 in the case of patients undergoing hemodialysis. Actual dialysis clearance was measured for use in secondary analyses. It was recommended that all patients receive dietary advice, management of anemia and hyperphosphatemia, and treatment for hypertension, as recommended in contemporary guidelines.<sup>10,21-24</sup>

#### STUDY OUTCOMES

The primary outcome was death from any cause. 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). Secondary outcomes

that were recorded as part of the trial protocol but that are not reported in this article included nutritional status and echocardiographic findings. A comprehensive trial-based economic evaluation, including detailed data on quality of life, was also conducted, but the results are not reported in detail here.

#### INTERIM ANALYSIS AND DATA MONITORING

An independent end-points committee, whose members were unaware of the treatment assignments, reviewed all primary outcome events (deaths) and determined the cause of death in each case. A separate, independent data and safety monitoring committee reviewed blinded data from the trial after 50% and 75% of the predicted primary outcome events occurred. A stopping rule of a difference between the groups of at least 3 SD in the total number of deaths was used by the data and safety monitoring committee to justify any recommendation to terminate the trial prematurely. The 3-SD stopping rule corresponded to a nominal P value of 0.003 for the comparison of the rate of death between the two study groups and allowed the conventional significance level of  $P=0.05$  to be applied in the final analysis of the trial data, since the rule had only a negligible effect on the overall type I error rates across all analyses. No futility analysis was performed, because a result indicating a minimal difference between the treatment groups was considered to be important, and maximum precision in this instance was deemed to be desirable. The trial was not stopped prematurely. Owing to the nature of the intervention, it was not possible to conceal the treatment assignments from the patients, the local study nurses, or the investigators. However, the personnel who performed the statistical analysis were not aware of the treatment assignments.

The definitions of important nonfatal events were made a priori by the steering committee and were not reviewed by the end-point committee. Regular data checks at each study center confirmed adherence to these definitions.

#### STATISTICAL ANALYSIS

We estimated that with a study sample of 800 patients (400 in each group), the study would have 80% power to detect a clinically important difference in the absolute risk of death of approximately 10 percentage points between the two groups over an anticipated 3-year recruitment period and

a 3-year follow-up period, assuming an estimated rate of death of 36.5% in the late-start group, with a two-sided type 1 error rate of 5%. The expected 3-year rate of death in the late-start group was determined with the use of life-table methods from data collected by the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) between 1988 and 1998.

We used a time-to-event analysis to compare the proportions of patients with primary and secondary outcomes in the two groups. Summaries of continuous variables are presented as means ( $\pm$ SD) for normally distributed data and as medians with interquartile ranges for skewed data; categorical variables are presented as frequencies (percentages). Continuous variables were compared with the use of Student's *t*-test or the Mann-Whitney test (for nonnormally distributed data), and categorical data with the use of chi-square tests. Survival estimates and curves were generated according to the Kaplan-Meier method. All patients were followed until death or the end of the trial, with censoring of data at the time a patient underwent transplantation or was lost to follow-up. A Cox model adjusted for baseline covariates was estimated to determine the association of baseline factors with outcomes. We also performed a post hoc analysis in which the GFR at the start of dialysis, as estimated with the use of the MDRD equation,<sup>25</sup> was compared between the patients in the early-start group and those in the late-start group. All survival analyses were performed according to the intention-to-treat principle. The statistical analyses were performed with the use of SAS software, version 9.1.3 (SAS Institute) and the R statistical package, version 2.8.1 (the R Foundation for Statistical Computing). All statistical tests were two-tailed, and a *P* value of less than 0.05 was considered to indicate statistical significance.

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## RESULTS

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### CHARACTERISTICS OF THE PATIENTS

Between July 2000 and November 2008, a total of 828 patients (244 in New Zealand and 584 in Australia) were randomly assigned to early initiation (404 patients) or late initiation (424) of dialysis (Fig. 1). Patients were followed until November 2009. During the recruitment phase of the trial (July 1, 2000, through November 14, 2006), a total of 12,101 patients started dialysis in Australia and New Zealand but were not included in

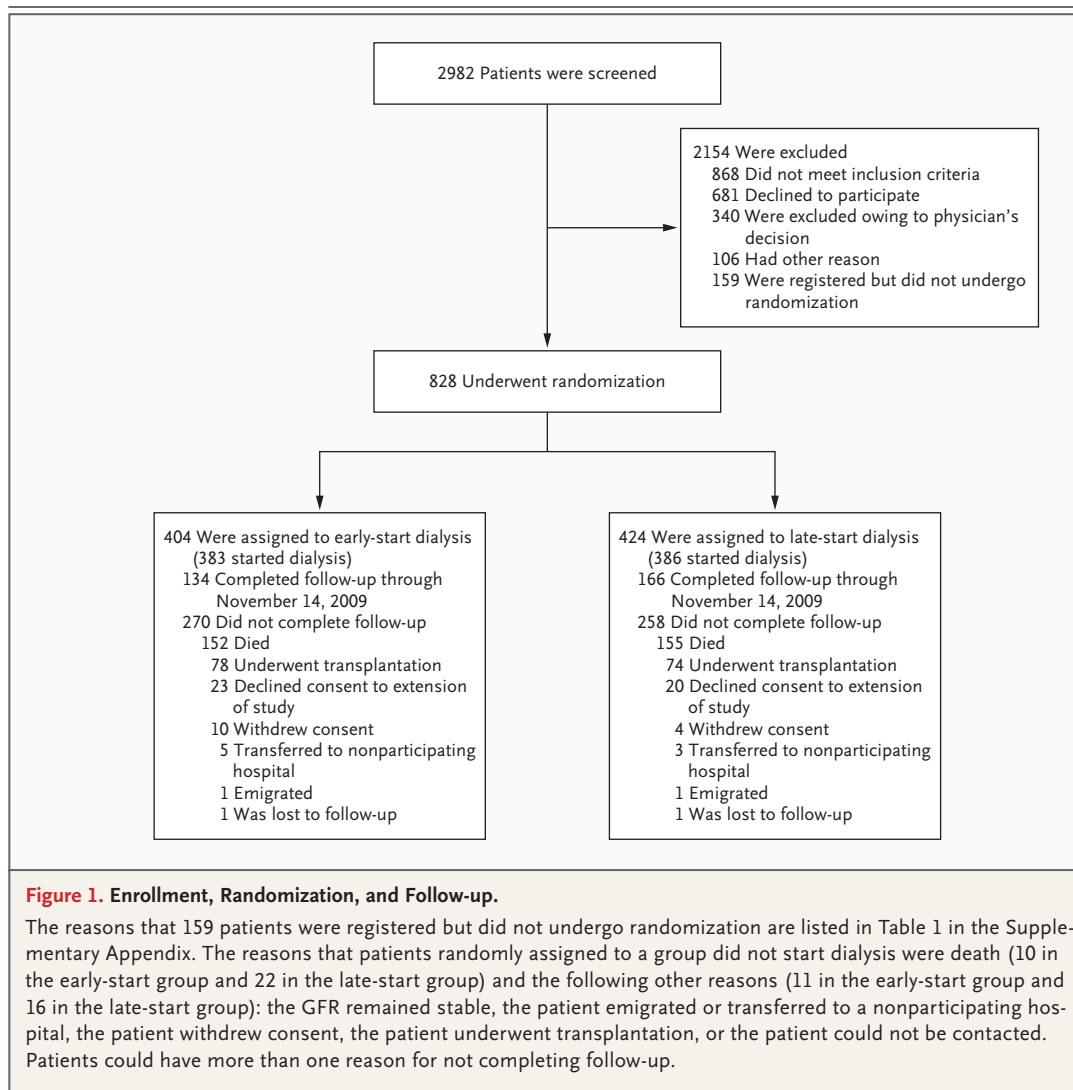
the trial (8235 at centers that were participating in the trial and 3866 at centers that were not participating) (data obtained from the ANZDATA Registry). A total of 152 participants received kidney transplants during the study period (78 in the early-start group and 74 in the late-start group), and their data were censored at the time of transplantation (6 died after censoring).

The two groups were well matched with respect to all baseline characteristics (Table 1). The median duration of follow-up was 3.64 years (range, 0.03 to 9.15) in the early-start group and 3.57 years (range, 0.02 to 8.78) in the late-start group. The two groups did not differ significantly with respect to pharmacologic interventions during the trial period.

### INITIATION OF DIALYSIS

The median time from randomization to the initiation of dialysis was 1.80 months (95% confidence interval [CI], 1.60 to 2.23) in the early-start group, as compared with 7.40 months (95% CI, 6.23 to 8.27) in the late-start group (hazard ratio for commencement of dialysis in the early-start group, 2.09; 95% CI, 1.81 to 2.41; *P*<0.001) (Fig. 2A). At the time of the initiation of dialysis, the mean estimated GFR, as calculated with the use of the Cockcroft-Gault equation, was 12.0 ml per minute in the early-start group, as compared with 9.8 ml per minute in the late-start group (mean difference, 2.2 ml per minute; 95% CI, 1.8 to 2.6; *P*<0.001). Among the patients who were randomly assigned to the early-start group, 75 (18.6%) started dialysis with an estimated GFR of less than 10.0 ml per minute. In the late-start group, 322 (75.9%) started dialysis with an estimated GFR of more than 7.0 ml per minute. A detailed explanation of the reasons for these protocol violations is included in Table 2 in the Supplementary Appendix. We also calculated the mean estimated GFR at the start of dialysis with the use of the MDRD equation; the results were 9.0 and 7.2 ml per minute, in the early-start and late-start groups, respectively (mean difference, 1.8 ml per minute; 95% CI, 1.4 to 2.2; *P*<0.001).

Peritoneal dialysis was the initial method of dialysis in the case of 195 patients in the early-start group and 171 patients in the late-start group. Hemodialysis was the initial method of dialysis in the case of 188 and 215 patients in the early-start and late-start groups, respectively. Incremental dialysis (defined as fewer than three hemodialysis sessions per week or less than 8 li-



ters of peritoneal dialysate exchange) was used in the case of 63 patients in the early-start group and 64 in the late-start group. The temporary placement of a catheter for dialysis access was required before the commencement of dialysis in 15 patients in the early-start group and 35 in the late-start group. A total of 59 patients who had been randomly assigned to a group had not commenced dialysis by the end of the trial (21 in the early-start group and 38 in the late-start group). The main reasons were a GFR that had not fallen to the assigned range for initiation of dialysis (6 patients in the early-start group and 8 in the late-start group) or death (10 patients in the early-start group and 22 in the late-start group). No patient died of uremia.

#### PRIMARY OUTCOME

A total of 307 patients died during the follow-up period — 152 in the early-start group and 155 in the late-start group. The causes of the deaths are summarized in Table 2. There was no significant difference in survival between patients in the late-start group and patients in the early-start group (hazard ratio for death in the early-start group, 1.04; 95% CI, 0.83 to 1.30;  $P=0.75$ ) (Fig. 2B). Early initiation of dialysis did not significantly affect the rate of death from any cause in any of the prespecified subgroups (Fig. 3). A sensitivity analysis that included deaths occurring after transplantation also showed no significant difference in survival between the two groups (hazard ratio with an early start, 1.01; 95% CI, 0.81 to 1.26;  $P=0.92$ ).

**SECONDARY OUTCOMES**

None of the a priori secondary outcomes (cardiovascular and infectious events and treatment-associated complications, including the use of tem-

porary dialysis catheters) were influenced by the timing of dialysis (Table 2). No significant difference was observed between the two groups in quality of life, as measured by the Assessment of

**Table 1. Baseline Characteristics of the Patients.\***

Variable	Early-Start Group (N = 404)	Late-Start Group (N = 424)
Sex (no.)		
Female	143	143
Male	261	281
Age (yr)	60.2±12.8	60.5±12.3
Time since first seen by nephrologist (mo)		
Median	32.5	29.4
Interquartile range	9.8–84.2	9.8–75
Race or ethnic group (%) †		
White	70.0	72.9
Asian	9.2	8.5
Maori	6.7	5.7
Pacific Islander	5.7	5.9
Aboriginal or Torres Strait Islander	3.2	2.1
Other ‡	5.2	5.0
Primary cause of end-stage renal disease (%)		
Diabetes	33.9	34.0
Glomerulonephritis	16.1	17.2
Polycystic kidney disease	10.1	11.1
Hypertension	7.9	7.8
Analgesic nephropathy	4.7	4.0
Reflux nephropathy	4.7	3.3
Renovascular disease	3.7	5.4
Interstitial nephritis	2.2	0.9
Obstructive nephropathy	1.2	0.2
Failing kidney transplant	3.2	3.5
Other	15.3	16.0
Coexisting conditions (%)		
Diabetes	42.6	43.2
Hyperlipidemia	60.9	60.8
Cardiovascular disease	39.6	38.2
Ischemic heart disease	29.5	27.1
Peripheral vascular disease	17.1	18.6
Congestive heart failure	4.5	6.4
Stroke	2.7	2.1
Smoking status (%)		
Current smoker	11.4	11.1
Former smoker	50.7	47.2
Never smoked	37.9	41.8

Table 1. (Continued.)		
Variable	Early-Start Group (N = 404)	Late-Start Group (N = 424)
Medications (%)		
ACE inhibitor	48.8	47.6
Angiotensin II blocker	21.0	23.1
Statin	56.7	55.7
Erythropoietin-stimulating agent	40.1	41.5
Planned dialysis method (%)		
Continuous ambulatory peritoneal dialysis	57.7	54.9
Hemodialysis	42.3	45.1
Clinical characteristics		
Weight (kg)	81.6±18.4	82.5±19.5
Body-mass index <sup>§</sup>	29.0±5.8	28.9±6.3
Blood pressure (mm Hg)		
Systolic	143.3±20.9	141.7±20.3
Diastolic	79.4±11.1	78.3±11.4
Results of blood tests <sup>¶</sup>		
Creatinine (μmol/liter)	532.2±130.7	528.3±121.8
Glomerular filtration rate (ml/min/1.73 m <sup>2</sup> )		
With Cockcroft–Gault equation	13.0±1.4	13.1±1.4
With MDRD equation	9.8±2.3	9.9±2.2
Albumin (g/liter)	38.5±5.1	38.4±4.8
Phosphate (mmol/liter)	1.8±0.4	1.8±0.4
Hemoglobin (g/liter)	114.0±16.7	113.7±16.6

\* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, and MDRD Modification of Diet in Renal Disease.

† Race or ethnic group was self-reported.

‡ This category also includes patients from more than one racial or ethnic group.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ To convert the values for creatinine to milligrams per deciliter, divide by 88.4. To convert the values for phosphate to milligrams per deciliter, divide by 0.3229.

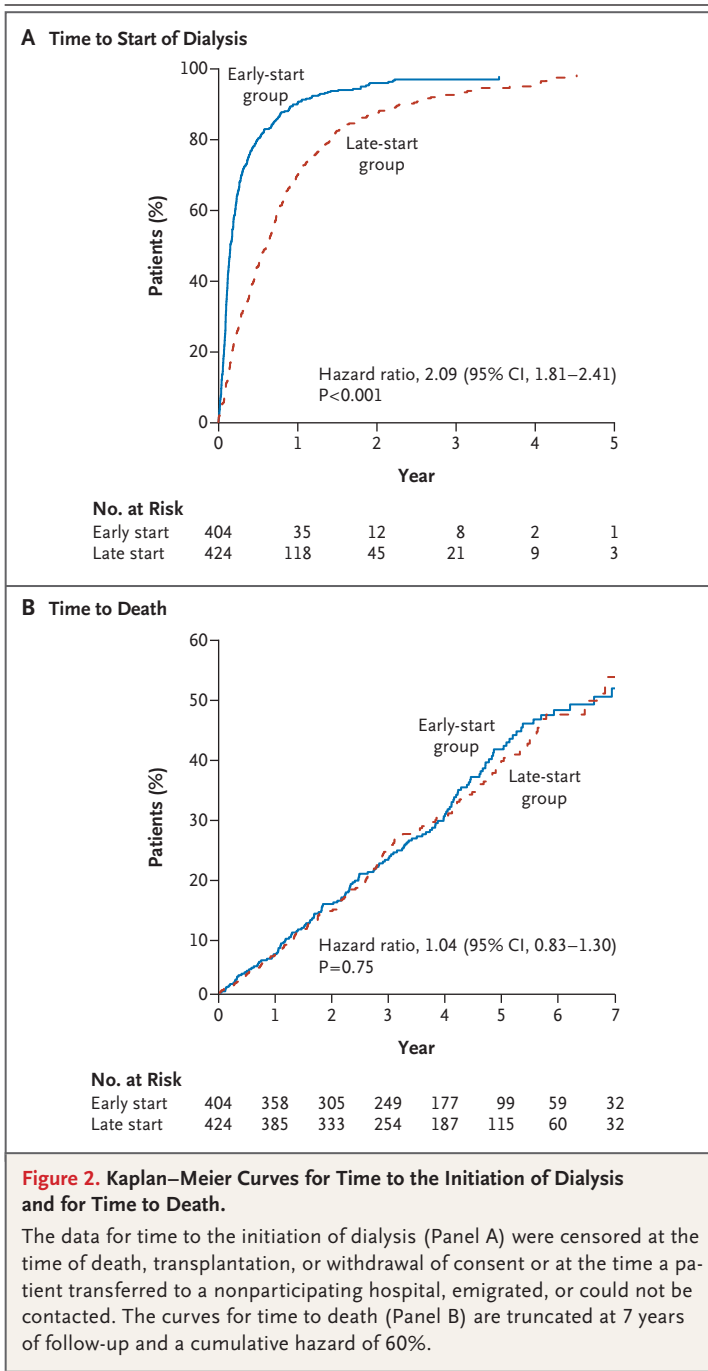
Quality of Life instrument,<sup>26</sup> during the follow-up period of the trial.

## DISCUSSION

In this study involving patients with chronic kidney disease, early initiation of dialysis had no significant effect on the rate of death from any cause or on cardiovascular events, infectious events, or complications of dialysis. The results of analyses of predefined subgroups were consistent with these results, despite clinically important differences between the groups in both estimated GFR and time to the initiation of dialysis. The results show that with careful clinical management of chronic kidney disease, dialysis can be

delayed for some patients until the GFR drops below 7.0 ml per minute or until more traditional clinical indicators for the initiation of dialysis are present.

These findings differ from those of some previously published observational cohort and case–control studies, which showed that early initiation of dialysis was associated with improved survival.<sup>7–9,27,28</sup> Conversely, other observational studies have suggested that early initiation of dialysis had no effect on survival<sup>15</sup> or potentially worsened survival.<sup>11–14</sup> However, all the previous studies were nonrandomized and were subject to potential confounding factors, including biases related to referral time, lead time, and patient selection — factors that do not apply to the IDEAL



trial. Older age and coexisting conditions have been invoked to explain worse outcomes among patients who had a higher GFR when dialysis was initiated<sup>13</sup>; however, our study does not support this theory, given the fact that the number and type of coexisting conditions were similar between the study groups.

Guidelines from national and international expert panels have recommended the initiation of dialysis at relatively high levels of renal function, despite the lack of robust evidence in support of this approach. In 1997, the National Kidney Foundation<sup>10</sup> recommended that dialysis be initiated when the estimated GFR is approximately 10.5 ml per minute, on the basis of the minimum target level of total (residual renal and dialysis) clearance for peritoneal dialysis. In 2006, the National Kidney Foundation updated these guidelines<sup>29,30</sup> to specify that the benefits, risks, and disadvantages of renal-replacement therapy should be considered when the estimated GFR is less than 15.0 ml per minute and also suggested that the initiation of dialysis therapy when the estimated GFR is higher than 15.0 ml per minute may be warranted when patients have coexisting conditions or symptoms of uremia.<sup>29,30</sup> The Canadian Society of Nephrology<sup>22</sup> recommends the initiation of dialysis when the estimated GFR is less than 12.0 ml per minute, with a proviso that dialysis can be deferred if there is no evidence of uremia or malnutrition. The Caring for Australasians with Renal Impairment (CARI) guidelines<sup>31</sup> specify an estimated GFR of 10.0 ml per minute for initiation of dialysis in the case of patients with evidence of uremia or malnutrition and a lower estimated GFR for initiation in the case of patients without uremia or malnutrition.

The GFR targets in these guidelines have clearly influenced the clinical practice of nephrology. According to the U.S. Renal Data System, the proportion of patients in whom dialysis was initiated when the estimated GFR was higher than 10.0 ml per minute increased from 19% in 1996 to 45% in 2005,<sup>5</sup> accounting for a very large fraction of the rise in the frequency of incident dialysis during that period. Our results indicate that such trends toward early initiation of dialysis, which have enormous implications in terms of the cost and infrastructure of dialysis services, are unlikely to improve clinical outcomes. The results of our trial support the caveats in the available guidelines, highlighting the importance of close clinical follow-up of patients who have low levels of renal function and of initiating dialysis once more traditional indicators for dialysis are present and suggesting that dialysis should not be started on the basis of an estimate of GFR alone. No significant difference in fluid and electrolyte distur-



**Table 2. Primary and Secondary Outcomes, Including Adverse Events.**

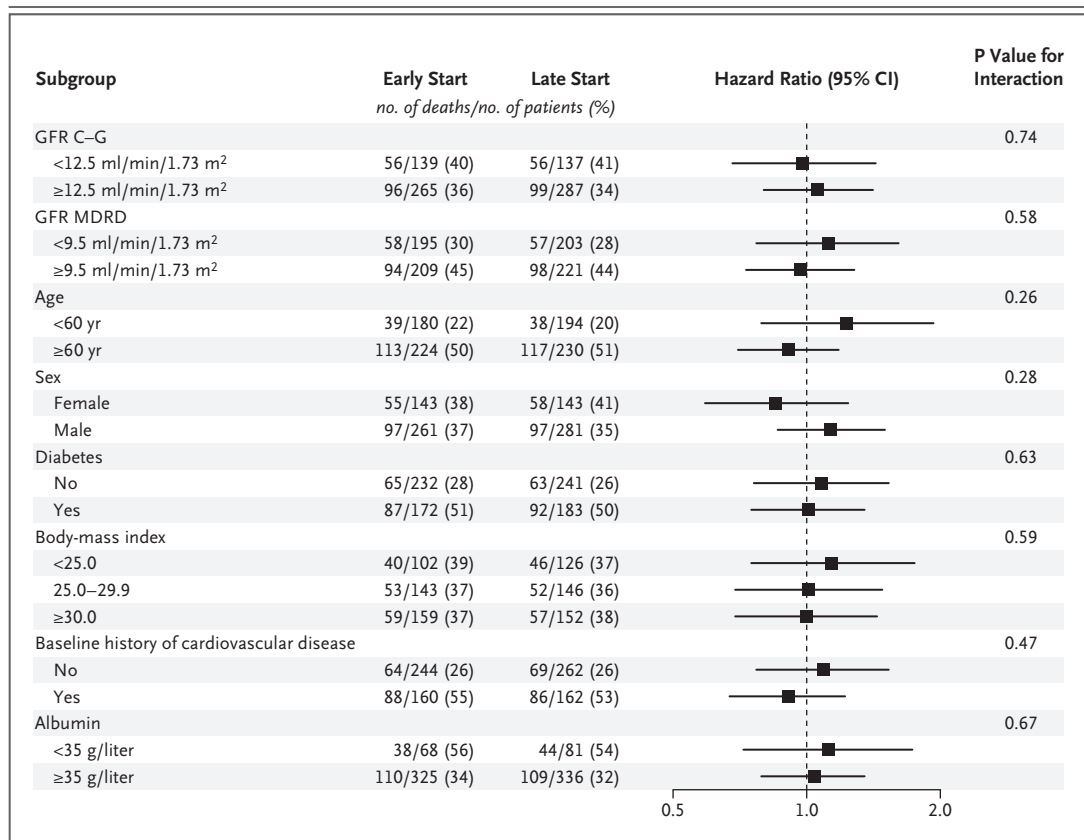
Outcome	Early-Start Group (N = 404)		Late-Start Group (N = 424)		Hazard Ratio with Early Start (95% CI)	P Value
	No. of Events	No. of Events/ 100 Patient-Yr	No. of Events	No. of Events/ 100 Patient-Yr		
Primary outcome: death from any cause	152	10.2	155	9.8	1.04 (0.83–1.30)	0.75
Secondary outcomes						
Composite cardiovascular events	139	10.9	127	8.8	1.23 (0.97–1.56)	0.09
Cardiovascular death	63	4.2	71	4.5	0.94 (0.67–1.32)	0.70
Nonfatal myocardial infarction	47	3.4	37	2.4	1.39 (0.91–2.15)	0.13
Nonfatal stroke	33	2.3	29	1.9	1.21 (0.73–2.00)	0.45
Hospitalization with new-onset angina	42	3.0	39	2.6	1.15 (0.75–1.78)	0.52
Transient ischemic attack	9	0.6	4	0.3	2.36 (0.73–7.68)	0.15
Composite infectious events	148	12.4	174	14.3	0.87 (0.70–1.08)	0.20
Death from infection	39	2.6	28	1.8	1.46 (0.90–2.38)	0.12
Hospitalization for infection	135	11.3	170	13.9	0.81 (0.65–1.02)	0.07
Complications of dialysis						
Need for access revision	145	13.2	147	12.4	1.08 (0.85–1.35)	0.54
Access-site infection	47	3.4	50	3.5	0.99 (0.67–1.48)	0.97
Serious fluid or electrolyte disorder	146	13.2	175	15.0	0.88 (0.71–1.10)	0.26
Placement of temporary dialysis catheter	118	10.0	124	9.7	1.03 (0.80–1.32)	0.85
Death as a result of treatment withdrawal	24	1.6	22	1.4	1.17 (0.66–2.08)	0.60
Death from cancer	14	0.9	16	1.0	0.92 (0.45–1.89)	0.82
Death from another cause	12	0.8	18	1.1	0.72 (0.35–1.49)	0.37

bances was seen between the study groups, and no difference in quality of life was observed between the groups at any stage of the study.

Our study was performed across a wide spectrum of clinical practice settings (urban and rural locations and general and university hospitals) in two countries. The follow-up of patients was long and complete. However, the study has certain limitations, including our use of an estimated GFR assessment that was based on the Cockcroft–Gault equation,<sup>17</sup> corrected for body-surface area.<sup>18</sup> Although alternative equations for GFR assessment were available (e.g., MDRD<sup>25</sup>), these methods were not widely used when the trial was designed and had not been validated in patients with low levels of renal function; however, a post hoc analysis of survival with baseline GFR estimated according to the MDRD equation revealed no significant between-group differences in outcomes. The lack of use of a uniform meth-

od of creatinine assessment in our study may be criticized. However, any difference in creatinine values between the randomized groups was likely to have been mitigated by the fact that patients were stratified according to study center. Although the majority of the patients assigned to the late-start group did not commence dialysis at the level of GFR defined in the protocol and the mean difference in estimated GFR was only 2.2 ml per minute, there was a difference of 6 months between the groups in the start time for dialysis, reflecting the importance of close clinical follow-up in this patient population. Although the confidence intervals do not exclude a clinically relevant benefit of early initiation of dialysis, they do tip the balance of evidence toward the view that no such benefit exists.

In conclusion, our study shows that among patients with progressive chronic kidney disease, clinical outcomes, including survival, are similar



**Figure 3.** Effect of the Timing of Dialysis Initiation in Subgroups.

The forest plot shows the hazard ratio (and 95% confidence intervals) for the primary outcome of death from any cause, with early initiation as compared with late initiation of dialysis, according to each of the prespecified subgroups. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. GFR C–G denotes glomerular filtration rate estimated with the Cockcroft–Gault equation, and GFR MDRD the glomerular filtration rate estimated with the Modification of Diet in Renal Disease equation.

between patients in whom dialysis is initiated early and those for whom dialysis is electively delayed. The results show that with careful clinical management, dialysis may be delayed until either the GFR drops below 7.0 ml per minute or more traditional clinical indicators for the initiation of dialysis are present.

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## APPENDIX

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