Early Initiation of Dialysis Fails to Prolong Survival in Patients with End-Stage Renal Failure

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Abstract. There is a trend to start dialysis earlier in patients with chronic renal failure. Studies that suggest improved survival from earlier initiation of dialysis are flawed in that they have measured survival from start of dialysis rather than from a time point before dialysis, when patients have the same renal function. This flaw is termed lead-time bias. Using the electronic patient record at the renal unit of Glasgow Royal Infirmary, all patients were identified who had received dialysis for chronic renal failure and who had sufficient data to calculate the time point at which they reached an estimated creatinine clearance (eC_{Cr}) of 20 ml/min ($n = 275$). This date was used to time survival. The patients were divided into early and late start groups by the median eC_{Cr} for all patients at initiation of dialysis, which was 8.3 ml/min. There was no significant benefit in patient survival from earlier initiation of dialysis. A Cox proportional hazards model demonstrated a significant inverse relationship between eC_{Cr} at start of dialysis and survival (hazard ratio, 1.1; $P = 0.02$), *i.e.*, patients who started dialysis with a lower eC_{Cr} tended to survive longer. This relationship retained significance when gender, age, weight, presence of diabetes, mode of first dialysis, initial dialysis access, hemoglobin, serum albumin, blood leukocyte count, Wright/Khan index, and eC_{Cr} at the start of dialysis were taken into account. This study fails to support a policy of earlier initiation of dialysis for patients with end-stage renal failure.

There has been a trend in recent years toward earlier initiation of dialysis in chronic renal failure. This has been supported by several studies (1–4) and review articles (5–7). The current Dialysis Outcomes Quality Initiative (DOQI) guidelines suggest that dialysis should be started when renal function expressed as weekly Kt/V drops below 2.0 (8). This is equivalent to creatinine clearance of 9 to 13 ml/min, which is higher than the median estimated creatinine clearance at start of dialysis of 7.97 ml/min (IQR, 6.3 to 10.3) reported in Scotland in 1997 (9).

The suggestion that earlier initiation of dialysis is beneficial was first given support by Bonomini *et al.* (1,2) in the 1970s, when they showed that early initiation of dialysis led to a decrease in mortality and hospitalization and an increased number of patients in full-time employment. The CANUSA study also showed significantly poorer survival for patients with lower levels of renal function when starting dialysis. The mean creatinine clearance at the start of dialysis for all patients was 38 L/wk (3.8 ml/min). Twelve- and twenty-four–month survival for those with creatinine clearance lower than 38 L/wk at start of dialysis was 82.1% and 73.6%, respectively, compared with 94.7% and 90.8%, respectively, for those with creatinine clearance greater than 38 L/wk (6). Tattersall *et al.* (3) also demonstrated reduced survival in patients with less residual renal function at start of dialysis, although these patients were also significantly older and had significantly more comorbidity.

The relevance of the Bonomini study to current clinical practice is questionable, as patients in the late start group were treated with a low-protein diet for at least 2 yr before starting dialysis. The other studies failed to take account of the effect of lead-time bias. Lead-time is the interval between the start of a study and a defined event. An error in the conclusions of a study will occur if patients are entered at different stages in the course of their illness. Apparent prolonged survival may simply be due to earlier registration of patients, that is, by recording a longer lead-time. This error is called lead-time bias. In the context of initiation of dialysis, lead-time bias refers to the effect whereby measuring survival from the start of dialysis increases apparent survival of those started with more residual renal function *i.e.*, earlier in the course of the disease, than those who start dialysis with less residual renal function.

In the recently published NECOSAD study, Korevaar *et al.* (10) estimated the effects of lead-time bias on dialysis survival by using prediction software based on the Finnish Cancer Registry. This study suggested that any perceived survival benefit from early start could be accounted for by lead-time bias. In the present study, we have used measured data from individual patients to eliminate the effect of lead-time bias in assessing survival on dialysis for chronic renal failure. We achieved this by measuring survival from the point before

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dialysis at which renal function in each patient declined to a specific level (estimated creatinine clearance [eC_{Cr}] of 20 ml/min) rather than from the start of dialysis.

Materials and Methods

The electronic patient record at Glasgow Royal Infirmary (GRI) contains data on over 13,000 patients and has been compiled prospectively since 1987 (11). Patients are registered at the time of referral to the renal unit. The system automatically estimates the eC_{Cr} by the Cockcroft and Gault method (12) for every serum creatinine result. Using data from a previous study, we were able to demonstrate that the highest eC_{Cr} at start of dialysis was 17 ml/min. We therefore chose the date on which eC_{Cr} declined to 20 ml/min as our "time zero." The method of retrieving and refining our data is summarized in Figure 1.

First, we identified all those patients who had ever had an eC_{Cr} less than 20 ml/min ($n = 2095$) and then identified those who had received renal replacement therapy (RRT) for end-stage renal disease (ESRD) ($n = 933$). This excluded those patients who had not yet reached dialysis or had received dialysis for acute renal failure. We then took the value and date of eC_{Cr} on either side of 20 ml/min and calculated the date when eC_{Cr} would be equal to 20 ml/min assuming a linear decline in renal function between these two points. The median time between these 2 points was 84 d with a median difference in the value of eC_{Cr} of 4.9 ml/min. Patients with no eC_{Cr} greater than 20 ml/min, *i.e.*, referred with eC_{Cr} less than 20 ml/min, were excluded. There is clear evidence on the adverse impact of late referral on outcome (9,13–19), and the potential bias that the inclusion of late referrals might have created was removed by selecting only those patients who were referred when eC_{Cr} was ≥20 ml/min. To be certain that we had eliminated the effect of late referral, we also excluded those patients with less than 180 d between referral to a nephrologist and initiation of dialysis. This left 235 patients who had received dialysis for chronic renal failure, were not late referrals, and had sufficient data to estimate when eC_{Cr} was 20 ml/min. These patients' records were then checked manually to ensure that the date for eC_{Cr} was the last time that eC_{Cr} crossed this threshold and that there was then a decline in renal function until the patients started dialysis. We also confirmed that none of those patients subsequently recovered renal function. The median eC_{Cr} at initiation of dialysis was 8.3 ml/min (inter-quartile range [IQR], 6.7 to 10.5), and we used this figure to divide the patients into early and late start groups. The early start group was defined by eC_{Cr} at start of dialysis ≥8.3 ml/min, and the late start group was defined as eC_{Cr} of <8.3 ml/min.

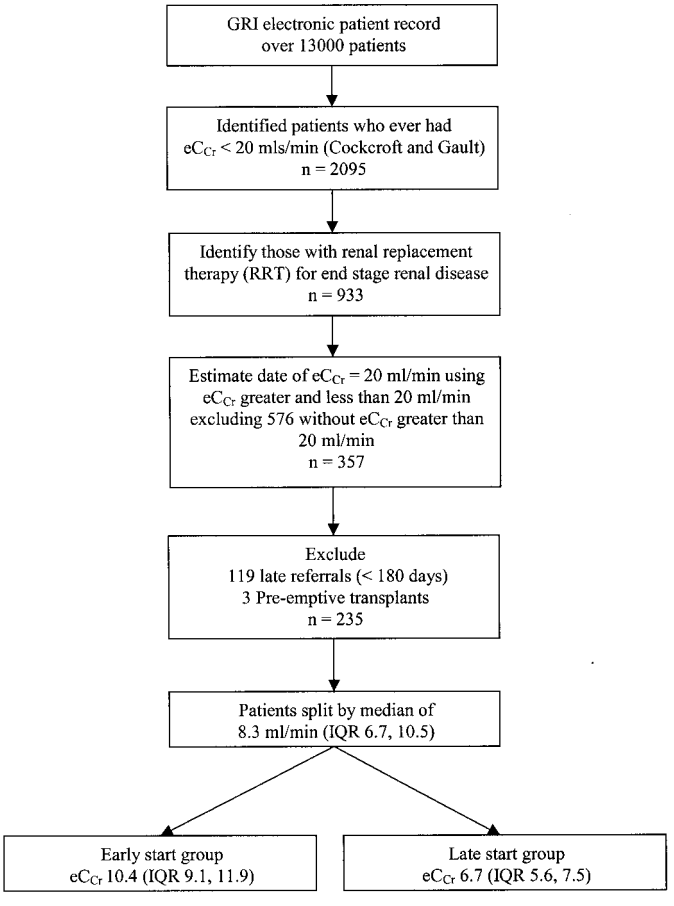

Figure 1. Approach to gathering and refining data.

We then collected demographic and laboratory data from these patients both when $eC_{Cr} = 20$ ml/min and immediately before starting dialysis. Unless a variable was present on the exact date of $eC_{Cr} = 20$ ml/min, we took the mean value of the variable obtained immediately before and after $eC_{Cr} = 20$ ml/min. The different variables collected and their values are shown in Tables 1 and 2. Primary renal diagnosis using the ERA-EDTA coding system and cause of death are shown in Table 3. Comparison of these variables between the early and late start groups was made using χ^2 and Mann-Whitney U tests. All statistical analyses were two-sided, and a $P < 0.05$ was considered statistically significant. Comparison of survival was made with the log-rank test and expressed as Kaplan-Meier plots. Endpoints were either death or date of data retrieval (February10, 2000). Comorbidity was expressed using Wright/Khan index (20, 21). This is a three-point score of low, medium, or high comorbidity and takes into account patient age, presence of diabetes, malignancy, and organ-specific diseases. Metcalfe *et al.* (9) recently showed that in a Scottish population, patients with high and medium comorbidity had early mortality rates that were 4.7 and 2.2 times higher than those with low comorbidity. Patients were labeled as having diabetes if at any time during the study period this diagnosis was made. The diagnosis of diabetes was made in accordance with the prevailing World Health Organization (WHO) definition (22).

Our initial analysis showed that there was an excess of patients with diabetes who started dialysis with a higher eC_{Cr}. These patients also had higher levels of proteinuria and comorbidity, and it was felt that their inclusion would bias against the early start group in any subsequent survival analysis. We therefore created Kaplan-Meier survival plots on the 184 patients who remained after the patients with diabetes were removed. The median eC_{Cr} at start of dialysis for these 184 patients was 8.0 ml/min (IQR, 6.4 to 9.8), and this median was used to divide these patients into early and late start groups for the Kaplan-Meier plots.

A Cox proportional hazards model was also created. In this model, gender, age, weight, presence of diabetes, mode of first dialysis, whether initial dialysis access was via a temporary central line, hemoglobin, serum albumin, blood leukocyte count, mean arterial BP, Wright/Khan index from the time of $eC_{Cr} = 20$ ml/min, and eC_{Cr} at the start of dialysis were selected as independent variables, and patient survival as the dependent variable. The independent variables were selected if they had a $P < 0.2$ on univariate analysis or because they were felt to be important (such as gender, weight, and hemoglobin). Cox regression was initially performed as a single step, but a backwards-stepwise model was also performed to ensure the conclusions were robust. All statistical analyses were carried out using SPSS for Windows version 9.0 (SPSS Inc., Chicago IL).

Table 1. Patient demographics when eC_{Cr} was 20 ml/min and before starting dialysis[a]

	235 Patients Including Diabetics			184 Patients Excluding Diabetics		
	Early Start ≥8.3 ml/min	Late Start <8.3 ml/min	*P*	Early Start ≥8.0 ml/min	Late Start <8.0 ml/min	*P*
Number of patients	119	116		97	87	
Male/female	92/27	65/51	0.001[b]	79/18	45/42	0.001[b]
Median eC_{Cr} at start of dialysis (IQR)	10.4 (9.1 to 11.9)	6.7 (5.6 to 7.5)		9.8 (8.5 to 11.2)	6.3 (5.2 to 7.1)	
Number of deaths	37	38	0.79	20	29	0.05
Number of patients with diabetes	39	12	<0.001	—	—	—
Number of subsequent renal transplants	28	39	0.09	31	33	0.40
First access for hemodialysis						
temporary central venous catheter	48	57		33	43	
arteriovenous fistula	27	22		23	16	
unknown	8	8	0.552[b]	7	8	0.284[b]
Patient age (yr)						
when eC_{Cr} = 20 ml/min	49.1	53.6	0.07	46.3	52.0	0.07
at start of dialysis	50.9	56.2	0.04	47.8	55.8	0.02
Patient weight (kg)						
when eC_{Cr} = 20 ml/min	76.2	67.0	<0.001	73.6	65.5	<0.001
at start of dialysis	74.7	63.5	<0.001	72.0	61.9	<0.001
Mode of dialysis						
hemodialysis	83	87		63	67	
peritoneal dialysis	36	29	0.39[b]	34	20	0.08[b]
Slope of eC_{Cr} (ml/min per mo)	−0.72	−0.63	0.50	−0.74	−0.51	0.08
Median mean arterial pressure (mmHg)						
when eC_{Cr} = 20 ml/min	101.3	101.9	0.66	103.8	100.7	0.28
immediately before dialysis	105.7	101.3	0.09	103.7	100.0	0.22
Comorbidity (Wright/Khan index)						
when eC_{Cr} = 20 ml/min						
low risk	30	68		35	33	
medium risk	55	68		58	50	
high risk	34	10	<0.001[b]	4	4	0.95[b]
at start of dialysis						
low risk	30	38		35	33	
medium risk	52	65		56	47	
high risk	37	13	0.001[b]	6	7	0.83[b]

[a] Data are shown for all 235 patients and for 184 patients after those with diabetes are removed. Both groups of patients are split into early and late start groups by the median eC_{Cr} at start of dialysis. Mann Whitney *U* test used in all cases except where indicated.

[b] Pearson's χ^2.

Table 2. Baseline laboratory characteristics of patients when their eC_{Cr} was 20 ml/min and before starting dialysis[a]

	235 Patients Including Diabetics			184 Patients Excluding Diabetics		
	Early Start ≥8.3 ml/min	Late Start <8.3 ml/min	*P*	Early Start ≥8.0 ml/min	Late Start <8.0 ml/min	*P*
Number of patients	119	116		97	87	
Urea reduction ratio (%)	67.3 (44)	67.0 (47)		68.6 (34)	66.6 (38)	
Total cholesterol (mmol/L)						
when eC_{Cr} = 20 ml/min	5.5 (5)	5.9 (4)	0.14	5.3 (4)	6.0 (4)	0.02
immediately before dialysis	5.4 (11)	5.7 (18)	0.18	5.3 (8)	5.8 (17)	0.07
Hemoglobin (g/dl)						
when eC_{Cr} = 20 ml/min	10.8 (0)	11.4 (0)	0.04	11.1 (0)	11.4 (0)	0.88
immediately before dialysis	9.6 (4)	8.7 (2)	0.001	9.5 (4)	8.6 (2)	0.001
Blood leucocyte count ($\times 10^9$/L)						
when eC_{Cr} = 20 ml/min	7.7 (0)	7.7 (0)	0.61	7.3 (0)	7.6 (0)	0.34
immediately before dialysis	7.6 (4)	7.4 (2)	0.29	7.2 (4)	7.3 (2)	0.51
Serum albumin (g/L)						
when eC_{Cr} = 20 ml/min	39.0 (0)	40.0 (0)	0.22	39.5 (0)	40.0 (0)	0.98
immediately before dialysis	38.0 (2)	38.0 (3)	0.63	39.0 (1)	38.0 (3)	0.4
Calcium × Phosphate product (mmol/L)						
when eC_{Cr} = 20 ml/min	3.4 (0)	3.1 (0)	0.001	3.4 (0)	3.1 (0)	0.001
immediately before dialysis	4.9 (11)	5.0 (6)	0.33	4.9 (8)	4.9 (5)	0.67
C-reactive protein (mg/L)						
when eC_{Cr} = 20 ml/min	8.0 (1)	10.0 (2)	0.31	7.8 (1)	10.0 (2)	0.04
at start of dialysis	7.5 (5)	13.5 (10)	0.08	9.0 (4)	14 (10)	0.08
Urinary albumin excretion (mg/L)						
when eC_{Cr} = 20 ml/min	1135.8 (25)	767.0 (33)	0.05	817.5 (23)	592.0 (30)	0.15
at start of dialysis	1056.0 (31)	782.0 (39)	0.24	828.0 (28)	775.0 (35)	0.38
Proteinuria (g/d)						
when eC_{Cr} = 20 ml/min	3.8 (47)	2.9 (48)	0.15	2.9 (37)	2.9 (36)	0.64
at start of dialysis	5.2 (54)	3.0 (50)	0.01	3.9 (40)	2.9 (37)	0.09

[a] Data are expressed as median and shown for all 235 patients and for 184 patients after those with diabetes are removed. Both groups of patients are split into early and late start groups by the median eC_{Cr} at start of dialysis. Mann Whitney *U* test used in all cases. Number of patients with missing variables are shown in brackets.

Results

The differences between early and late start groups when eC_{Cr} = 20 ml/min and at start of dialysis are shown in Tables 1, 2, and 3. Data are shown for all 235 patients and also after removal of those with diabetes (n = 184). For the nondiabetic patients, the only significant differences at start of dialysis were that the early start patients were younger, had lower weight, and had higher hemoglobin levels. Kaplan-Meier plots for survival were created for the nondiabetic patients only. These are shown in Figures 2 and 3. Figure 2 shows survival from eC_{Cr} = 20 to endpoint, and Figure 3 shows survival from start of dialysis to endpoint.

These plots demonstrate that lead-time bias is a real phenomenon in studies of survival and that not allowing for it could lead to potentially misleading results.

Cox Proportional Hazards Model

The results of Cox regression are shown in Table 4. This table shows the results when the variables were analyzed in a single step and also shows the final model after backward logistical regression. Survival is timed from eC_{Cr} = 20 ml/min. As expected, age and comorbidity were strong predictors of death. The Wright/Khan index includes diabetes, and this is likely to be the reason that diabetes does not reach significance in this model. If either diabetes or Wright/Khan index is removed, the other variable becomes more significant. In the final model, the hazard ratio of death associated with eC_{Cr} at start of dialysis was 1.1, *i.e.*, that for every 1 ml/min extra renal function at start of dialysis was associated with a 10% increased risk or hazard of death (P = 0.02).

Deaths before Dialysis

One possible source of error in this study was the exclusion of potentially eligible patients who died before starting dialysis. Patients approaching dialysis in our unit are discussed at a weekly meeting, and the decision to accept for dialysis is recorded in the electronic patient record. We identified 22 patients who fulfilled our search criteria outlined above and had been accepted for dialysis but died before reaching dialysis; ten of them had diabetes. Of these, only six had an eC_{Cr}

Table 3. Primary renal diagnosis (ERA-EDTA) and cause of death[a]

	235 Patients Including Diabetics			184 Patients Excluding Diabetics		
	≥8.3 ml/min	<8.3 ml/min	χ^2	≥8.0 ml/min	<8.0 ml/min	χ^2
Primary renal diagnosis						
primary glomerulonephritis	30	31		36	24	
interstitial nephropathies	25	34		29	29	
multisystem diseases	18	22		21	17	
diabetes	35	10		—	—	
not known or other	11	19	$P = 0.001$	11	17	$P = 0.31$
Cause of death						
withdrawn	4	2		2	1	
cardiovascular/cerebrovascular	16	12		6	10	
sepsis	4	3		4	2	
respiratory failure	1	1		1	1	
cancer	1	6		2	5	
unknown/other	11	14		5	10	
total	37	38	$P = 0.49$	20	29	$P = 0.31$

[a] Statistical comparison made using Pearson's χ^2 test.

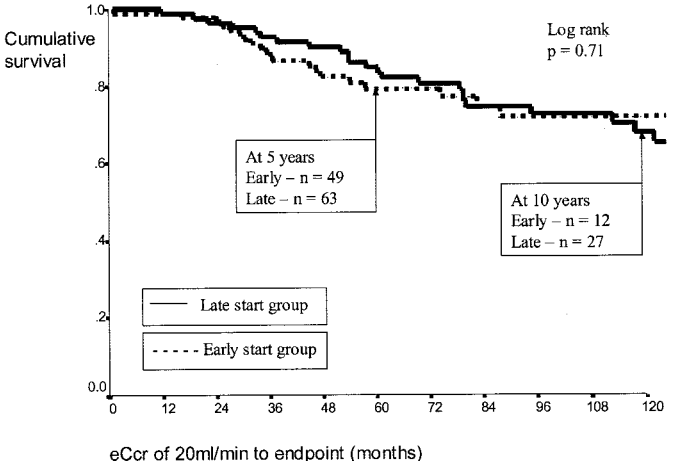

Figure 2. Ten-year survival of 184 nondiabetic patients from estimated creatinine clearance (eC_{Cr}) of 20 ml/min. Survival was censored if a patient was still alive when data was retrieved (February 10, 2000). Patients have been split into early start ($n = 97$) and late start ($n = 87$) groups by the median eC_{Cr} of 8.0 ml/min at start of dialysis.

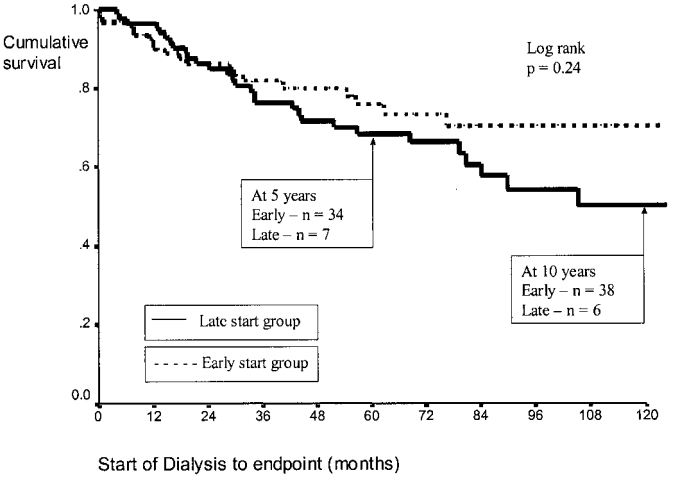

Figure 3. Ten-year survival of 184 nondiabetic patients from start of dialysis. Survival was censored if a patient was still alive when data was retrieved (February 10, 2000). Patients have been split into early start ($n = 97$) and late start ($n = 87$) groups by the median eC_{Cr} of 8.0 ml/min at start of dialysis.

<8.0 ml/min at time of death. Therefore, only these six would definitely have been in the late start group had they survived long enough. We have analyzed survival after adding either these 6 patients or all 22 patients to the late start group. Adding all 22 patients to the late start group biases the result against this group, but even under these conditions and after removal of patients with diabetes, there is still no significant benefit from earlier initiation of dialysis ($n = 206$; log rank, $P = 0.71$).

Discussion

We have been able to demonstrate and remove the potentially misleading effect of lead-time bias on survival of patients starting dialysis for ESRD. We have also eliminated the potential impact of late referral and studied the effect of many variables that are usually associated with increased morbidity and mortality. Even when these factors were taken into account, there was still no benefit from earlier initiation of dialysis. In fact, our data suggest that there is a small but significant increased risk associated with earlier initiation of dialysis.

We have analyzed our data on an intention-to-treat basis, and the only endpoints were death or end of study. However, to assess the impact of subsequent renal transplantation, we

Table 4. Cox proportional hazards model of 235 patients starting dialysis for ESRD using Cockcroft and Gault formula for estimating creatinine clearance (12)[a]

Variable (Reference Group)	Single Step			Backwards Logistical Regression		
	Hazard Ratio	95% CI	Significance	Hazard Ratio	95% CI	Significance
Gender (hazard for male = 1.0)	1.55	0.91 to 2.64	0.105	1.78	1.09 to 2.91	0.022
eC_{Cr} at start of dialysis (per ml/min)	1.10	1.00 to 1.20	0.051	1.11	1.01 to 1.21	0.024
Mode of dialysis (hazard for PD patients = 1.0)	1.51	0.70 to 3.25	0.29	—	—	—
Initial access via central line (hazard for no = 1.0)	1.63	0.90 to 2.95	0.109	2.18	1.35 to 3.51	0.001
Diabetes (hazard for no diabetes = 1.0)	1.43	0.69 to 2.95	0.330	—	—	—
Albumin (per mg/L)	0.99	0.95 to 1.04	0.790	—	—	—
White cell count (per 1×10^9/l)	1.14	1.04 to 1.24	0.003	1.13	1.04 to 1.23	0.004
Mean arterial pressure (per mmHg)	1.01	1.00 to 1.02	0.006	1.01	1.00 to 1.02	0.013
Hemoglobin (per g/dl)	0.92	0.79 to 1.08	0.320	—	—	—
Wright/Khan index (per point increase)	2.46	1.42 to 4.26	0.001	2.95	1.92 to 4.54	<0.0001
Age (per yr)	1.04	1.02 to 1.06	0.0004	1.04	1.02 to 1.06	0.0006
Weight (per kg)	0.99	0.98 to 1.01	0.529	—	—	—

[a] Variables entered were either significant on univariate analysis ($P < 0.2$) or felt to be important, such as gender, weight, and hemoglobin. Variables used were from around the point when estimated creatinine clearance for each patient was 20 ml/min. Survival is timed from eC_{Cr} = 20 ml/min to endpoint. Analysis was performed initially as a single step and then as backward logistical regression.

also performed analysis after censoring survival for transplantation. The Kaplan-Meier plots were similar with a log rank $P = 0.186$. The same variables were also retained as significant in the final Cox proportional hazards model.

Our final study population has a higher proportion of patients with glomerulonephritis (26%) and interstitial nephropathy (25%) than reported by the Scottsih Renal Registry (SRR) in 1999 (16% and 22%, respectively) (23). There is, however, a similar number of patients with diabetes (19% compared with 18% in the SRR). This effectively means that there are fewer patients with multisystem disease as a cause of renal failure. This is not surprising, as, by excluding late referrals, we are more likely to have removed those with multisystem diseases rather than those with more slowly progressive renal disease such as glomerulonephritis and interstitial nephropathy. This is supported by the findings of Ratcliffe *et al.* (16), who found a higher proportion of patients with interstitial nephropathy among those who were referred earlier. The median age of our study population at start of dialysis was 54.6 yr. The median date of starting dialysis in our study population was March 21, 1995. From the SRR 1999 report, it can be seen that the median age at start of dialysis in 1995 was 61.9 yr, but this included patients presenting late, who tend to be older. This trend was found by Metcalfe *et al.* (9) in patients starting dialysis in Scotland. Thus, in terms of cause of renal failure and age, our study population is similar to patients starting dialysis in Scotland as a whole during the time period of the study.

There were fewer female patients in the early start group. One likely reason is that female patients tend to have a lower serum creatinine for a given GFR than male patients and may have been started later for this reason. For unknown reasons, female patients had a lower survival rate than male patients, which would tend to benefit the early start group.

We did not specifically assess nutritional status, but there were no significant difference in serum albumin concentration between the early and late start groups. It is not possible to ascertain whether the lower cholesterol in the early start group reflects poor nutrition status or indicates a lower cardiovascular risk. There was also a significant difference in weight between the two groups, with the early start group being 8 kg heavier on average than the late start group (Tables 1). This difference in weight between the groups might partially be explained by the higher proportion of male to female patients in the early start group. Also, heavier people are likely to have a higher serum creatinine for a given level of renal function. This was found in our study population, where there was a small but significant relationship between weight and serum creatinine at start of dialysis ($R^2 = 3.6\%$; $P = 0.002$). Higher weight was also associated with higher eC_{Cr} at start of dialysis ($R^2 = 18.8\%$; $P < 0.001$). Tables 1, 2, and 3 also demonstrate that after patients with diabetes were removed, the only significant differences between the groups at the start of dialysis were in hemoglobin, age, and weight. These factors would tend to benefit the early start group.

One potential source of bias in our study is that patients starting dialysis more recently may have benefited from increased intensity of dialysis and an increased focus on cardiovascular risk reduction than those who started dialysis over a decade ago. In our study, however, the median date for starting dialysis in the late start group was November 1994 and the median date for the early start group was March 1996. If changes in practice had any effect on the outcome, then they would be likely to favor the earlier start group. Table 1 shows that each group of patients received a similar dialysis dose as assessed by urea reduction ratio (URR). As a unit, we have taken part in national audit within Scotland under the auspices

of the Scottish Renal Registry since 1990 (23–25) and within the United Kingdom under the auspices of the Renal Association (26–28). During this time, we have delivered a quality of dialysis either close to or above the targets set by these associations.

We have insufficient data on reasons for starting dialysis to make a meaningful comparison between the early and late start groups, but the usual reason was typical uremic symptoms such as lethargy, anorexia, nausea, and itch, with a small number starting for symptomatic fluid overload. It is likely then that those patients who started dialysis with less renal function did so simply because they were better able to tolerate the effects of uremia. It is this conventional practice that is being challenged by proponents of early initiation of dialysis. Our results do not suggest that all patients should start dialysis later, but rather that the current practice of allowing patients who tolerate uremia to delay the start of dialysis does not disadvantage them in terms of survival.

In the absence of adequate evidence, the best time to start dialysis for patients with ESRD is not known. Dialysis has many side effects, and it is not surprising that starting dialysis early fails to improve survival. Previous studies addressing this point have been confounded by lead-time bias. If early initiation of dialysis did indeed improve survival, then the effect would need to be sufficiently large to justify the implications for patients and healthcare funding.

We have calculated the power required for a prospective study that would eliminate lead-time bias. For the purposes of power calculation, we assumed 50% mortality at 5 yr. With 372 patients in each group, a study would have 80% power to detect a 10% difference in mortality at 5 yr. This assumes a constant hazard ratio of 0.756, an equal disease state, and no dropouts. To be able to remove the effect of lead-time bias, patients would need to be recruited and randomized well before they started dialysis. This would reduce the proportion of patients available for study, as a high proportion of patients starting dialysis are referred to nephrologists too late to be recruited into such a trial. In our own study, only 357 (38%) of the 933 patients who underwent dialysis for ESRD had enough follow-up to calculate $eC_{Cr} = 20$ ml/min and therefore remove lead-time bias. Similar findings were reported by Metcalfe *et al.* (13), who found that only 227 patients (43%) had greater than 1 mo of nephrology follow-up and had vascular access ready for use. It is therefore likely that only approximately 40% of patients starting dialysis would be suitable for entry into a prospective trial. Such a trial would therefore need to be multicentered, and recruitment of all suitable patients in a country the size of Scotland would require an enrollment period of approximately 4 yr. Against this background, it may be that such a randomized, prospective trial will never be performed, placing a greater emphasis on the results of retrospective and cohort studies.

The conclusions from this study are supported by two recent publications. The study of Korevaar *et al.* (10) demonstrated that any survival benefit from earlier initiation of dialysis could be accounted for by lead-time bias. A recent analysis of the USRDS database by Fink *et al.* (30) concluded that higher levels of estimated GFR (29) at the start of dialysis were associated with higher mortality even when other confounders were allowed for ($P < 0.0001$).

Our data do not show any survival advantage from earlier initiation of dialysis for ESRD, a practice that has enormous personal, social, and economic implications. Until evidence becomes available from a prospective randomized trial that eliminates the effect of lead-time bias, early initiation of dialysis cannot be supported.

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