RESEARCH

Association between estimated glomerular filtration rate at initiation of dialysis and mortality

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∞∞∞ See related commentary by Stel and Jager

ABSTRACT

Background: Recent studies have reported a trend toward earlier initiation of dialysis (i.e., at higher levels of glomerular filtration rate) and an association between early initiation and increased risk of death. We examined trends in initiation of hemodialysis within Canada and compared the risk of death between patients with early and late initiation of dialysis.

Methods: The analytic cohort consisted of 25 910 patients at least 18 years of age who initiated hemodialysis, as identified from the Canadian Organ Replacement Register (2001–2007). We defined the initiation of dialysis as early if the estimated glomerular filtration rate was greater than 10.5 mL/min per 1.73 m². We fitted time-dependent proportional-hazards Cox models to compare the risk of death between patients with early and late initiation of dialysis.

Results: Between 2001 and 2007, mean estimated glomerular filtration rate at initiation of dialysis increased from 9.3 (standard deviation [SD] 5.2) to 10.2 (SD 7.1) ($p < 0.001$), and the proportion of early starts rose from 28% (95% confidence interval [CI] 27%–30%) to 36% (95% CI 34%–37%). Mean glomerular filtration rate was 15.5 (SD 7.7) mL/min per 1.73 m² among those with early initiation and 7.1 (SD 2.0) mL/min per 1.73 m² among those with late initiation. The unadjusted hazard ratio (HR) for mortality with early relative to late initiation was 1.48 (95% CI 1.43–1.54). The HR decreased to 1.18 (95% CI 1.13–1.23) after adjustment for demographic characteristics, serum albumin, primary cause of end-stage renal disease, vascular access type, comorbidities, late referral and transplant status. The mortality differential between early and late initiation per 1000 patient-years narrowed after one year of follow-up, but never crossed and began widening again after 24 months of follow-up. The differences were significant at 6, 12, 30 and 36 months.

Interpretation: In Canada, dialysis is being initiated at increasingly higher levels of glomerular filtration rate. A higher glomerular filtration rate at initiation of dialysis is associated with an increased risk of death that is not fully explained by differences in baseline characteristics.

recorded or not accessible for data-gathering, a large international survey of physicians in 2000 revealed that the two leading determinants of early initiation were uremic signs and symptoms (38%) and residual kidney function (32%), with 90% of respondents indicating that initiating dialysis earlier (by 6–12 months) would give some major advantage in terms of outcomes.[5] The timing of initiation of dialysis is based on clinical judgment and the interpretation of signs, symptoms and laboratory test results, with possibly greater emphasis recently on estimated glomerular filtration rate following the introduction of national guidelines.[6,7] These guidelines were influenced by studies conducted in the 1980s and 1990s, which suggested that late initiation was potentially harmful.[8,9] In 2006, the US National Kidney Foundation suggested that initiation of dialysis be considered before stage 5 chronic kidney disease (estimated glomerular filtration rate < 15 mL/min per 1.73 m²) if symptoms were related to both comorbidities and level of residual kidney function.[10] The guidelines were based on existing observational information and never advocated initiating dialysis at a specific value of estimated glomerular filtration rate. However, studies conducted since 2001 have shown no survival benefit with initiation of hemodialysis at higher values of estimated glomerular filtration rate.[4,11–14]

Using data from the Canadian Organ Replacement Register, we examined trends in the timing of hemodialysis initiation between 2001 and 2007, characterized patients with early and late initiation of dialysis and compared the risk of death between these groups over time while controlling for baseline imbalances. In this article, we discuss the confounding effects of selection, survivor, misclassification, lead-time and indication bias.

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Examination of dialysis registry data, both in the United States and Europe, has shown that this procedure is being initiated for patients with increasingly higher levels of estimated glomerular filtration rate.[1–4] Although the indications for dialysis are often not

Methods

Data source

We obtained data from the Canadian Organ Replacement Register, a national registry maintained by the Canadian Institute for Health Information.[15] This registry records the incidence, prevalence and outcome for all patients undergoing long-term dialysis and all solid organ transplant recipients in Canada. Dialysis service providers collect the data by completing survey forms for each patient at the initiation of dialysis and yearly thereafter, with status recorded as of Dec. 31. Patients provide their data voluntarily. We analyzed data for all adult patients (i.e., at least 18 years of age at the start of renal replacement therapy) with a recorded value for serum creatinine who received hemodialysis (in-centre or home) as their first form of renal replacement therapy between Jan. 1, 2001, and Dec. 31, 2007.

Definitions

We used the modification of diet in renal disease equation $(186 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ [if female] $\times 1.21$ [if black])[16] to determine estimated glomerular filtration rate. For this calculation, we used the last recorded serum creatinine (SCr) measurement before initiation of dialysis. We defined the initiation of dialysis as early if estimated glomerular filtration rate was above 10.5 mL/min per 1.73 m².[4,6,17] This threshold is greater than that in the updated guideline of the National Kidney Foundation Disease Outcomes Quality Initiative,[10] which recommends initiating dialysis at estimated glomerular filtration rate of 10 mL/min per 1.73 m². We estimated the burden of comorbid disease using the end-stage renal disease comorbidity index.[18] Vascular access for initial dialysis was by arteriovenous fistula, arteriovenous graft or central venous catheter. We documented the presence or absence of coronary artery disease (angina, myocardial infarction or coronary artery bypass surgery), peripheral vascular disease, hypertension, diabetes mellitus (types 1 and 2) and cerebrovascular disease in three categories: yes, no and unknown. The categories for "no" and "unknown" constituted the reference group. We defined late referral as the patient having first seen a nephrologist within three months before initiation of dialysis, with albumin being the last recorded measurement before initiation of dialysis.

Statistical analysis

We followed cohort members from initiation of dialysis until death, loss to follow-up or the end of the observation period (Dec. 31, 2007). We compared patients' characteristics using χ^2, Wilcoxon or t tests, as appropriate. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) from time-dependent proportional-hazards Cox models. We adjusted the models for the following variables: age, sex, ethnicity, serum albumin, primary cause of end-stage renal disease, type of vascular access (arteriovenous fistula and arteriovenous graft combined v. central venous catheter), end-stage renal disease comorbidity index, late referral and transplant status. Change in treatment modality from dialysis to transplant was included as a time-varying covariate. We used Poisson regression to compare mortality rates (expressed per 1000 patient-years on dialysis) between early and late initiation in six-month intervals over three years. We compared cause-specific mortality rates for patients with early and late initiation of dialysis using the Cochran–Mantel–Haenszel test for general association. We report the data as means and standard deviations.

Results

Study sample

We identified 29 178 potentially eligible patients who initiated dialysis between 2001 and 2007. We excluded 3268 patients (11.2%) because serum creatinine values were missing. The study sample therefore consisted of 25 910 adult patients. The median follow-up time was 2.3 years. Of these patients, 8441 (32.6%) had early initiation of dialysis, at estimated glomerular filtration rate above 10.5 mL/min per 1.73 m². The remainder (17 469 or 67.4%) had late initiation of dialysis, at estimated glomerular filtration rate of 10.5 mL/min per 1.73 m² or less. Mean estimated glomerular filtration rate was 15.5 (standard deviation [SD] 7.7) mL/min per 1.73 m² among those with early initiation and 7.1 (SD 2.0) mL/min per 1.73 m² among those with late initiation. The group with early initiation appeared less healthy, since most potential risk factors for death were more common in this group (Table 1), the exception being late referral, which was more common among those with late initiation of dialysis. Patients with early initiation were older, more likely to be male and more likely to be white. In addition, the prevalence of diabetes was higher, the prevalence of glomerulonephritis and renal transplantation was lower, and the end-stage renal disease comorbidity index was greater.

Trends in initiation of dialysis, 2001–2007

Between 2001 and 2007, the mean estimated glomerular filtration rate at the time of initiation of dialysis increased by about 10%, from 9.3 (SD 5.2) to 10.2 (SD 7.1) mL/min per 1.73 m² ($p < 0.001$ for trend), and nearly one-third of the cohort underwent early initiation, at estimated glomerular filtration rate above 10.5 mL/min per 1.73 m². During this period, the proportion of patients with early initiation of dialysis rose from 28% (95% CI 27%–30%) to 36% (95% CI 34%–37%) (Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.100349/DC1).

Trends in mortality in relation to initiation of dialysis

Kaplan–Meier survival curves for early and late initiation showed that the difference in survival was attenuated after adjustment for baseline characteristics (Appendix 2, available at www.cmaj.ca/cgi/content/full/cmaj.100349/DC1). Nonetheless, a significant difference remained after three years of follow-up. Similarly, after adjustment for differences in demographic characteristics, serum albumin, renal diagnosis, type of vascular access, comorbidities, late referral and transplant status, the HR for mortality decreased from 1.48 (95% CI 1.43–1.54) to 1.18 (95% CI 1.13–1.23), but remained statistically significant (Table 2). The adjusted mortality differential between patients with early and late initiation of dialysis nar-

rowed after one year of follow-up, but the mortality rates never converged, and the differential began to widen again after two years (Appendix 3, available at www.cmaj.ca/cgi /content/full/cmaj.100349/DC1). The differences were significant at 6, 12, 30 and 36 months. After three years of follow-up, there were 27 more deaths per 1000 patient-years in the group with early initiation relative to the group with late initiation.

Cause-specific mortality

Cause of death was available for 8910 (73.6%) of the 12 111 patients who died (Table 3). No significant difference in cause-specific mortality was evident between patients with early and late initiation of hemodialysis ($p = 0.13$).

Interpretation

The results of this study, which arise from the publicly funded national health care system in Canada, confirm analyses of renal registries in the United States[1,12,13] the United Kingdom[11] and Europe.[4] There has been a consistent lack of benefit with early initiation of dialysis (as defined by estimated glomerular filtration rate) across study populations from heterogeneous health care delivery systems, which may differ in terms of standard of care or financial incentives for initiation of dialysis. This lack of benefit suggests that the results are not driven by a particular model of health care and are robust to differences among renal registries in terms of patient characteristics, procedures for collecting data and methods of ascertaining comorbidity.

Until the recent publication of the Initiating Dialysis Early and Late (IDEAL) trial, a randomized controlled trial that showed no benefit of early initiation of dialysis,[14] evidence on the ideal timing of dialysis initiation came solely from observational studies. Although much of that early observational research suggested a benefit with early initiation,[8,9] recent studies have not.[1,4,11□13,19] The apparent survival advantage of early initiation in the previous observational studies may be explained by greater rates of late referral among patients with late initiation, with patients for whom dialysis was initiated early being more likely to have benefited from predialysis care and being more

likely to have a fistula.[20] As well, the early studies failed to account for lead-time bias, which favours survival in the early-initiation group, as shown by Traynor and associates.[11]

Table 1: Baseline characteristics of 25 910 adult patients for whom hemodialysis was initiated between 2001 and 2007 in Canada

Characteristic	Stage of initiation; no. (%) of patients*		p value
	Early† n = 8441	Late‡ n = 17 469	
Age, yr, mean (SD)	67.5 (14.0)	63.7 (15.2)	< 0.001
Sex, male	5656 (67.0)	9 853 (56.4)	< 0.001
Ethnicity			< 0.001
Asian	329 (3.9)	1 013 (5.8)	
Black	253 (3.0)	542 (3.1)	
White	6576 (77.9)	12 979 (74.3)	
Other	726 (8.6)	2 079 (11.9)	
Unknown	557 (6.6)	856 (4.9)	
Estimated glomerular filtration rate, ml/min per 1.73 m²			
Mean (SD)	15.5 (7.7)	7.1 (2.0)	< 0.001
Median (IQR)	13.4 (3.8)	7.2 (3.0)	< 0.001
Serum albumin before dialysis, g/L			
Mean (SD)	32.0 (7.0)	31.9 (6.8)	0.29
Median (IQR)	33.0 (9.0)	32.0 (9.0)	0.033
Primary cause of renal disease			0.018
Glomerulonephritis	608 (7.2)	2 247 (12.9)	
Diabetes mellitus	3427 (40.6)	5 917 (33.9)	
Renal vascular disease	1865 (22.1)	3 364 (19.3)	
Other	1427 (16.9)	3 765 (21.6)	
Cause uncertain or unknown	1114 (13.2)	2 176 (12.5)	
Late referral	2807 (35.9)	6 585 (40.6)	< 0.001
Dialysis access via arteriovenous fistula or arteriorvenous graft	1774 (22.3)	3 799 (22.7)	0.46
Comorbidity index for end-stage renal disease, mean (SD)	2.6 (2.3)	1.9 (2.1)	< 0.001
Comorbidities			
Coronary artery disease	3790 (44.9)	5 468 (31.3)	< 0.001
Peripheral vascular disease	2195 (26.0)	3 144 (18.0)	< 0.001
Cerebrovascular disease	1418 (16.8)	2 306 (13.2)	< 0.001
Diabetes mellitus	4448 (52.7)	7 577 (43.4)	< 0.001
Hypertension	6930 (82.1)	14 377 (82.3)	0.65
Pulmonary edema	2760 (32.7)	4 193 (24.0)	< 0.001
Lung disease	1418 (16.8)	2 184 (12.5)	< 0.001
Other malignancy or serious disease	2026 (24.0)	3 529 (20.2)	< 0.001
Transplant§	490 (5.8)	2 166 (12.4)	< 0.001

Note: IQR = interquartile range, SD = standard deviation.
*Unless stated otherwise.
†Early initiation was defined as initiation with estimated glomerular filtration rate > 10.5 mL/min per 1.73 m².
‡Late initiation was defined as initiation with estimated glomerular filtration rate ≤ 10.5 mL/min per 1.73 m².
§Transplantation was performed during follow-up, after initiation of dialysis.

Lead-time bias is a phenomenon whereby patients entering a study earlier in their disease process (e.g., at higher residual renal function) will appear to survive longer than those who enter at a later stage in their disease.[11] Our analysis has shown a clear survival benefit for initiating dialysis late without correction of the data for lead-time bias. Making that correction would produce an even greater survival advantage.

Whereas lead-time bias favours survival in the early-initiation group, several other biases favour survival in the late-initiation group, including selection, immortal time, misclassification, indication and survivor biases.

More specifically, patients who appear at risk for malnutrition may be more likely to be selected for early initiation of dialysis. In this study and others,[21,22] patients with early initiation of dialysis differed from those with late initiation on important prognostic indicators. Although adjusting for imbalances in baseline characteristics attenuated the association between early initiation and mortality, the association remained significant. Furthermore, sensitivity analyses using propensity-score matching produced higher HRs (Appendix 4, available at www.cmaj.ca/cgi/content/full/cmaj.100349/DC1), which suggests that the increased mortality rate among patients with early initiation of dialysis is not completely explained by the presence of sicker patients in this group. This finding is consistent with those reported by Beddhu and colleagues.[12]

Also important to consider is the potential for the immortal time bias, which can occur when selection bias combines with survivor effects.[23] In this context, the immortal time bias favours survival among patients with late initiation of dialysis, who must have survived long enough for their estimated glomerular filtration rate to fall below 10.5 mL/min per 1.73 m². The resulting "survival of the fittest" effect in the late-initiation group could produce a healthier, more robust cohort at lower risk of dying. However, our results are consistent with those of Traynor and associates,[11] who corrected for this type of bias by starting follow-up at a common level of renal function, before initiation of dialysis. Even after accounting for additional deaths in the interval between entry into the study and initiation of dialysis, no significant benefit for early initiation was evident.

Finally, misclassifying patients as having early initiation is more likely to occur among sick, frail or elderly patients and those with diabetes, since they are at greater risk of sarcopenia or protein inanition, with resultant lower levels of serum creatinine and falsely high levels of estimated glomerular filtration rate. Misclassification bias may be greater when the modification of diet in renal disease formula is used to calculate glomerular filtration rate, rather than calculating creatinine and urea clearance.[12,24] We conducted our analyses using both glomerular filtration rate estimated from the modification of diet in renal disease equation and serum creatinine clearance as a continuous variable, obtaining the same results (Appendix 5, available at www.cmaj.ca/cgi/content/full/cmaj.100349/DC1). However, we

Table 2: Hazard ratios for mortality among 25 910 adult patients for whom hemodialysis was initiated between 2001 and 2007 in Canada

Predictor	HR for mortality* (95% CI)	
	Unadjusted	Adjusted†
Early initiation of dialysis‡	1.48 (1.43–1.54)	1.18 (1.13–1.23)
Demographic characteristics		
Age (per 10–year increment)	1.43 (1.41–1.45)	1.41 (1.39–1.43)
Male sex	1.04 (1.00–1.07)	1.08 (1.04–1.12)
Ethnicity (reference white)		
Asian	0.62 (0.57–0.68)	0.66 (0.60–0.73)
Black	0.43 (0.38–0.49)	0.52 (0.45–0.60)
Other	0.69 (0.65–0.73)	0.62 (0.53–0.72)
Unknown	1.16 (1.09–1.24)	1.16 (1.07–1.26)
Clinical characteristics		
Serum albumin before dialysis (per 1 g/dL increase)	0.78 (0.76–0.81)	0.78 (0.75–0.80)
Renal diagnosis (reference glomerulonephritis)		
Diabetes mellitus	1.77 (1.64–1.89)	1.48 (1.37–1.60)
Renal vascular disease	2.02 (1.88–2.18)	1.26 (1.16–1.37)
Unknown	2.07 (1.91–2.23)	1.49 (1.37–1.64)
Other	1.70 (1.57–1.83)	1.55 (1.42–1.69)
Access type (arteriovenous fistula or arteriovenous graft v. central venous access)	0.62 (0.59–0.65)	0.73 (0.69–0.77)
Comorbidity index for end-stage renal disease (reference 0)		
1	1.55 (1.44–1.67)	1.35 (1.24–1.47)
2	1.34 (1.28–1.41)	1.20 (1.13–1.27)
3	1.83 (1.72–1.94)	1.42 (1.32–1.52)
4	1.82 (1.72–1.92)	1.44 (1.34–1.53)
5	2.26 (2.13–2.41)	1.74 (1.62–1.87)
6	2.34 (2.17–2.52)	1.86 (1.71–2.03)
≥ 7	2.66 (2.47–2.87)	1.92 (1.76–2.10)
Late referral	1.29 (1.25–1.34)	1.11 (1.07–1.16)
Transplant§	0.07 (0.06–0.09)	0.15 (0.12–0.19)

Note: CI = confidence interval, HR = hazard ratio.
*Hazard ratios were estimated from a time-dependent Cox proportional-hazards regression.
†Adjusted for age, sex, ethnicity, serum albumin, renal diagnosis, vascular access type, comorbidity index for end-stage renal disease, late referral and transplant status, as appropriate.
‡Early initiation of dialysis was defined as estimated glomerular filtration rate > 10.5 mL/min per 1.73m².
§Transplant status was modelled as a time–varying effect.

were unable to measure creatinine clearance directly and therefore cannot exclude misclassification bias due to differences in muscle mass between the groups.

With the exception of lead-time bias, imbalances in risk factors at baseline coupled with the potential for misclassification and immortal time biases favour survival in the late-initiation group. Although adjustment for baseline imbalances lessened the mortality differential, a significant difference persisted. The remaining mortality differential between patients with early and late initiation of dialysis would be expected to converge over time as the sicker patients (predominantly allocated or misclassified into the early-initiation group) die, leaving groups that share similar mortality risks. Our data did show an initial trend toward convergence after one year of follow-up (Appendix 3, available at www.cmaj.ca/cgi/content/full/cmaj.100349/DC1), but the differential significantly widened again after two years, which suggests that mortality differences may be influenced by competing causes, with a varying time effect.

In contrast to the results of the IDEAL trial,[14] which showed no benefit of early initiation, our study suggests a possible harmful effect. This difference may result from incomplete statistical control for differences in baseline risk factors between patients with early and late initiation of dialysis, but it may also reflect important differences between the study samples. Whereas our analysis of 25 910 patients captured more than 90% of all patients in Canada for whom hemodialysis was initiated during the study period, the IDEAL trial (n = 871) captured only 10% of patients in the study country of Australia. More importantly, the mean estimated glomerular filtration rate among patients with early initiation, as determined by the modification of diet in renal disease equation, was markedly higher in our study than in the IDEAL trial (15.5 v. 9.0 mL/min per 1.73 m²) and there was a greater difference between the groups with early and late initiation (8.4 v. 1.8 mL/min per 1.73 m²).

Table 3: Cause of death in 12 111 adult patients for whom hemodialysis was initiated between 2001 and 2007 in Canada*

| Cause of death | Stage of initiation; no. (%) of patients | |
	Early† n = 4498	Late‡ n = 7613
Cardiac	1120 (24.9)	1804 (23.7)
Infection	400 (8.9)	624 (8.2)
Vascular	198 (4.4)	396 (5.2)
Gastrointestinal	121 (2.7)	221 (2.9)
Respiratory	58 (1.3)	99 (1.3)
Social§	652 (14.5)	1112 (14.6)
Other	742 (16.5)	1363 (17.9)
Uncertain or not determined	1207 (26.8)	1994 (26.2)

*Stage of initiation was not significantly associated with cause of death (p = 0.13).
†Early initiation was defined as estimated glomerular filtration rate >10.5 mL/min per 1.73 m².
‡Late initiation was defined as estimated glomerular filtration rate ≤ 10.5 mL/min per 1.73 m².
§Refusal of further treatment or cessation of therapy for any other reason.

A nonsignificant increase in cardiovascular deaths in the early-initiation group was observed in both this study and the IDEAL trial.[14] Sudden cardiac death is the most common cause of death among patients undergoing hemodialysis,[25–27] and some researchers have suggested that sudden cardiac death may be precipitated by the dialysis procedure itself.[28,29] Patients with higher residual renal function have less intradialytic weight gain because clearance is preserved, and they may be at greater risk for hypotension because of ultrafiltration from the dialysis. The increased risk of hypotension with its attendant effect on cardiac ischemia, combined with myocardial stunning,[28,30] could contribute to increased mortality among patients with initiation of dialysis at higher levels of estimated glomerular filtration rate. Consistent with this hypothesis, Termorshuizen and coworkers[2] found that excess ultrafiltration in relation to intradialytic weight gain was associated with increased mortality.

A recent analysis of data from the Canadian Organ Replacement Register showed a sharp increase in initiation of dialysis among those older than 75 years for the period 1998 to 2001. The higher rate was maintained until 2005, after which it declined slightly, from 760 per million in 2005 to 708 per million in 2008.[15] Concern about a rising tide of early dialysis initiation may have encouraged interest in maximizing conservative therapy for elderly patients. Importantly, initiating long-term hemodialysis in elderly patients with ischemic heart disease or multiple comorbidities does not appear to confer a survival benefit over conservative treatment.[21,31] Moreover, the potential decrease in quality of life, loss of independence and functional decline that may follow initiation of dialysis at higher levels of estimated glomerular filtration rate are important to consider. Recent studies have shown that early initiation of dialysis does not improve health-related quality of life and may in fact worsen it.[32,33] A small prospective study evaluating initiation of dialysis at estimated glomerular filtration rate below 6 mL/min per 1.73 m² in a cohort of patients with low comorbidity revealed a significant gain in the amount of time free from dialysis, with good quality-of-life scores and major economic savings.[34]

Limitations

In addition to the biases inherent to observational data, this study had limitations associated with the use of registry data. Although 92.3% of the patients undergoing dialysis in Canada were captured in the Canadian Organ Replacement Register, overreporting may have resulted from the capture of patients receiving dialysis for acute renal failure in the comparison data source.[35] A major limitation of this and many other studies is potential confounding by indication because of a lack of accurate records of signs and symptoms of uremia that are reported to be major determinants of initiation of dialysis.[1–5] It is impossible to completely eliminate bias by indication; however, any residual confounding not captured by our methods of adjustment would have to be substantial to mask a benefit of early initiation. In contrast to previous studies, we employed several different analytical techniques (Kaplan–Meier analysis, six-month by three-year mortality analysis, multivariable Cox proportional-hazards regression and analysis of propensity scores) to tease apart and better understand the relation between timing of dialysis initiation and mortality risk.

Conclusions

The consistent absence of a survival benefit with early initiation of dialysis across a variety of study designs, populations and health care delivery systems supports the conclusion that early initiation confers no survival benefit and argues against pre-emptive initiation of dialysis in asymptomatic patients. In contrast to early initiation of dialysis, early referral to a nephrologist is consistently associated with better survival. Further research is needed to determine the objective signs, symptoms and laboratory test results associated with increased mortality and decreased quality of life among patients with advanced renal failure. Rigorous comparative testing of these indicators in relation to the optimal timing of initiation of dialysis, survival, quality of life and cost effectiveness is necessary to inform future evidence-based national guidelines on this subject.

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