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REVIEW

WHEN TO START DIALYSIS TREATMENT: WHERE DO WE STAND?

Johanna C. Korevaar,[1] Jeannette G. van Manen,[2] Elisabeth W. Boeschoten,[3] Friedo W. Dekker,[2] and Raymond T. Krediet,[4] for The NECOSAD Study Group[a]

Department of Clinical Epidemiology and Biostatistics,[1] Academic Medical Center, University of Amsterdam; Department of Clinical Epidemiology,[2] Leiden University Medical Center, University of Leiden; Hans Mak Institute,[3] Naarden; Department of Nephrology,[4] Academic Medical Center, University of Amsterdam, The Netherlands

♦ ***Background:*** **Since the publication of opinion-based guidelines regarding the timing of dialysis treatment, there has been a trend toward earlier initiation.**

♦ ***Objective:*** **In this review, the existing guidelines and the currently published studies that evaluate them are discussed.**

♦ ***Results:*** **These studies could not demonstrate a clear benefit on survival or quality of life for patients who started with relatively higher renal function.**

♦ ***Conclusion:*** **Early start of dialysis treatment should not be confused with early referral to the nephrologist. It is concluded that initiation of dialysis should not depend on a predefined magnitude of renal function, but should be tailored to the individual patient.**

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KEY WORDS: Initiation of dialysis; referral; guidelines.

Despite major improvements in technology and advances in knowledge, there are no uniform objective criteria for the initiation of long-term dialysis therapy. In 1997, the US National Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF-DOQI) workgroup published an opinion-based guideline on the initiation of long-term dialysis therapy (1). This guideline was based mainly on urea clearance (renal Kt/V urea) and estimated protein intake, calculated from urea excretion in the urine [normalized protein equivalent of nitrogen appearance (nPNA)]. The workgroup advised that dialysis should start when renal Kt/V urea had fallen to 2.0 per week. This value equals a glomerular filtration rate (GFR) of about 10.5 mL/minute. A lower Kt/V urea would be acceptable only when nPNA was at least 0.8 g/kg daily. These recommendations were retained in the guidelines update published in 2001. Following the US DOQI initiative, the clinical practice guidelines of the Canadian Society of Nephrology for treatment of patients with chronic renal failure were published in 1999 (2). The Canadian guidelines regarding the timing of initiation of dialysis were not essentially different from the US guidelines. The main difference comprised a small shift of emphasize from Kt/V urea to creatinine clearance. In 2002, the European Best Practice Guidelines were published (3). Those guidelines recommended ini-

[a] The NECOSAD Study Group also includes A.J. Apperloo, J.N.M. Barendregt, R.J. Birnie, M. Boekhout, W.H. Boer, H.R. Büller, F.T. de Charro, C.J. Doorenbos, W.J. Fagel, C.F.M. Franssen, L.A.M. Frenken, W. Geerlings, P.G.G. Gerlag, J.P.M.C. Gorgels, W. Grave, R.M. Huisman, K.J. Jager, K. Jie, W.A.H. Koning–Mulder, M.I. Koolen, T.K. Kremer Hovinga, A.T.J. Lavrijssen, A.W. Mulder, K.J. Parlevliet, J.B. Rosman, M.J.M. Schonk, M.M.J. Schuurmans, P. Stevens, J.G.P. Tijssen, R.M. Valentijn, E.F.H. van Bommel, W.T. van Dorp, A. van Es, J.A.C.A. van Geelen, J.L.C.M. van Saase, G. Vastenburg, C.A. Verburg, V.M.C. Verstappen, H.H. Vincent, P. Vos.

Correspondence to: J.C. Korevaar, Department of Clinical Epidemiology & Biostatistics (J1B-209), Academic Medical Center, University of Amsterdam, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands.

j.korevaar@amc.uva.nl

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tiating dialysis at a GFR level between 8 and 10 mL/minute/1.73 m^2.

Several studies from the USA (4) and Europe (5) reported lower renal Kt/V urea or creatinine clearance than recommended by the guidelines at the start of dialysis in many patients. Implementation of the new guidelines would, therefore, lead to earlier initiation of dialysis treatment in similar cases. This would have a major impact on the daily life of patients, exposing them at an earlier stage to dialysis. Earlier initiation would also necessitate an increase in dialysis staff and probably in dialysis units as well, inevitably leading to increased costs. Before treatment decisions can be made based upon such a guideline, the benefits and risks of alternative strategies should be made explicit, and should be weighed by patient preferences and costs. Yet, despite the lack of evidence for these new guidelines, there has been a trend toward an earlier initiation of dialysis treatment in recent years (6,7).

EVIDENCE FOR THE GUIDELINES

The suggestion that earlier initiation of dialysis is beneficial was given by, among others, Bonomini *et al*. (8) and Tattersall (5) *et al*. Yet, these studies were hampered by some methodological problems: renal function was estimated from a serum sample, a small number of patients were included, and, more importantly, these studies did not take the effect of lead time into account. Lead time is the effect of whether the observed lower mortality risk, and thus longer survival time, in patients who were classified as timely starters was simply a reflection of initiating dialysis at an earlier stage of the disease. If this were the case, an observed advantage would not represent an improvement in the course of the disease.

We recently explored empirical support for the current guidelines by analyzing the association between the timing of dialysis initiation and the effect on survival and health-related quality of life (HRQOL) in a prospective cohort study among patients new on dialysis treatment in The Netherlands (NECOSAD Study) (9). Ninety-four (37%) of 253 patients started dialysis treatment later than recommended by the US guideline (late starters). The adjusted difference in estimated survival time after 3 years on dialysis treatment was small: a benefit of 2.5 months [95% confidence interval (CI) 1.1 – 4.0) in favor of timely starters. Conversely, the average delay in dialysis initiation for late starters, thus the extra time free of dialysis, was at least 4.1 months. So, the gain in survival for the timely starters was most likely a reflection of lead time instead of a real advantage of a timely start (9). All patients, timely and late starters, showed a marked improvement in HRQOL during the first 6 months after the start of dialysis treatment. Compared to patients who started too late, patients who started in time had a significantly higher HRQOL for a number of dimensions immediately after the start of treatment. By 12 months of dialysis treatment, these differences had disappeared and HRQOL was similar for both groups (10). It is unclear whether this short-term benefit outweighs the extra restrictions associated with earlier dialysis treatment.

These findings were confirmed by a study from Traynor *et al*. (11). They included patients as soon as they reached a creatinine clearance of 20 mL/min. That date was used to time survival. Patients were divided into early and late start by the median creatinine clearance (8.3 mL/min). They did not observe a benefit in patient survival from earlier initiation of dialysis, but found the opposite; that is, patients who started dialysis with a lower creatinine clearance tended to survive longer. Other authors have also demonstrated this inverse relationship (12,13).

In a study published by Foggensteiner *et al.*, a single-exchange peritoneal dialysis treatment was started in 39 patients as soon as their renal Kt/V urea became 2.0 (14). Those authors found that, on average, it took 297 days (9.8 months) before those patients needed to increase their dialysis treatment. By that time, renal Kt/V urea had declined to 1.43 per week. They concluded that this treatment was acceptable to the patients and complications were low. However, in daily clinical practice, a renal Kt/V urea of 1.43 is a common level of renal function at the time patients start dialysis treatment. Moreover, a decline from 2.0 to 1.43 in 10 months is similar to the decline reported in predialysis patients (15,16). Therefore, one can put forward the question, what would have happened to these patients if they would not have started peritoneal dialysis at a renal Kt/V urea of 2.0, but would have received proper predialysis care in the meantime.

The first, multicenter, randomized controlled trial is currently underway in Australia and New Zealand to determine whether the timing of dialysis initiation has an effect on survival in end-stage renal disease patients (IDEAL Study). Patients are randomized to commence dialysis by GFR: early start, GFR 10 – 14 mL/min/1.73 m^2; late start, GFR 5 – 7 mL/min/1.73 m^2. The follow-up of this study will be completed by December 2007 (17).

EARLY START OR TIMELY REFERRAL

An important issue that confuses the discussion around timing of dialysis treatment is the distinction

between the timing of referral to the nephrologist and the timing of initiation with dialysis treatment. These are two completely different subjects and should not be intermixed. Obviously, a timely referral to the nephrologist is important. Only patients who are referred in time have the opportunity to have a planned initiation and can obtain proper predialysis care. Late referral and less predialysis care are associated with poor outcome. Patients who were referred less than 4 months before the start of dialysis had a significantly increased mortality risk (hazards ratio 1.6, 95% CI 1.04 – 2.39) compared to patients who were referred more than 12 months before the start of dialysis (18). This increased mortality risk was independent of demographic characteristics, socioeconomic status, and comorbidity. Moreover, late referral influences modality choice. Patients who did obtain predialysis care had a stronger preference for peritoneal dialysis compared to patients who did not receive predialysis care (19). In addition, patients who were referred late and started with peritoneal dialysis were more likely to switch to hemodialysis during the first 6 months compared to patients who were referred in time (20). A recently published study by Caskey *et al.* demonstrated that early-referral patients with a planned first dialysis treatment had better HRQOL scores, especially for the mental and emotional health scores, compared to late-referred patients (21).

During the period 1997–2001, according to nephrologists in The Netherlands, 24% of patients did not receive proper predialysis care (19). A similar percentage was found in a European study in eight different countries: 24% of the patients were referred less than 1 month before the start of dialysis (22). It can be concluded that patients with chronic renal failure should be referred in time, allowing them to receive proper predialysis care, to be educated about modalities of renal replacement therapy, and to have a planned initiation of dialysis.

CONCLUSION

Based on the recent studies discussed above, there is no clear benefit to patient survival or HRQOL for patients who start dialysis with a relatively higher renal function. Perhaps it is time to shift from the idea that all individual patients need to start dialysis at a fixed renal clearance. This assumption is supported by the observation that the evolution of uremic symptoms varies from patient to patient. Moreover, in both the ADEMEX Study (23) and the HEMO Study (24), no clear benefit of one fixed level of small solute clearance was obtained. To determine the optimal timing of dialysis treatment, more aspects than clearances should be taken into account, such as fluid status, inflammation, hypertension, nutritional status, quality of life, and patient complaints. As long as a patient is doing well with a lower renal function than that recommended by DOQI, signs and symptoms of uremia should be monitored closely. When these are absent, initiation of dialysis treatment can be postponed. The focus on just one aspect of treatment might not lead to improved patient outcome.

An evidence-based recommendation on the timing of the initiation of dialysis treatment is still hard to give. No beneficial effect on patient survival due to an early start could be established. Moreover, the HRQOL advantage of an early start had disappeared within 1 year. Consequently, with a timely referral, good predialysis care, and careful monitoring, it is the patient himself, in consultation with the nephrologist, who should weigh both sides and determine the best individual timing.

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