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COMMENTARY

Dialysis delayed is death prevented: A clinical perspective on the RENAAL study

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In this era of evidence-based medicine, before any new treatment can be approved, clinical trials are required to establish treatment efficacy in terms of relevant clinical end points. For most large trials in kidney disease, the hard end point employed is "renal death" or end-stage renal disease (ESRD). Both terms are used interchangeably to denote the extent of renal failure that, if untreated by dialysis or transplantation, would result in the death of the patient from complications of uremia. As dialysis has become an acceptable and commonplace treatment, ESRD is rarely fatal. However, there remain many situations where safe dialysis is impractical or inappropriate. For example, many of the patients with pre-ESRD in the Western world may be unsuitable for renal replacement therapy (RRT) because of age, frailty, or a co-morbid illness with poor prognostic outcome. In addition, the majority of the hundreds of thousands of patients with renal failure reside in developing countries without the resources or infrastructure to provide for universal RRT. In these circumstances, dialysis delayed is death prevented.

In addition, within the intensive review of a clinical trial, initiation of RRT is almost always timely and optimized in order to avoid the consequences of terminal uremia and reduce morbidity and mortality. But in the "real world," particularly the disadvantaged regions where health resources are limited, conditions are seldom optimal for ESRD patients. Dialysis tends to be considered, if at all, only after conservative therapy becomes insufficient for controlling the clinical or biologic dysfunctions of the uremic state. The National Kidney Foundation-Dialysis Outcome Quality Initiative (NKF DOQI™) guidelines recommend that patients begin dialysis when the glomerular filtration rate (GFR) falls below 10.5 mL/min in order to prevent uremic complications. For patients with diabetes, there is consensus that RRT should be initiated even earlier [1]. But in reality, dialysis is delayed, with 57% of all patients in the United States starting dialysis with a residual GFR less than 7 mL/min [2]. This implies that the majority of patients are uremic for a considerable time before starting RRT. While late initiation of dialysis may be indicative of late presentation or tardy referral, at least some of the delay is due to impaired access to RRT outside tertiary care centers. Women and certain non-Caucasian racial groups are more likely to have delayed initiation of dialysis [3]. Furthermore, American patients who do not have insurance have significantly greater odds of late initiation of dialysis compared to patients with private insurance [3]. Therefore, in most regions of the world, and especially outside the setting of the clinical trial, the frequency of uremic symptoms, malnutrition, and the possibility of life-threatening complications are all increased in patients prior to starting dialysis.

Recent trials in the prevention of ESRD deserve to be considered in light of these "real world" conditions. Many studies have been criticized on the grounds that their interventions appear to lack applicability outside the highly specialized setting of the clinical trial. Results achieved in such studies can seldom be reproduced in routine practice. But the opposite argument may also be made. It may be observed that as a result of being confined to the highly specialized setting, a trial may potentially underestimate the extent of benefits that may be achieved in everyday practice. A case in point is the recent RENAAL trial [4] that showed a 28.8% risk reduction for ESRD with therapy with the angiotensin II antagonist losartan ($P = 0.002$). However, the all-cause mortality (including both pre- and post-ESRD deaths) was not significantly different from placebo (−2%) possibly as this study was performed in centers where chronic dialysis was routinely available.

One could speculate that if the RENAAL trial had been performed in less advantaged areas of the globe,

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where RRT is not readily available and recognition of renal disease occurs late or not at all, ERSD prevented could equate to reduced mortality. Using the composite outcome "death or ESRD" to identify both actual predialysis mortality and renal death, losartan resulted in a 20% reduction in risk. In the absence of RRT, this directly translates into fewer deaths. In America, over 20% of all patients with pre-ESRD are said to be unsuitable for RRT [5]. In addition, the RENAAL study excluded patients with heart failure and significant vascular disease. Again, had the RENAAL study included these kinds of patients, the all-cause mortality may have been different.

Approximately two thirds of all deaths (214/313, 64%) in the RENAAL study occurred *before* starting dialysis, the majority due to premature cardiovascular disease. The reasons for this may be multifactorial, including hypertension, oxidative stress, inflammation, malnutrition, and dyslipidemia [6]. The uremic environment per se may also be atherogenic. The uremic syndrome is characterized by deterioration in biochemical and physiologic functions in parallel with the progression of renal disease. As with some large studies in the past [7], RENAAL also demonstrated that, independent to other baseline covariates, serum creatinine was a significant risk factor for all-cause mortality (76% risk increase per 1 mg/dL increase in serum creatinine, $P < 0.0001$) and cardiovascular mortality (83% risk increase per 1 mg/dL increase in serum creatinine, $P = 0.0001$) in patients with type 2 diabetes and nephropathy. In effect, the more advanced the renal disease, the greater the perturbation of uremic indices and the greater the mortality risk.

If slowing progression to ESRD actually reduces mortality, it is possible that this benefit may only be detected in patients where the pre-ESRD milieu was postponed by therapy. However, in the study setting and in accordance with guidelines (compared to the "real world"), few patients are allowed to become and stay uremic. In particular, the timely initiation of RRT attenuates the complications of chronic renal failure such as malnutrition and cardiovascular disease and consequently results in reduced morbidity, mortality, and cost [3] (possibly as a result of initiating dialysis earlier in the disease process [8]). Patients reaching ESRD in the RENAAL study started dialysis earlier than is current practice in the "real world" outside the trial setting. The estimated mean GFR for patients starting RRT (in whom serum creatinine was available 3 months prior to ESRD) was 10.8 mL/min/1.73 m^2 (median = 10.3). In the "real world," with dialysis initiated on average at 7 mL/min/1.73 m^2 the duration of "pre-ESRD" is much longer, increasing the potential for mortality during this time. In quantitative terms (using the pooled rate of disease progression of 4 to 5 mL/min/1.73 m^2/year) RRT in the RENAAL study provided nearly 8 to 12 months less of uremia than is currently standard in most places in the world.

In addition, although including patients with lesser degrees of renal impairment [e.g., serum creatinine 1.3 mg/dL (115 μmol/L)] may have been valuable to demonstrate that losartan works equally well in early and advanced diabetic nephropathy, patients with only mild renal impairment at the outset may not have been exposed to a uremic milieu during the average 3½ years of the study course. Both the timely initiation of dialysis and inclusion of patients with early diabetic renal disease may to some extent explain why predialysis mortality could be underrepresented in the RENAAL study.

If prevention of ESRD represents the prevention of renal death, efficacy analysis should therefore consider pre-ESRD outcomes and establish death *or* dialysis as the primary end point. In effect, death and dialysis are competing events in the study population. However, one third of all deaths (99/313, 32%) in the RENAAL study occurred *after* starting dialysis. Of all patients reaching ESRD, 22.6% (77/341) died within the first year of RRT. This mortality rate is higher than the first annual mortality of around 15% seen in most dialysis centers [9, 10], presumably reflecting the impact of diabetic co-morbidity on dialysis outcomes. While it is possible that at least some of post-ESRD mortality in the RENAAL study was not modified by dialysis, the timely initiation of RRT in study patients would also have been exposed earlier to the life-threatening complications associated with dialysis (i.e., sepsis, hypotension, and repeated invasive interventions). Furthermore, once a patient starts dialysis, many different factors may contribute to mortality, and dialysis itself may introduce other risk factors for mortality. Consequently, the inclusion of post-ESRD deaths in the total mortality figure may bias away from potentially more clinically relevant predialysis events. Future trials evaluating the renoprotective effects of an intervention could do better to analyze death or ESRD together as competing events in time to first-event analysis.

In addition to reducing total ESRD events, the rate of decline in renal function was significantly slowed in patients treated with losartan (4.4 vs. 5.2, $P < 0.01$) reducing reduce the number of days with ESRD by 213 days per patient (abstract; Keane et al, *J Am Soc Nephrol* 13:264A, 2002). In the "real world," where dialysis delayed equals death prevented, this means a longer life span. Even in centers that are able to offer universal RRT, the capacity to delay the progression of renal disease may also be compatible with a more conservative approach to care, allowing for the planning and timely initiation of RRT and reducing the need for and the consequences of emergent dialysis. In nondiabetic chronic nephropathies, the capacity to delayed progression to ESRD by angiotensin-converting enzyme (ACE) inhibitor therapy results not only in the prolongation of patients survival, but also in an increased proportion of time spent on conservative therapy [11]. Moreover, many

patients die of complications related to the uremic state without knowing they have renal disease.

The number of patients with ESRD is growing at an exponential rate. From 1978 to 1995, the incidence of new patients on maintenance dialysis has increased fourfold in the United States and in the European community, and doubled within the last 10 years in Japan [12]. The single most important cause is diabetes, which has now reached epidemic proportions, particularly in emerging countries. Although mortality in patients with diabetes on dialysis is still very high, a sustained improvement of patient survival on dialysis therapies has been achieved during the past two decades. While it is widely agreed that resource availability should not be a reason to limit access to dialysis, this global epidemic of renal disease creates significant economic strain, particularly in developing countries. The inevitable escalation in the cost of ESRD treatment from patient numbers alone appears incompatible with the increasing pressures for the containment of health-care expenditures imposed in most countries. As a consequence, vigorous attempts should be made to reduce the financial burden of ESRD therapies. However, the best way to facilitate the goals for the early treatment of uremic complications and cost-effective RRT measures remains to slow the growth rate of patients requiring RRT. For developing countries, lacking the fiscal resources to provide for RRT, the RENAAL trial represents a new public health message—that the prevention of death in ESRD is possible, even in advanced disease, as progression can be effectively retarded. Even in the Western world, where over 20% of patients may be unsuitable for RRT, losartan may prove both renoprotective and potentially life saving.

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