**Letter and Reply**

**Initiation of dialysis—the right timing and the right tools**

Sir,

Two interesting studies have been published in *Nephrology Dialysis Transplantation* linking kidney function at initiation of dialysis to survival [1,2]. The authors of these papers, in concordance with each other, found that starting dialysis with relatively high estimated glomerular filtration rate (eGFR) was associated with higher mortality. Their findings appear to contradict the concept of an ‘early’ or ‘healthy’ start of renal replacement therapy. Although these results are very interesting, they should not be misinterpreted or be used to change unfavourably the current practice of patient care.

The four-variable MDRD equation was implemented in both studies to evaluate kidney function. As rightly acknowledged by Sawhney et al. [1], this equation may not be valid in advanced renal failure. While it has been well validated in moderate and severe kidney function impairment, it appears that in end-stage renal disease (ESRD) serum creatinine concentration is relatively more influenced by muscle mass. This phenomenon is well illustrated by the fact that in the MDRD study [3] the two regression curves for black and white patients become more divergent at the low GFR. Importantly, the main reason for different GFR MDRD estimation formulas was the racial difference in relative muscle mass [3]. In this respect, previous studies have linked survival of incident peritoneal dialysis patients to 24-h urinary creatinine used as a crude measure of muscle mass [4]. Our own study found similar association between survival and peritoneal creatinine excretion in anuric female patients [5].

Thus, “healthy” well nourished, high muscle mass patients with high serum creatinine will have relatively low eGFR, and, at the same time, reduced mortality, while malnourished, frail patients with comorbidities will have high eGFR due to decreased creatinine appearance, but relatively worse survival.

This phenomenon is illustrated in the paper by Sawhney et al. [1] by the differences in average patient age and prevalence of diabetes in different GFR groups. Older age and higher prevalence of diabetes are seen in patients with high GFR. The difference in clinical condition and comorbidities across different GFR groups is also illustrated by disparities in the percentages of patients receiving kidney transplants, reflecting, in fact, transplant eligibility of these patients. Importantly, in this study, patient comorbidity has not been evaluated and only old age and diabetes prevalence were used as surrogate markers of increased comorbidity. In the paper by Stel et al. [2], the comorbidity data were available only in a small part of the studied population, and its inclusion in the multivariate analysis model made the associations between GFR and survival weaker, especially in patients with increased age and diabetes.

We would like to point out that although MDRD GFR estimation is very easy to perform, both DOQI [6] and European Best Practice Guidelines [7] recommend the use of urine collection to estimate renal function in the context of initiation of dialysis.

Both studies are retrospective and observational in design. Most likely, the individual decision to initiate dialysis was based on clinical judgment of the nephrologist. This takes into consideration not only estimation of kidney function, but also many clinical parameters like well-being of the patient, nutrition status, signs of overhydration and metabolic disturbances related to diminishing kidney function. Thus, irrespective of the influence of muscle mass on GFR estimation, it is likely that in fact patients in compromised clinical condition and with many comorbidities, who have, as a consequence, decreased predicted survival would start dialysis earlier with relatively higher GFR.

Regardless of the criticism of the methods employed in the two studies, they present a novel and important contribution into the discussion on the timing of dialysis initiation. They seem to implicate that this decision probably should not be taken solely on the grounds of patient reaching any predefined clearance values. Whenever the estimation of kidney function is needed to guide the decision of dialysis initiation, urine collection should be performed.

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Reply

Sir,

We appreciate the interest and contribution of Liberek et al. to the controversy regarding timely initiation of dialysis. We agree that the findings of our study should not be used to advocate a late or low eGFR start on dialysis. In fact, as an observational cohort study, our study simply describes outcomes of those in whom dialysis was started at different levels of eGFR, and the data suggest that eGFR values should not be used in isolation, either to make a judgement on starting dialysis or as an auditing tool for the quality of ESRF care [1]. In fact, we describe an excellent example of ‘confounding by indication’: those with higher eGFR appear to be sicker, thus leading physicians to commence dialysis. Interestingly, however, the European Best Practice Guidelines [2] recommend ensuring that all patients have started dialysis before eGFR $< 6 \text{ ml/min/1.73 m}^2$, regardless of the presence or absence of signs and symptoms.

Methods of assessing residual renal function that consider weight, and thus indirectly muscle mass and nutrition, such as creatinine clearance, are preferable in this setting and particularly relevant in Liberek’s own study [3] of peritoneal dialysis patients in whom appropriate nutrition had a significant role. Traynor et al. [4] published results on survival and dialysis initiation utilizing the Cockcroft–Gault formula, which at least incorporates weight. The results are consistent with our findings and also contradict the concept of ‘early’ or ‘healthy’ start.

While our study uses age and diabetes as indicators of comorbidity, both van Manen et al. [5] and Stel et al. [6] have found that after adjusting for age and diabetes, further adjustments for comorbidity made little further difference in European populations. Furthermore, it is interesting that Stel et al. found that the distribution of causes of death was similar in high, medium and low eGFR groups [6].

Finally, we welcome the sentiment that the individual decision of dialysis timing involves a clinical judgement of nephrologists on the basis of a variety of clinical features, particularly fluid overload in patients with left ventricular dysfunction. This is valuable to consider not only when met with studies that counter-intuitively appear to suggest a benefit in delaying the start of dialysis, but also when met with contradictory recommendations of a healthy early start. While we hope that the randomized controlled IDEAL trial [7] may be able provide some answers next year, meanwhile our study and that of Stel et al. demonstrate that nephrology is a specialty that values the physician who adopts a patient-centred approach.

Conflict of interest statement. KS is the Chair of the Scottish Renal Registry. AL is provincial executive director of the BC Provincial Renal Agency, BCPRA.

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