When to start chronic dialysis: tunnel vision induced by numbers?

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In this issue of NDT, Hwang et al. [1] report the retrospective analysis of the relation between estimated glomerular filtration rate at the start of dialysis (start eGFR) and outcome. The conclusion is that a higher start eGFR is related to higher mortality, as was also found in previous cohort studies [2–5]. Of more interest, as in a recent analysis of the REIN study [6], a higher start eGFR was associated with higher comorbidity [1]. Thus, the Hwang paper further fuels the heated debate on the timing of start of dialysis in several ways. The most prevalent ‘en vogue’ answer to the question of when it is best to start dialysis is—early start is detrimental. This viewpoint is the complete opposite of the previous mantra claiming that an early start improves outcome. The most scientifically honest answer is rather—we simply do not know.

In this era of ‘evidence-based medicine’, this might seem a paradoxical point of view, when taking into account that an entire set of studies [2–4] reached a definitive and unanimous conclusion, in disfavour of an early start. This editorial lists some reasons why we should exercise caution in regard to the current line of thinking, taking the Hwang paper [1] as an example.

Maintaining the same logic until the bitter end?

There is a worrisome, but logical, consequence to all the retrospective studies on start eGFR published so far: they all find a linear inverse association between start eGFR and mortality, with not a single indication of a J shape. Consequently, we should either accept the data and delay starting dialysis until patients become anuric or accept that there is something wrong with the data and question the conclusions. Patients die of uraemia before they become anuric unless they are dialysed, which is in contradiction with the data as currently presented. In addition, several registries report a historical trend towards starting dialysis at higher eGFRs over the last decade, and at the same time, there is also a decline in mortality, which again conflicts with the interpretation that a higher start eGFR is deleterious [7,8].

A second observation is at least as puzzling: if physicians use eGFR as a parameter to start dialysis, why then is there such a large variability among start eGFR values in...
these retrospective cohort studies? Consequently, physicians are either demonstrating an arbitrary and unpredictable behaviour or not using eGFR as a starting criterion; both would make the study of an association between start eGFR and outcome pointless. Like everyone else, Hwang et al. use ‘start eGFR’ as a criterion to define early and late start. However, in real life, decisions to start dialysis are, to a large extent, based on clinical parameters, so that patients are started on dialysis only when they become symptomatic. If the parameter used in a retrospective study to define early and late start is not the one that was actually applied during the decision making, the accuracy of the definition of ‘early’ and ‘late’ can be questioned, and thus, also the conclusion that ‘early start is detrimental’. There is definitely a need for a survey among physicians on the criteria they really use for starting dialysis. Only by applying these criteria as a reference for the timing of start of dialysis in future studies will it be possible for meaningful conclusions to be drawn.

A carpenter using an elastic wire as yardstick …

Are all physicians wrong, and should we use eGFR as a criterion to start dialysis? According to the data, the answer would be—definitely no—according to European Best Practice Guidelines (EBPG), no as well. In contrast to what is stated in most studies, EBPG do NOT advocate using a certain threshold of eGFR, but rather encourage the use of clinical parameters (nutrition, electrolytes and volume status) [9]. Sound reasoning would tell us—again, no. Indeed, eGFR is a debatable parameter of residual renal function (RRF). None of the currently used formulas, be it Cockcroft and Gault, MDRD or other, have been validated in the low range of RRF, and wide confidence intervals have been observed for reported point estimates. In the study of Hwang et al., this means that a patient in Quintile 3 in reality can belong to Quintiles 1–5. In addition, serum creatinine not only depends upon RRF, but also upon nutritional intake, muscle mass and fluid overload, which all relate inversely to RRF. A low serum creatinine may thus not only indicate good RRF, but also bad nutritional and physical status and vice versa. In addition, as physicians mostly take clinical status—and not eGFR—as a yardstick of when to start dialysis, a high start eGFR is thus a surrogate for worse clinical condition [1,6], and the inverse relation between eGFR and outcome should not come as a surprise. The idea that one can cope with this by multivariate adjustment is noble, but probably incorrect. The Hwang paper elegantly demonstrates that many determinants remain unrecognized in these large databases: only 50% of excess mortality is explained, and even less so in patients who start at higher eGFRs.

Summarizing, if eGFR is an unreliable marker of RRF and if the decision to start dialysis or not, in clinical practice, is based on other elements than eGFR, can we then make meaningful conclusions from a retrospective cohort analysis about the impact on outcome of timing of start of dialysis as defined by eGFR?

Survival of the fittest: Darwin still alive and kicking in 2010 …

Korevaar et al. [4] correctly point to the lead-time bias in the analysis of patients starting dialysis ‘early vs late’, as the apparent survival advantage of early starters equals the delay in start of dialysis in the late starters, making overall survival comparable in the two groups. This argument, however, has a Janus appearance: all available cohort studies until now only included patients who actually did start dialysis: so, one must survive and be in good health to start dialysis at a lower start eGFR; all other patients either died or had to start early because their condition did not allow them to wait longer. Mainly, the fittest patients will be strong enough to survive until eGFR has decreased low enough (e.g. 4.3 mL/min/1.73 m² in the Hwang study), generating an undeniable ‘survival of the fittest’ lead-time bias. An equally important form of lead-time bias is created further by excluding patients who died during the first 90 days after starting dialysis [1]. Whereas this approach was chosen to exclude acute kidney injury, it also plausibly excludes those with chronic kidney disease (CKD) who die early after starting dialysis in an emergency, while being beyond the point of no return, because the start of dialysis was delayed too long; as a consequence, some of the late starters with the worst outcomes have not been enrolled in the analysis. The negative effects of dialysis, which are another explanation of the increased mortality of higher start eGFR, are also prone to strike harder in the highly comorbid patients, most of whom have will have started at a higher eGFR [1–6].

There is yet another vicious circle that should be taken into account: all studies correct for ‘comorbidity at start of dialysis’. Herein looms the chicken and egg problem of which came first: part of the comorbidity adjusted for at dialysis start might have been avoided if dialysis would have been started earlier. In addition, very crude, mostly dichotomous, markers of comorbidity are used; consequently, a young patient with fluid overload because of late dialysis start will receive the same label, ‘congestive heart failure’, as the elderly diabetic with CKD Stage 4 who develops pulmonary oedema, necessitating an emergency start of dialysis at an eGFR of 15 mL/min. It is clear that the probability to survive differs widely among both, independent of start eGFR. This example also highlights that the term ‘early’ start is a misnomer if it is defined by eGFR, rather than by patient condition.

Should we then simply discard the findings of all these cohort studies? Certainly not, as they are instructive for all those who are willing to learn a valuable lesson: eGFR is not a good marker to time start of dialysis, and most likely, the majority of physicians do not use it in the rigorous way the developers of these cohort studies assume. If we do not turn away from the hypnotizing tale of eGFR numbers in the discussion of timing of dialysis start, even randomized controlled trials in this area risk emanating in erroneous conclusions [10]. We need to be sure we look for the appropriate signs before jumping to conclusions: clinical factors—and not eGFR—should guide the start of dialysis, in the same way as is recommended by EBPG [9].
Immunoadsorption in nephrology and kidney transplantation

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Immunoadsorption finds incremental implementation in the treatment of several autoimmune disorders as well as for kidney transplant indications (see Table 1). As opposed to plasmapheresis, immunoadsorption allows not only a more specific but also a more effective clearance of circulating immunoglobulins without the side effects associated with the substitution of fresh frozen plasma or albumin. In addition, even multiple plasma volumes may be processed, and a reduction of immunoglobulins of 80% and more is feasible [1]. However, one has to consider that plasmapheresis is not only utilized for removal of immunoglobulins but also for the substitution of different plasma components such as ADAMTS-13 in the case of thrombotic thrombocytopenic purpura [2]. Therefore, plasma infusion itself may have beneficial effects independent of the removal of circulating pathogenic substances. The use of plasmapheresis for the treatment of different kidney diseases remains controversial due to a lack of randomized controlled trials demonstrating the benefit of this procedure. This applies even more to immunoadsorption. However, for some indications especially in the field of kidney transplantation, there is now growing evidence pointing to the large potential of this treatment modality. This editorial comment will focus on the available evidence on immunoadsorption in kidney diseases and kidney transplant indications.

General considerations

Immunoadsorption devices

In general, one has to differentiate single-use versus reusable immunoadsorption devices and antigen-unspecific versus antigen-specific columns. These are dextran sulphate (e.g. Selesorb) and DNA-binding columns, especially for the treatment of systemic lupus erythematosus (SLE). IMPH-350/IMTR-350 are single-use columns with phenylalanine and tryptophan as ligands which bind a broader spectrum of antibodies. The protein A (Immunosorba) immunoadsorption device consists of two parallel, regenerable columns that bind IgG subclasses 1, 2 and 4 with high affinity, and IgG 3, IgA and IgM with variable affinity. The synthetic peptide peptide-GAM, which is bound to sepharose (Globaffin), is comparable to the pro-