EUDIAL – An Official ERA-EDTA Working Group
ERA-EDTA Operative Headquarters
Via XXIV Maggio 38, 43123 Parma, Italy
Tel: +39 0521 989078 – Fax: +39 0521 959242
Mob. +39 370 3538784
Email eudial@era-edta.org
www.era-edta.org

The reasons for a clinical trial on incremental haemodialysis

During the upcoming decade about 1 million people in the US are expected to make the transition to dialysis therapy [1]. The majority of dialysis patients are currently treated with a fixed dose thrice-weekly haemodialysis (HD) (3HD/wk) regimen irrespective of whether they are starting dialysis therapy (incident) or have been receiving dialysis for some time (prevalent) and without consideration for their residual kidney function (RKF) [2]. The 3HD/wk regimen has been assumed, until recently, almost as a dogma in the dialysis community [3, 4]. Incredibly, the 3HD/wk schedule has been widely accepted worldwide without ever undergoing any randomized controlled trial (RCT) to examine whether less frequent HD treatments would be inadequate or harmful [5].

Over the past 30 years, major trials of HD adequacy, modality (nocturnal, home or in-centre) and frequency (daily HD) have been anchored to 3HD/wk regimens as the gold standard, including the HEMO Study that failed to prove survival advantages of higher HD dose [4]. Interestingly, a recent RCT suggested that more frequent (more than 3HD/wk, such as daily) HD may provide patient outcome benefits [6]. Owing to this background, it is easily understandable why a HD frequency of less than 3HD/wk is rarely prescribed in Europe (currently in only 5.2% of all patients in Europe [7], and even much less so in the US and Canada, probably less than 1% [8]). In contrast to Europe and the US, a recent study reported that 26% of the Chinese dialysis populations are treated using a 2HD/wk schedule [9], which may be the result of socioeconomic conditions, including less access to dialysis therapy and inadequate resource availability.

The optimal regimen for incident patients is not known. It is plausible that the routine practice of fixed-dose 3HD/wk in incident patients with substantial RKF may be harmful,

EUDIAL – An Official ERA-EDTA Working Group
ERA-EDTA Operative Headquarters
Via XXIV Maggio 38, 43123 Parma, Italy
Tel: +39 0521 989078 – Fax: +39 0521 959242
Mob. +39 370 3538784
Email eudial@era-edta.org
www.era-edta.org

contributing to accelerated loss of RKF [10, 11]. Incremental HD is based on the simple idea of adjusting its dose according to the metrics of RKF. In agreement with the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [12], the term "incremental HD" implies that the dose and/or frequency of treatment can be lower at dialysis inception, in the presence of a substantial RKF, but should be progressively and timely increased to compensate for any subsequent reduction in RKF. Indeed, most patients initiating dialysis have some degree of RKF, often a residual renal urea clearance (Kru) > 3 mL/min and a urine output (UO) > 600 mL/day.

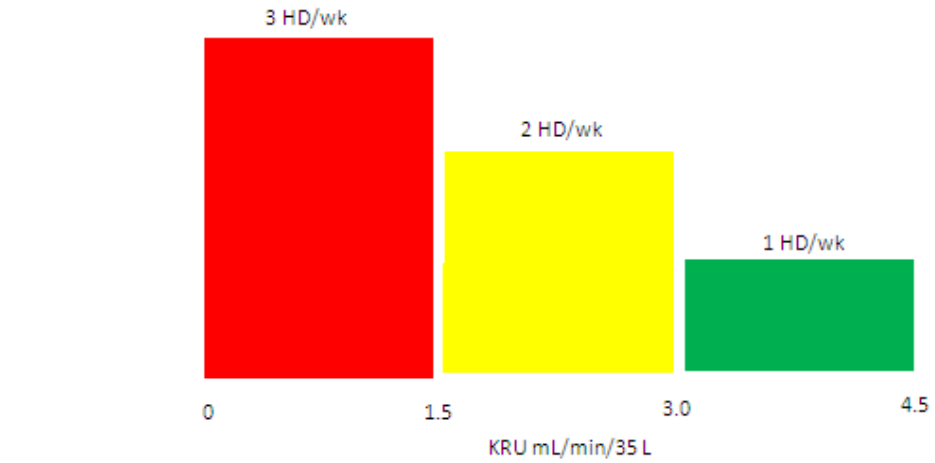
Given the importance of RKF preservation in conservative therapy, it seems a contradiction to ignore the contribution of RKF in incident HD patients. What is important to note is that the challenge of preserving RKF or UO in HD patients has never been taken seriously. Clinical practice guidelines generally advise against less than a 3HD/wk schedule as inferior. These guidelines do not recommend incremental transition from less to more frequent HD over time, while, ironically, according to most peritoneal dialysis (PD) guidelines, PD dose is to be adjusted upwards parallel to the decline in RKF, the preservation of which is a high priority target in PD [5, 13].

The recently heightened interest in incremental HD [14] has been hindered by the current urea kinetic model (UKM)-based prescription that, by overestimating the dialysis needs, in the presence of substantial RKF, would require such high values for both the RKF and dialysis dose (Kt/V) [15] that it would be difficult to prescribe less frequent treatments. This could cast doubts on the usefulness of the UKM as a guide to the prescription of incremental HD and push the search of alternative indices of dialysis adequacy. While agreeing that evaluating the dialysis adequacy should not rely on a single index, we would like to remark

the need to keep UKM as the gold standard, not only because it is the only established tool for assessing and prescribing dialysis [16 - 18], but mostly because we have to realize that it is not responsible for the overestimation of dialysis needs in the presence of RKF. The problem is not intrinsic to the UKM, but rather is generated by a misconception or rather misunderstanding: actually, the equivalence between Kru and dialyser urea clearance (Kd), correctly assumed by the UKM, only means that one millilitre per minute of Kd clears the urea from the blood just as one mL/min of Kru does [16, 19]. By no means should such kinetic equivalence imply that 1 mL/min of Kd is clinically equivalent to 1 mL/min of urea clearance provided by the native kidneys.

Therefore, an RCT comparing incremental HD with the standard 3HD/wk schedule and focused on hard outcomes, such as survival and RKF loss, is needed. The recent paper by Casino and Basile suggested that the variable target model (VTM) of UKM, which gives more clinical weight to the RKF, allows less frequent HD treatments at lower RKF as opposed to the fixed target model (FTM), based on the wrong concept of the clinical equivalence between Kru and Kd [15] (Figure).

EUDIAL – An Official ERA-EDTA Working Group
ERA-EDTA Operative Headquarters
Via XXIV Maggio 38, 43123 Parma, Italy
Tel: +39 0521 989078 – Fax: +39 0521 959242
Mob. +39 370 3538784
Email eudial@era-edta.org
www.era-edta.org



At the present time no RCT testing incremental HD has yet been published [20]. To this end, the EUDIAL Working Group of ERA-EDTA is starting the "RandomizEd clinicAL triaL on the effIcacy and saFety of incremental haEmodialysis" (REAL LIFE), using the VTM by Casino and Basile in incident HD patients [21]. Keystones of this study are the following concepts:

1. incremental dialysis represents a "continuum and integration of pre-dialysis care" [22], with a smooth "transition" from a conservative management of chronic kidney disease to the full 3HD/wk regimen [11, 20, 23, 24]. Interestingly, such a smooth transition has been advocated in opposition to the "abrupt" start with a full thrice-weekly schedule, that could be responsible of the exceptionally high annualized mortality rate of about 40% for the first few months after HD inception [23]. Accordingly, the patient on transition to the full HD therapy should be seen as a patient essentially on conservative therapy, with dialysis being added on top of all

dietary and/or pharmacologic measures well established for the conservative treatment. On this basis, it is of paramount importance to focus on RKF preservation, both by avoiding any substances or maneuvers that can damage it, and implementing any intervention that could preserve it [23, 25];

2. to prescribe and deliver the adequate dose of dialysis as a function of Kru is mandatory. Actually, the VTM has been devised to this aim. An important corollary is that any clinical problem, such as high levels of serum potassium and/or phosphate, as well as metabolic acidosis, arterial hypertension, volume overload, etc., should be primarily treated with dietary and/or pharmacological interventions, if possible, without increasing the dose and/or frequency of dialysis.

In conclusion, the basic hypothesis of the study is that just by delivering the needed dialysis dose, as predicted by VTM, one could preserve RKF, which in turn should reduce the occurrence of cardiovascular diseases and improve the survival of the patients.

EUDIAL – An Official ERA-EDTA Working Group
ERA-EDTA Operative Headquarters
Via XXIV Maggio 38, 43123 Parma, Italy
Tel: +39 0521 989078 – Fax: +39 0521 959242
Mob. +39 370 3538784
Email eudial@era-edta.org
www.era-edta.org

REFERENCES

1. Saran R, Li Y, Robinson B et al (2016) US Renal Data System 2015 Annual Data Report: epidemiology of kidney disease in the US. Am J Kidney Dis 67 (Suppl 1): S1 – S305
2. Toth-Manikowski SM, Shafi T (2016) Hemodialysis prescription for incident patients: twice seems nice, but is it incremental? Am J Kidney Dis 68: 180 - 183
3. Lowrie EG, Laird NM, Parker TF et al (1981) Effect of the hemodialysis prescription of patient morbidity: report from the National Cooperative Dialysis Study. N Engl J Med 305: 1176 - 1181
4. Eknoyan G, Beck GJ, Cheung AK et al (2002) Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 347: 2010 - 2019
5. NKF-K/DOQI clinical practice guidelines for hemodialysis adequacy (2001) update 2000. Am J Kidney Dis 37 (Suppl 1): S7 – S64
6. Chertow GM, Levin NW, Beck GJ et al (2010) In-center hemodialysis six times per week versus three times per week. N Engl J Med 363: 2287 - 2300
7. Couchoud C, Kooman J, Finne P et al (2009) From registry data collection to international comparisons: examples of haemodialysis duration and frequency. Nephrol Dial Transplant 24: 217 - 224
8. Rhee CM, Unruh M, Chen J et al (2013) Infrequent dialysis: a new paradigm for hemodialysis initiation. Semin Dial 26: 720 - 727
9. Zhang M, Wang M, Li H et al (2014) Association of initial twice-weekly hemodialysis treatment with preservation of residual kidney function in ESRD patients. Am J Nephrol 40: 140 - 150
10. Daugirdas JT, Green T, Rocco MV et al (2013) Effect of frequent hemodialysis on residual kidney function. Kidney Int 83: 949 - 958
11. Golper TA, Mehrotra R (2015) The intact nephron hypothesis in reverse: an argument to support incremental dialysis. Nephrol Dial Transplant 30: 1602 - 1604
12. NKF-DOQI clinical practice guidelines for peritoneal dialysis adequacy (1997). Am J Kidney Dis 30 (Suppl 2): S67 – S136
13. Sandrini M, Vizzardi V, Valerio F et al (2016) Incremental peritoneal dialysis: a 10 year single-centre experience. J Nephrol 29: 871 – 879
14. Basile C, Casino FG, Kalantar-Zadeh K (2017) Is incremental hemodialysis ready to return on the scene? From empiricism to kinetic modelling. J Nephrol 30: 521 - 529
15. Casino FG, Basile C (2017) The variable target model: a paradigm shift in the incremental haemodialysis prescription. Nephrol Dial Transplant 32: 182 - 190
16. National Kidney Foundation. KDOQI clinical practice guidelines for hemodialysis adequacy: 2015 update (2015) Am J Kidney Dis 66: 884 - 930
17. Sargent JA, Gotch FA (1980) Mathematic modeling of dialysis therapy. Kidney Int 10 (Suppl): S2 – S10
18. European Best Practice Guidelines (2002) II.3 Haemodialysis dose and residual renal function (Kr). Nephrol Dial Transplant 17 (Suppl 7): S24
19. Casino FG, Lopez T (1996) The equivalent renal urea clearance: a new parameter to assess dialysis dose. Nephrol Dial Transplant 11: 1574 – 1581

EUDIAL – An Official ERA-EDTA Working Group
ERA-EDTA Operative Headquarters
Via XXIV Maggio 38, 43123 Parma, Italy
Tel: +39 0521 989078 – Fax: +39 0521 959242
Mob. +39 370 3538784
Email eudial@era-edta.org
www.era-edta.org

20. Basile C, Casino FG on behalf of the EUDIAL Working Group of ERA- EDTA (2019) Incremental haemodialysis and residual kidney function: more and more observations but no trials. Nephrol Dial Transplant 34: 1806 – 1811
21. Casino FG, Basile C, Kirmizis D et al on behalf of the EUDIAL Working Group of ERA-EDTA (2020) The reasons for a clinical trial on incremental haemodialysis. Nephrol Dial Transplant DOI: gfaa220
22. Agarwal A, Saran R, Nolph KD (1999) Continuum and integration of pre-dialysis care and dialysis modalities. Perit Dial Int 19 (Suppl 2): S276 – S280
23. Kalantar-Zadeh K, Unruh M, Zager PG et al (2014) Twice-weekly and incremental hemodialysis treatment for initiation of kidney replacement therapy. Am J Kidney Dis 64: 181 – 186
24. Golper TA. Incremental hemodialysis: how I do it (2016) Semin Dial 29: 476 – 480
25. Hur I, Lee JK, Kalantar-Zadeh K et al (2019) Individualized hemodialysis treatment: a perspective on residual kidney function and precision medicine in nephrology. Cardiorenal Med 9: 69 – 82