Nephrol Dial Transplant (2020) 1–5
doi: 10.1093/ndt/gfaa220

ndt
Nephrology Dialysis Transplantation

The reasons for a clinical trial on incremental haemodialysis

Francesco G. Casino[1,2,*], Carlo Basile [1,3,*], Dimitrios Kirmizis[4], Mehmet Kanbay[5], Frank van der Sande[6], Daniel Schneditz [7], Sandip Mitra[8], Andrew Davenport[9] and Loreto Gesuldo[10]on Behalf of the Eudial Working Group of ERA-EDTA

[1]Division of Nephrology, Miulli General Hospital, Acquaviva delle Fonti, Italy, [2]Dalysis Centers SM2, Policoro, Italy, [3]Associazione Nefrologica Gabriella Sebastio, Martina Franca, Italy, [4]Department of Nephrology, Colchester General Hospital, Essex, UK, [5]Division of Nephrology, Department of Medicine, Koc University School of Medicine, Istanbul, Turkey, [6]Division of Nephrology, Department of Internal Medicine, University Hospital Maastricht, Maastricht, The Netherlands, [7]Otto Loewi Research Center, Medical University of Graz, Graz, Austria, [8]Manchester Academy of Health Sciences Centre, Manchester University Hospitals Foundation Trust and University of Manchester, Manchester, UK, [9]Division of Medicine, UCL Centre for Nephrology, Royal Free Hospital, University College London, London, UK and [10]Department of Nephrology, Dialysis and Transplantation, Azienda Ospedaliero-Universitaria Consorziale Policlinico, Bari, Italy

*These authors contributed equally to this work.
Correspondence to: Carlo Basile; E-mail: basile.miulli@libero.it

ADDITIONAL CONTENT

An author video to accompany this article is available at https://academic.oup.com/ndt/pages/author_videos.

INTRODUCTION

There is growing interest in an incremental approach to haemodialysis (HD) for incident end-stage kidney disease (ESKD) patients, starting with one or two sessions per week [1–5]. Such an approach not only seems to preserve residual kidney function (RKF) and improve health-related quality of life with similar or higher survival rates than those observed in patients receiving the standard thrice-weekly HD regimen, but also allows saving economic resources [6–10].

The term 'incremental HD' means that, in the presence of substantial RKF, both dialysis dose and frequency can be low at dialysis inception but should be progressively increased to compensate for any subsequent reduction in RKF [11–13]. The current principle for calculating the amount of dialysis required to compensate for RKF reduction is based on the constancy of the value of total (renal + dialytic) weekly clearance as expressed by the equivalent continuous clearance (ECC) of urea [11–13]. Two versions of ECC exist, the standard *Kt/V* [14] and the equivalent renal urea clearance (EKR) [15]. For the sake of simplification, only EKR will be used. The assumption of a constancy of the total EKR (renal + dialytic), the so-called fixed target model of EKR, implies the attribution of a clinical equivalence to dialytic EKR (EKRd) and renal urea clearance (Kru), which is a mistake [16]. A variable target model (VTM) has recently been introduced to correct this mistake [16]. In short, the total EKR should vary from a minimum value, provided only by the native kidneys, to a maximum value, provided only by the dialysis treatment [16] (Figure 1). The minimum value corresponds to a hypothesized threshold Kru (Kru_{Thr}) for starting HD even in the absence of signs or symptoms of uraemia; at this level, by definition, there is no need for dialysis, so the target ECC is just Kru_{Thr} [16] (Figure 1). The maximum value corresponds to the adequate equilibrated *Kt/V* (*eKt/V*) in anuric patients on a 3 HD/week regimen [16] (Figure 1). The mistake of attributing a clinical equivalence to dialytic urea clearance and Kru is not trivial, because it leads to overestimates of dialysis needs in the presence of substantial RKF, requiring such high values for both RKF and dialysis dose (*Kt/V*) that it would be difficult to prescribe less frequent treatments [1, 16]. Moreover, delivering more dialysis than really needed could accelerate the decline of RKF [17], likely due to many factors, such as more blood–membrane and blood–dialysate interactions, intradialytic arterial hypotension with cardiac and renal ischaemia, as well as disruption of the compensating mechanisms set in motion by intact nephrons in response to nephron loss [17–19].

The above concept [16, 20] can be applied to both versions of ECC. In fact, the concept of an increased clinical weight of Kru introduced by the VTM [16, 20] is in line with the new version of standard *Kt/V,* which uses Kru at 100%, instead of a 'compressed' Kru used with the original standard *Kt/V* [13, 21].

Table 1 shows a simulation study using Solute-Solver software [22] based on the double-pool urea kinetic model recommended by the 2015 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [13]. It allows drawing two trajectories for the variable target as Kru approaches zero [20]: a low-level one with EKR increasing from 4 mL/min/35 L,

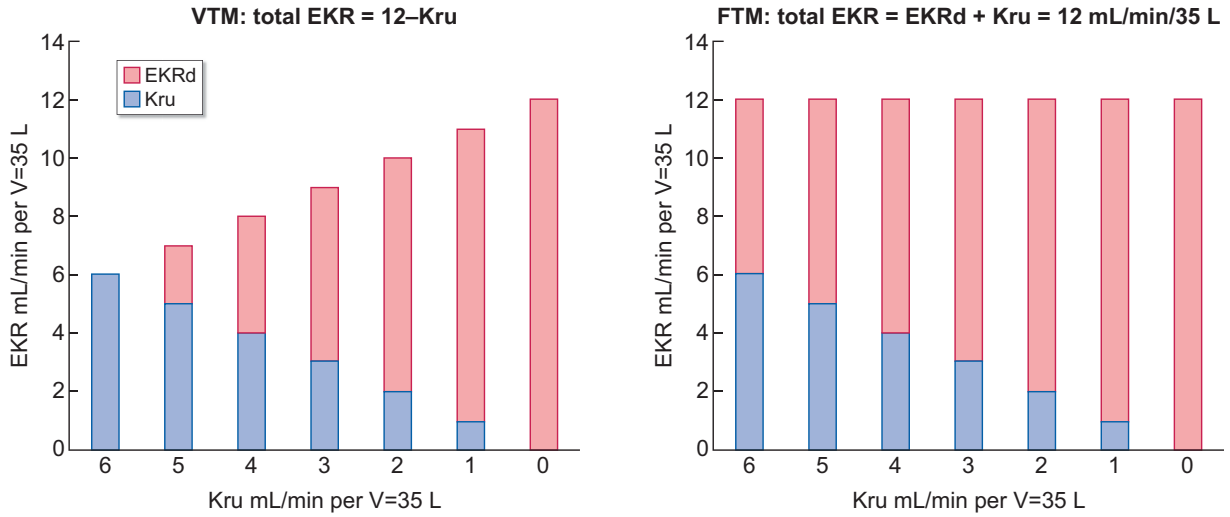

FIGURE 1: The VTM for the prescription of incremental dialysis. Total EKR is the total equivalent renal urea clearance [15]: it expresses the total clearance (dialytic + renal), i.e. the sum of the contribution of the dialyser urea clearance (Kd) to EKR (EKRd) and of the residual renal urea clearance (Kru). According to the fixed target model, the total target EKR should remain constant: 12 mL/min/35 L = $eKt/V \times 3$ sessions/week. This means that each mL/min of Kru should be replaced by increasing the dialysis component (EKRd) by the same amount. In contrast, according to the VTM, the total target EKR varies from a minimum value at the start of HD treatment (in this case Kru = 6 mL/min/35 L) to a maximum value when Kru = 0. This reduces the amount of dialysis dose required (red bars).

Table 1. A simulation study using Solute-Solver software [22] based on the double-pool urea kinetic model recommended by the 2015 KDOQI guidelines [13]

Kru (mL/min/35 L)	EKR = 10–1.5 Kru (mL/min/35 L)	*eKt/V* 1 HD/week	*eKt/V* 2 HD/week	*eKt/V* 3 HD/week	EKR = 12 Kru (mL/min/35 L)	*eKt/V* 1 HD/week	*eKt/V* 2 HD/week	*eKt/V*3 HD/week
0.0	**10.00**	Unrealistic	1.75	1.05	**12.0**	Unrealistic	Unrealistic	1.29
0.5	**9.25**	Unrealistic	1.46	0.90	**11.5**	Unrealistic	Unrealistic	1.17
1.0	**8.50**	Unrealistic	**1.21**	0.76	**11.0**	Unrealistic	Unrealistic	1.05
1.5	**7.75**	Unrealistic	0.97	0.61	**10.5**	Unrealistic	1.54	0.93
2.0	**7.00**	1.95	0.79	0.50	**10.0**	Unrealistic	**1.33**	0.82
2.5	**6.25**	**1.28**	0.56	0.38	**9.5**	Unrealistic	1.13	0.71
3.0	**5.50**	0.79	0.37	0.26	**9.0**	Unrealistic	0.94	0.61
3.5	**4.75**	0.37	0.19	0.14	**8.5**	2.1	0.77	0.51
4.0	**4.00**	0.00	0.00	0.00	**8.0**	**1.47**	0.61	0.41
4.5	**4.00**	0.00	0.00	0.00	**7.5**	1.0	0.45	0.31
5.0	**4.00**	0.00	0.00	0.00	**7.0**	0.63	0.30	0.21
5.5	**4.00**	0.00	0.00	0.00	**6.5**	0.30	0.15	–

The *eKt/V* values required to reach two different levels of target EKR (in bold) as a function of Kru and treatment schedule. The simulation was made for a patient with a urea distribution volume of 35 L and ultrafiltration volume per session of 1, 2 and 3 L, for 1, 2 and 3 HD/week regimens, respectively. The values in columns 3–5 refer to the lowest target in column 2; the values in columns 7–9 refer to the highest target in column 6.

corresponding to a glomerular filtration rate (GFR) of 6 mL/min/1.73 m^2, in agreement with the European Renal Best Practice position statement [23], to 10 mL/min/35 L, corresponding to an *eKt/V* of 1.05 for anuric patients on a 3 HD/week schedule, which is the adequate dialysis dose established by the Hemodialysis (HEMO) Study [24]; and a high-level one, with EKR increasing from 6 mL/min/35 L, corresponding to a GFR of 9 mL/min/1.73 m^2, to 12 mL/min/35 L, corresponding to an *eKt/V* of 1.29 on a 3 HD/week schedule (Table 1) [16].

The availability of two prescription lines, instead of a single one, allows defining a 'prescription zone' between the two lines. This can avoid both delivering unnecessarily high doses of dialysis, which could accelerate Kru decline, and maintaining a stable prescription in front of reductions in Kru. In particular, Table 1 shows that an *eKt/V* of 0.79 is adequate for a 1 HD/week schedule in the presence of Kru ≥3.0 mL/min/35 L, so that an *eKt/V* of 1.05 (+31%) should be largely adequate. Analogously, an *eKt/V* of 0.97 suffices on a 2 HD/week schedule, and even more, an *eKt/V* of 1.05 will be adequate because it corresponds to a single-pool *Kt/V* (sp*Kt/V*) of 1.2 [24]. On this basis, one could safely use a constant *eKt/V* of 1.05 on a 1 HD/week schedule until Kru is ≥3.0 mL/min/35 L and on a 2 HD/week schedule for Kru ≥1.5–<3.0 mL/min/35 L [20, 25]. Moreover, relying on a prescription zone with a constant *Kt/V* largely above the minimum value required reduces the need for a frequent Kru measurement.

The above construct is apparently sound but, obviously, it should be confirmed by a randomized clinical trial (RCT) before its clinical implementation.

THE REAL LIFE PROJECT

To this end, the European Dialysis (EUDIAL) Working Group of the ERA-EDTA is ready to start the 'RandomizEd clinicAL triaL on the effIcacy and saFety of incremental haEmodialysis' (REAL LIFE), using VTM on incident HD patients [25]. Keystones of this study are the following concepts: (i) Incremental dialysis represents a continuum and integration of pre-dialysis care [11], with a smooth transition from conservative management of chronic kidney disease (CKD) to the full 3 HD/week regimen [2, 19, 25, 26]. Interestingly, such a smooth transition has been advocated in opposition to the 'abrupt' start with a full thrice-weekly schedule, which could be responsible for the exceptionally high annualized mortality rate of ~40% for the first few months after HD inception [2]. 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 conservative treatment. On this basis, it is of paramount importance to focus on RKF preservation, both by avoiding any substances or manoeuvres that can damage it and implementing any intervention that could preserve it [2, 18]. (ii) To prescribe and deliver the adequate dose of dialysis as a function of Kru is mandatory. Actually, the VTM has been devised for 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 patients.

THE REAL LIFE PROTOCOL

REAL LIFE is a pragmatic, prospective, multicentre, open-label, investigator-led RCT comparing the intervention arm (incremental HD) with the control arm (standard 3 HD/week). The full study protocol is available as Supplementary Data. Here the key points of the RCT are summarized.

Enrolment and allocation (see Supplementary Data)

Both planned and unplanned incident adult ESKD patients, with GFR [preferably assessed by the mean of urea and creatinine clearances or by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation] between 5 and 10 mL/min/1.73 m^2, will be randomized 1:1 by means of a computer-generated code after written informed consent has been obtained before the third HD session (to avoid possible irreversible RKF damage from prior intensive dialysis treatment). The patients randomized to the control arm should receive the conventional treatment as usual from the local centre. The patients randomized to the intervention arm should be treated the same as the patients in the control arm, the only difference being the frequency of treatment (Figure 2).

Eligibility criteria

Inclusion and exclusion criteria are detailed in Figure 2 and in Supplementary Data.

Prescription of the dialysis dose

For the sake of simplification, all patients will receive the same dialysis dose (i.e. an eKt/V of 1.05, corresponding to an spKt/V of 1.2 per session), with the frequency of sessions changing as a function of the actual Kru, only for the patients in the intervention arm (Figure 2). The frequency should be once a week until the Kru falls to $<$3.0 mL/min/35 L, followed by a twice-weekly schedule until the Kru falls to $<$1.5 mL/min/35 L and then by a thrice-weekly HD schedule. If required, the patient could start directly on a twice-weekly HD schedule and keep on it until the Kru falls to $<$1.5 mL/min/35 L (Figure 2). The Kt/V should be assessed on a monthly basis with the Daugirdas formula [27]. The assessment of key kinetic parameters as well as the selection of operative parameters will be done using the Spreadsheet for the Prescription of incrEmental haEmoDialYsis (SPEEDY) [28], a prescription tool that uses essentially the same equations used by Solute-Solver software [22]. SPEEDY is freely available at www.era-edta.org/en/eudial. Kru should be normalized, as already reported, to 35 L [16, 28], and measured on a monthly basis, but not less than quarterly [13].

Progression criteria

Progression criteria are detailed in Figure 2 and in Supplementary Data.

Sample size

The sample size was derived from a prospective observational study by Teruel-Briones *et al.* [29] enrolling patients with an RKF in the range of the selection criteria of this study: 15 of 61 patients starting with the 2 HD/week regimen (25%) and 25 of 49 patients starting with the 3 HD/week regimen (51%) had lost RKF after a 2-year follow-up(see Supplementary Data). Thus a rate of 0.169 to reach the event, i.e. RKF loss, was estimated for the intervention arm and a relative hazard of 2.5 was estimated for the control arm.

Outcomes

Primary outcome. Survival of kidney function, with the event 'loss of RKF' defined as urine output $\leq$200 mL/day [30], is confirmed by a further collection after 2 weeks to exclude temporary illness.

Secondary outcomes. Details are given as Supplementary Data.

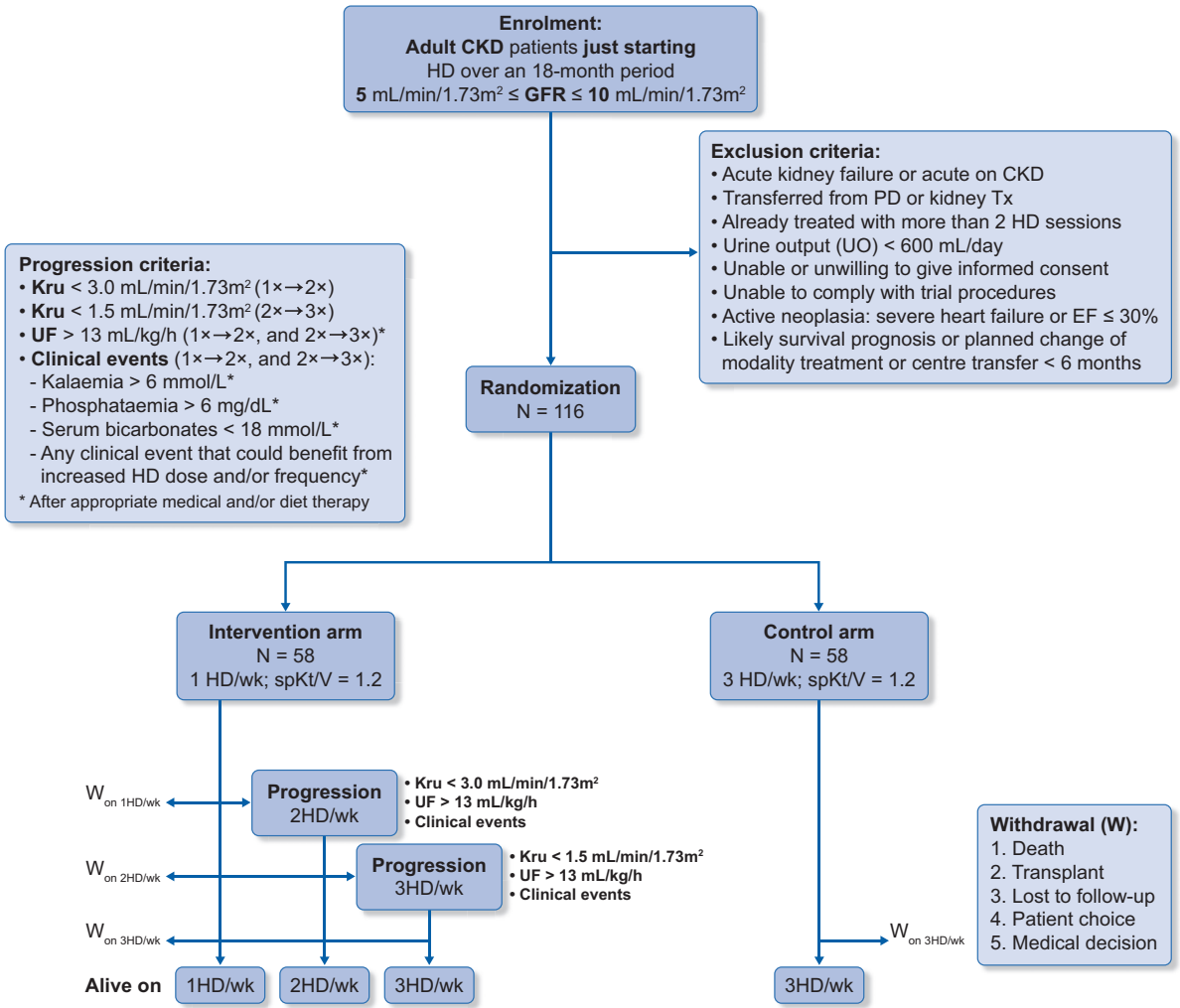

FIGURE 2: Flow chart of REAL LIFE. The patients randomized to the intervention and control arms will be administered the same treatment and dialysis dose (sp$Kt/V = 1.2$, i.e. $eKt/V = 1.05$) per session. The only difference is that the former will have one session and the latter three sessions per week. The progression from one to two sessions and then from two to three sessions can be driven either by a reduction in Kru, and/or the need of a high ultrafiltration volume and/or any clinical event (e.g. symptoms and/or signs of uraemia) that could benefit from an increased HD dose and/or frequency (see Supplementary Data).

Data collection and statistical analysis

Data at baseline and at the subsequent time intervals will be collected on web-based electronic case report forms at the specified time intervals (see Supplementary Data). Specifically, Kru must be computed from a timed urine collection, for instance, over the 24 h preceding the monthly HD session associated with the kinetic studies.

Monitoring of adverse events

Details are given as Supplementary Data.

Participant timeline and recruitment

The recruitment will start in September 2020. Participants will be recruited over an 18-month period at HD centres throughout Europe. The recruitment period will start from the enrolment of the first patient, with a follow-up of 24 months (see Supplementary Data).

Safety controls

Details are given as Supplementary Data.

A website functional to the operational activities of the RCT is being built-up at www.incrementaldialysis.eu (under construction).

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Kalantar-Zadeh K, Casino FG. Let us give twice-weekly hemodialysis a chance: revisiting the taboo. *Nephrol Dial Transplant* 2014; 29: 1618–1620
2. Kalantar-Zadeh K, Unruh M, Zager PG *et al.* Twice-weekly and incremental hemodialysis treatment for initiation of kidney replacement therapy. *Am J Kidney Dis* 2014; 64: 181–186
3. Basile C, Casino FG, Kalantar-Zadeh K. Is incremental hemodialysis ready to return on the scene? From empiricism to kinetic modelling. *J Nephrol* 2017; 30: 521–529
4. Ghahremani-Ghajar M, Rojas-Bautista V, Lau W-L *et al.* Incremental hemodialysis: the University of California Irvine experience. *Semin Dial* 2017; 30: 262–269
5. Murea M, Moossavi S, Garneata L *et al.* Narrative review of incremental hemodialysis. *Kidney Int Rep* 2020; 5: 135–148
6. Zhang M, Wang M, Li H *et al.* Association of initial twice-weekly hemodialysis treatment with preservation of residual kidney function in ESRD patients. *Am J Nephrol* 2014; 40: 140–150
7. Mathew AT, Fishbane S, Obi Y *et al.* Preservation of residual kidney function in hemodialysis patients: reviving an old concept. *Kidney Int* 2016; 90: 262–271
8. Fernandez-Lucas M, Teruel-Briones JL, Gomis-Couto A *et al.* Maintaining residual renal function in patients on haemodialysis: 5-year experience using a progressively increasing dialysis regimen. *Nefrologia* 2012; 32: 767–776
9. Mathew A, Obi Y, Rhee CM *et al.* Treatment frequency and mortality among incident hemodialysis patients in the United States comparing incremental with standard and more frequent dialysis. *Kidney Int* 2016; 90: 1071–1079
10. Obi Y, Streja E, Rhee CM *et al.* Incremental hemodialysis, residual kidney function, and mortality risk in incident dialysis patients: a cohort study. *Am J Kidney Dis* 2016; 68: 256–265
11. Agarwal A, Saran R, Nolph KD. Continuum and integration of pre-dialysis care and dialysis modalities. *Perit Dial Int* 1999; 19(Suppl 2): S276–S280
12. Mehrotra R, Nolph KD, Gotch F. Early initiation of chronic dialysis: role of incremental dialysis. *Perit Dial Int* 1997; 17: 426–430
13. National Kidney Foundation. KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update. *Am J Kidney Dis* 2015; 66: 884–930
14. Gotch FA. The current place of urea kinetic modelling with respect to different dialysis modalities. *Nephrol Dial Transplant* 1998; 13: 10–14
15. Casino FG, Lopez T. The equivalent renal urea clearance: a new parameter to assess dialysis dose. *Nephrol Dial Transplant* 1996; 11: 1574–1581
16. Casino FG, Basile C. The variable target model: a paradigm shift in the incremental haemodialysis prescription. *Nephrol Dial Transplant* 2017; 32: 182–190
17. Daugirdas JT, Green T, Rocco MV *et al.* Frequent nocturnal hemodialysis accelerates the decline of residual kidney function. *Kidney Int* 2013; 83: 949–958
18. Hur I, Lee JK, Kalantar-Zadeh K *et al.* Individualized hemodialysis treatment: a perspective on residual kidney function and precision medicine in nephrology. *Cardiorenal Med* 2019; 9: 69–82
19. Golper TA, Mehrotra R. The intact nephron hypothesis in reverse: an argument to support incremental dialysis. *Nephrol Dial Transplant* 2015; 30: 1602–1604
20. Casino FG, Basile C. How to set the stage for a full-fledged clinical trial testing 'incremental haemodialysis'. *Nephrol Dial Transplant* 2018; 33: 1103–1109
21. Daugirdas JT, Depner TA, Greene T *et al.* Standard Kt/V_{urea}: a method of calculation that includes effects of fluid removal and residual kidney clearance. *Kidney Int* 2010; 77: 637–644
22. Daugirdas JT, Depner TA, Greene T *et al.* Solute-Solver: a web-based tool for modeling urea kinetics for a broad range of hemodialysis schedules in multiple patients. *Am J Kidney Dis* 2009; 54: 798–809
23. Tattersall J, Dekker F, Heimburger O *et al.* When to start dialysis: updated guidance following publication of the Initiating Dialysis Early and Late (IDEAL) study. *Nephrol Dial Transplant* 2011; 26: 2082–2086.
24. Eknoyan G, Beck GJ, Cheung AK *et al.* Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 2002; 347: 2010–2019
25. Basile C, Casino FG, Basile C *et al.* Incremental haemodialysis and residual kidney function: more and more observations but no trials. *Nephrol Dial Transplant* 2019; 34: 1806–1811
26. Golper TA. Incremental hemodialysis: how I do it. *Semin Dial* 2016; 29: 476–480
27. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. *J Am Soc Nephrol* 1993; 4: 1205–1213
28. Casino FG, Basile C. A user-friendly tool for incremental haemodialysis prescription. *Nephrol Dial Transplant* 2018; 33: 1046–1053
29. Teruel-Briones JL, Fernández-Lucas M, Rivera-Gorrin M *et al.* Progression of residual renal function with an increase in dialysis: haemodialysis versus peritoneal dialysis. *Nefrologia* 2013; 33: 640–649
30. Moist LM, Port FK, Orzol SM *et al.* Predictors of loss of residual renal function among new dialysis patients. *J Am Soc Nephrol* 2000; 11: 556–564

Received: 25.4.2020; Editorial decision: 25.6.2020