Journal of Nephrology (2022) 35:1315–1327
https://doi.org/10.1007/s40620-022-01246-8

REVIEW

Does delivering more dialysis improve clinical outcomes? What randomized controlled trials have shown

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Received: 3 November 2021 / Accepted: 1 January 2022 / Published online: 18 January 2022

Abstract

Some randomized controlled trials (RCTs) have sought to determine whether different dialysis techniques, dialysis doses and frequencies of treatment are able to improve clinical outcomes in end-stage kidney disease (ESKD). Virtually all of these RCTs were enacted on the premise that 'more' haemodialysis might improve clinical outcomes compared to 'conventional' haemodialysis. Aim of the present narrative review was to analyse these landmark RCTs by posing the following question: were their intervention strategies (i.e., earlier dialysis start, higher haemodialysis dose, intensive haemodialysis, increase in convective transport, starting haemodialysis with three sessions per week) able to improve clinical outcomes? The answer is no. There are at least two main reasons why many RCTs have failed to demonstrate the expected benefits thus far: (1) in general, RCTs included relatively small cohorts and short follow-ups, thus producing low event rates and limited statistical power; (2) the designs of these studies did not take into account that ESKD does not result from a single disease entity: it is a collection of different diseases and subtypes of kidney dysfunction. Patients with advanced kidney failure requiring dialysis treatment differ on a multitude of levels including residual kidney function, biochemical parameters (e.g., acid base balance, serum electrolytes, mineral and bone disorder), and volume overload. In conclusion, the different intervention strategies of the RCTs herein reviewed were not able to improve clinical outcomes of ESKD patients. Higher quality studies are needed to guide patients and clinicians in the decision-making process. Future RCTs should account for the heterogeneity of patients when considering inclusion/exclusion criteria and study design, and should a priori consider subgroup analyses to highlight specific subgroups that can benefit most from a particular intervention.

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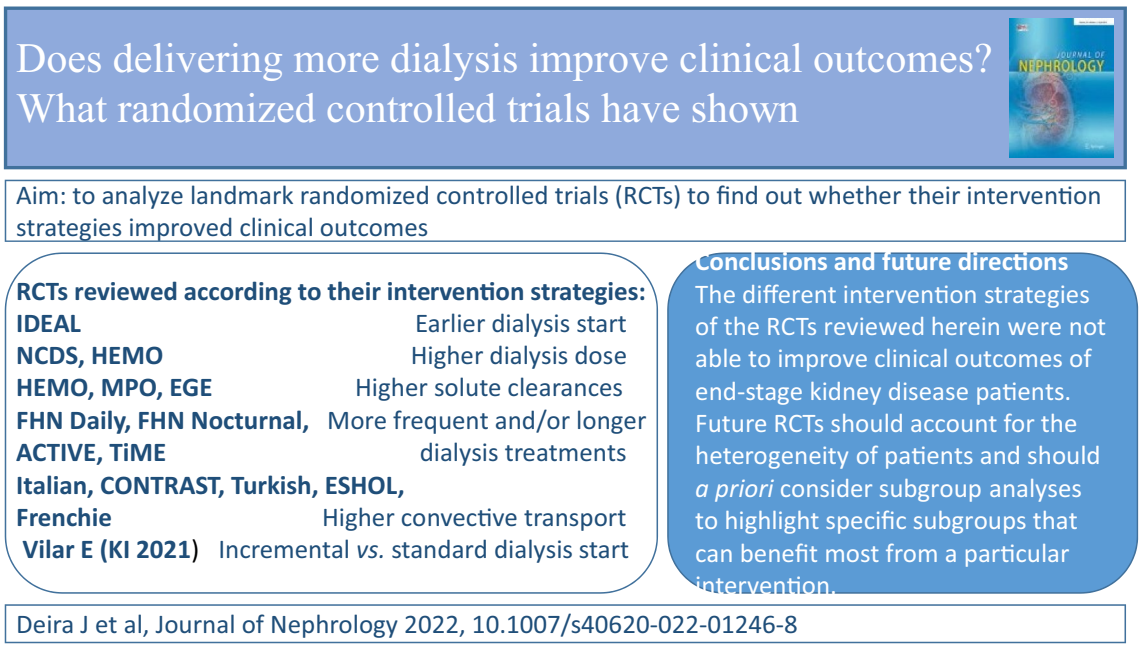
Graphical abstract



Keywords Haemodialysis · Randomized controlled trials · Mortality · Survival · End-stage kidney disease

Introduction

Advanced kidney failure requiring dialysis, commonly labelled end-stage kidney disease (ESKD), is a heterogeneous syndrome—a key reason that may explain why treating advanced kidney dysfunction is challenging and why many randomized controlled trials (RCTs) involving patients on dialysis have, to date, failed. Haemodialysis saves and prolongs the lives of patients with ESKD, and since its inception, numerous technological and pharmacological advances have increased their life expectancy from a few months to several years. Despite this progress, clinical outcomes in ESKD remain poor, with average annual mortality rates ranging between 10 and 20% [1]. The delay in improving outcomes in ESKD has generated the impetus to study different dialysis prescriptions and blood purification systems in hopes of improving patient survival and quality of life [1].

Several hypotheses have been tested in RCTs: (1) timing of dialysis initiation (early *vs.* late) [2]; (2) dialysis dose, i.e., low *vs.* high equilibrated Kt/V (eKt/V) [3, 4]; (3) removal of "middle-molecules": low *vs.* high-flux dialysis [4–6] and increased convective transport [7–13]); (4) dialysis frequency (standard *vs.* more frequent dialysis) [14, 15]; (5) quality of dialysate water (pure *vs.* ultrapure dialysate water) [6]. Aim of the present narrative review was to analyse these landmark RCTs by examining the effects of different dialysis interventions on clinical outcomes of patients affected by ESKD (Fig. 1). A review of RCTs involving patients with acute kidney injury was beyond the scope of this manuscript and readers are referred to specific publications [16, 17].

Does starting dialysis earlier improve clinical outcomes?

The decision to initiate kidney replacement therapy in patients with ESKD is based on clinical signs and symptoms along with laboratory data [18]. Several observational studies suggested that dialysis initiation at glomerular filtration rate (GFR) levels > 10 mL/min/1.73 m^2 allows for longer survival, better quality of life, and fewer hospitalizations [19, 20]. The mean GFR in patients starting dialysis in the US rose from 7.7 mL/min/1.73 m^2 in 1996 to 11.2 mL/min/1.73 m^2 in 2009, thus anticipating the onset of dialysis by 147 days [21].

Based on the premise that dialysis initiation at higher levels of GFR could have clinical advantages, the Initiating Dialysis Early and Late Study (IDEAL) was designed to determine whether an early start of haemodialysis reduces the rate of all-cause death compared to a late start [2]. After randomization, the early start group (404 patients) had a baseline mean GFR of 9.0 mL/min/1.73 m^2; the late start

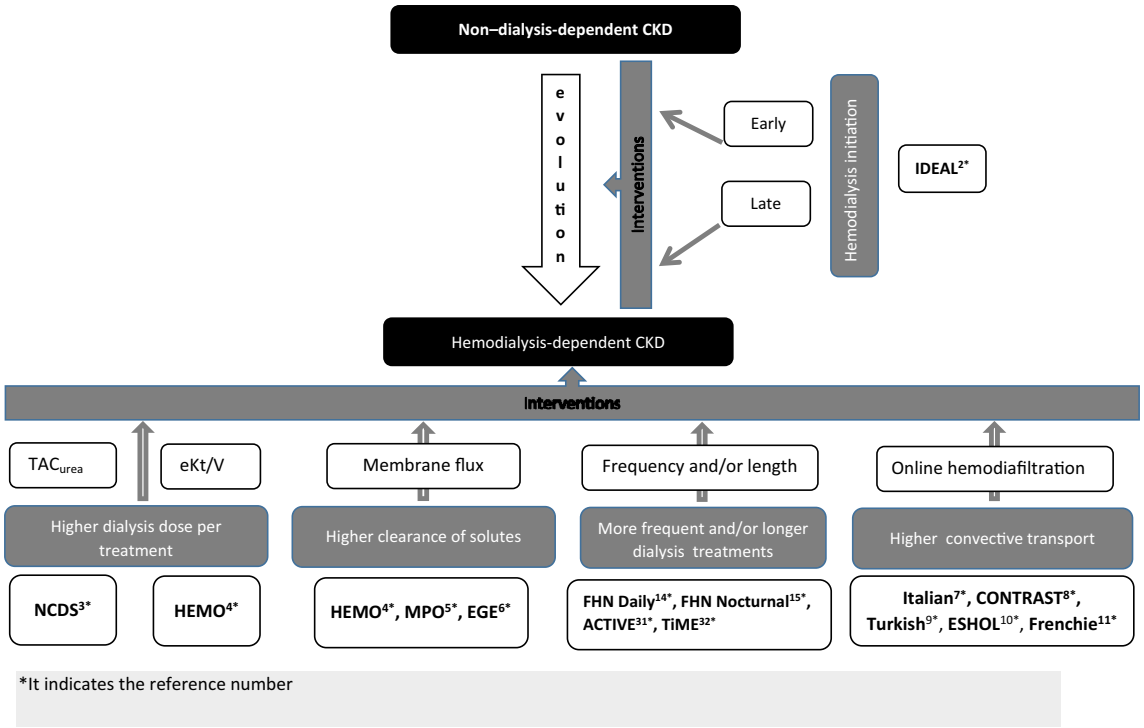


Fig. 1 Schematic representation of landmark RCTs according to intervention. CKD, chronic kidney disease; eKt/V, equilibrated Kt/V urea; TAC_{urea}, time-averaged urea concentration

group (424 patients) had a baseline mean GFR of 7.8 mL/min/1.73 m^2. The median difference in the start of dialysis between the two groups was 5.6 months. Mortality was 37.6% (152 of 404 patients) in the early start group and 36.6% in the late start group (155 of 424 patients) after 3.59 years of follow-up, with hazard ratio (HR) 1.04 when comparing early *vs.* late dialysis start, with 95% confidence interval (CI) 0.83–1.30; P = 0.75. These data challenged the established paradigm of using GFR as the primary guide for initiating maintenance dialysis and promoted significant changes in clinical practice guidelines [22, 23].

The results of a recently published nationwide (data extracted from the National Swedish Renal Registry) observational cohort study are congruent with the results of the IDEAL Trial: very early initiation of dialysis was associated with a modest reduction in mortality and cardiovascular events (a mean postponement of death of 1.6 months over five years of follow-up). However, dialysis would need to be started four years earlier [24].

Does higher haemodialysis dose improve clinical outcomes?

There are two factors related to dialysis clearance with implications for morbidity and mortality: the dialysis dose delivered and the size of molecules removed. The fractional clearance of urea (Kt/V) is the most commonly used index to quantify the dose of dialysis. Nevertheless, dialytic clearance of middle molecules, e.g., β^2-microglobulin, depends on the porosity or permeability of the dialyzer membrane. Thus, dialyzers were categorized into low- or high-flux according to the clearance of β^2-microglobulin and/or the ultrafiltration coefficient [22].

The National Cooperative Dialysis Study (NCDS) was the first RCT designed to evaluate the effects of different dialysis prescriptions on clinical outcomes [3]. It randomized 151 patients into four groups based on a two-by-two factorial design: long dialysis treatment time (4.5–5 h)*;* short dialysis treatment time (3 ± 0.5 h); high blood urea nitrogen averaged with respect to time (100 mg/dL)*;* low blood urea nitrogen averaged with respect to time (50 mg/dL). At the mean follow-up of 12 months, there was no difference in mortality between the four groups. Notably, despite the fact that hospitalization and withdrawal rates for medical reasons were significantly higher in the high-blood urea nitrogen group than in the low-blood urea nitrogen group, it was concluded that dialysis treatment time had no significant effects on patient outcomes [3].

Over the next two decades, a number of observational studies showed that higher dialysis dose and high-flux dialyzers were associated with better patient survival [21, 25]. However, these studies are inherently confounded by selection biases: actually, healthier and/or more compliant

patients were able to undergo longer dialysis treatments. Hence, the Hemodialysis (HEMO) Study was undertaken to determine whether increasing the dose of dialysis or using a high-flux dialyzer improves survival among haemodialysis patients [4]. In this trial, 1,846 prevalent patients receiving thrice-weekly haemodialysis were randomized based on a two-by-two factorial design to a standard dialysis dose (eKt/V 1.05) or to a high dialysis dose (eKt/V 1.45); to low-flux dialysis (mean β^2-microglobulin clearance < 10 mL/min) *vs.* high-flux dialysis (β^2-microglobulin clearance > 20 mL/min). Eligibility criteria included dialysis vintage ≥ 3 months, residual kidney urea clearance (KrU) < 1.5 mL/min and serum albumin ≥ 2.6 g/dL. Achieved eKt/V was 1.16 ± 0.08 in the standard dialysis dose group and 1.53 ± 0.09 in the high dialysis dose group; β^2-microglobulin clearance was 3 ± 7 and 34 ± 11 mL/min in the low- and high-flux dialysis groups, respectively. The primary outcome, death from any cause, was not significantly influenced either by the dialysis dose, with HR of death 0.96 (95% CI 0.84–1.10; P = 0.53) in the high dialysis dose compared to the standard dialysis dose group, or by the flux assignment, with HR of death 0.92 (95% CI 0.81–1.05; P = 0.23) in the high-flux group compared to the low-flux group. The investigators concluded that patients undergoing thrice-weekly haemodialysis had no major benefit from higher dose or use of a high-flux dialyzer [4].

Unlike the HEMO Study, the Membrane Permeability Outcome (MPO) Study was designed to compare the impact of membrane permeability on survival in incident patients [5]. In total, 738 patients were randomized 1:1 and stratified according to serum albumin levels ≤ 4 g/dL (n = 567) and > 4 g/dL (n = 171). Dialysis prescription was targeted for single pool Kt/V (spKt/V) ≥ 1.2 and participants were followed for 3–7.5 years. Ultrafiltration flux was 44.7 ± 9.1 mL/mmHg/h in the high-flux group and 9.8 ± 3.5 mL/mmHg/h in the low-flux group. Seventy-four deaths (23.3%) were observed in the high-flow group, and 88 (26.8%) in the low-flow group (HR 0.76; 95% CI 0.56–1.04; P = 0.09). The 3-year mortality rates were 17.5% and 20.7% in the high- and low- permeability groups, respectively; the 4-year mortality rates were 26.9% and 31.0% in the high- and low-permeability groups, respectively. The rate of hospital admissions (main secondary outcome) was also comparable between the two study groups. Although in subgroup analyses patients with serum albumin ≤ 4.0 g/dL had improved survival in the group treated with high-flux membranes, the treatment efficacy analysis revealed comparable results in the primary outcome of all-cause death between low- and high-permeability groups in the population as a whole.

The Multiple Interventions Related to Dialysis Procedures in Order to Reduce Cardiovascular Morbidity and Mortality in HD Patients was the third RCT dealing with the theme of membrane flow and the first investigating the impact of dialysate purity [6]. In this trial, 704 prevalent patients undergoing thrice-weekly dialysis were randomized to high-flow or low-flow dialyzers and ultrapure or standard dialysate using a two-by-two factorial design. The primary outcome was a composite of fatal and non-fatal cardiovascular events during a minimum of 3 years of follow-up. Serum β^2-microglobulin levels decreased significantly in the high-flux group compared with the low-flux group (β^2microglobulin-5.0 ± 13.6 mg/L *vs.* + 2.7 ± 14.3 mg/L, P < 0.001). The mean dialysate endotoxin levels decreased in the ultrapure dialysate arm (from 0.16 ± 0.26 EU/mL to 0.01 ± 0.01 EU/mL) and remained stable in the standard dialysate arm (from 0.14 ± 0.23 to 0.15 ± 0.22 EU/mL). Although a *post-hoc* analysis showed benefits in some subgroups, overall this study found no statistically significant differences in primary outcome between high-flux and low-flux dialysis (HR 0.73, 95% CI 0.49–1.08, P = 0.12) and between ultrapure and standard dialysate (HR 0.90, 95% CI 0.61–1.32, P = 0.60).

Does intensive haemodialysis improve clinical outcomes?

Intensive haemodialysis is defined as any schedule that increases the number of treatment sessions per week and/or the number of hours per session with respect to conventional haemodialysis [26]. Interestingly, despite the results obtained by the aforementioned RCTs (i.e., IDEAL, NCDS, HEMO, MPO), more intensive haemodialysis continued to be perceived as the approach that would improve patient outcomes. This perception was shown in a global survey of 324 nephrologists [27]. Most physicians reported that increasing the frequency, beyond three times per week, and the length of sessions performed at night, would lead to better clinical outcomes than traditional haemodialysis. What could explain this hypothesis? Physiologically, it is plausible that a longer time on dialysis would increase the removal of serum urea, phosphate, β^2-microglobulin, sodium and water, allowing for better blood pressure control and cardiac performance. In addition, the increase in the number of weekly sessions leads to a reduction in body weight gain between dialyses [28]. Thus, the further questions are:

Does more frequent haemodialysis improve clinical outcomes?

Two parallel-arm RCTs of frequent haemodialysis have been completed: the Frequent Hemodialysis Network (FHN) Daily Trial and the FHN Nocturnal Trial [14, 15]. The statements concerning frequent haemodialysis in the current NKF-KDOQI clinical practice guidelines are mainly based on the results of these RCTs [22].

The FHN Daily Trial was a parallel-group RCT designed to determine whether increasing the frequency of sessions would improve two composite co-primary outcomes: death or 12-month change in left ventricular mass (LVM), and death or 12-month change in the Physical Health composite Score [14]. The study included 245 prevalent patients, most of whom were anuric (60%). Participants were assigned to receive either six short in-centre sessions per week (mean 5.2 sessions, mean duration 2.6 h) (n = 125), or three times per week sessions (mean duration 3.5 h) (n = 120). By design, standard Kt/V (stKt/V) was significantly higher in the frequent haemodialysis group (3.54 ± 0.56 *vs.* 2.49 ± 0.27). Fourteen patients died, 5 in the frequent dialysis group (4%), and 9 in the conventional dialysis group (7.5%). At 12-month follow-up, frequent haemodialysis was associated with significant benefits with respect to both co-primary composite outcomes (HR for death or increase in LMV, 0.61; 95% CI 0.46–0.82; HR for death or a decrease in the Physical Health composite Score, 0.70; 95% CI 0.53–0.92). However, patients receiving frequent haemodialysis were more likely to undergo interventions related to vascular access failure (HR 1.71; 95% CI 1.08–2.73).

The FHN Nocturnal Trial was designed to compare frequent nocturnal home haemodialysis (six times per week) with conventional home haemodialysis (three times per week) powered for the same two composite co-primary outcomes of the FHN Daily Trial [15]. Forty-five prevalent patients were assigned to the frequent haemodialysis group and 42 to the conventional haemodialysis treatment group. Almost 50% of patients had been on dialysis > 1 year and had a urine output > 500 mL/day. Adherence was lower in the frequent haemodialysis group (72.7%) than in the conventional one (97.6%). As expected, patients in the frequent haemodialysis arm had a higher stKt/V (1.74 times). Two patients died in the frequent nocturnal haemodialysis arm and one in the conventional haemodialysis arm. Patients randomized to the frequent nocturnal haemodialysis arm had better control of hyperphosphatemia and systolic blood pressure, but also had more vascular access complications. Unlike the FHN Daily Trial, this RCT did not meet the statistical significance criteria for co-primary composite outcome of death or LVM, (HR 0.68; 95% Cl 0.44–1.07; P = 0.09), or of death or change in Physical Health Score (HR 0.91; 95% Cl 0.58–1.43; P = 0.68).

The results of the FHN Trials in long-term follow-up are controversial [29, 30]. In the extended follow-up of FHN Daily Trial (median 3.6 years), 20 of the 125 patients randomized to the frequent haemodialysis arm died, compared with 34 of the 120 patients randomized to the conventional arm (HR 0.54; 95% CI 0.31–0.93; P = 0.024). The authors concluded that frequent in-centre haemodialysis intervention significantly reduces long-term mortality [29]. This is in stark contrast to the results of the extended follow-up of the FHN Nocturnal Trial. After a median of 3.7 years, 14 deaths among 45 patients (31%) assigned to the frequent nocturnal haemodialysis arm and 5 deaths among 42 patients (11.9%) assigned to the conventional haemodialysis arm (three times per week) were observed, with HR of death for the frequent nocturnal haemodialysis arm of 3.88 (95% CI 1.27–11.79; P = 0.01). Although these results need to be interpreted with caution, the authors acknowledged that patients assigned to nocturnal haemodialysis experienced a higher mortality rate than those assigned to conventional haemodialysis [30].

Do longer haemodialysis treatments improve clinical outcomes?

Despite the lack of clear mortality benefits with more intensive haemodialysis, many centres have introduced programs of frequent short daytime haemodialysis sessions, of long thrice-weekly haemodialysis sessions (day or night) or long frequent haemodialysis sessions (either as facility-based or home-based). While such programs are clearly more expensive, the increased costs could be justified if they led to a better quality of life. The ACTIVE and TiME trials were conceived on the basis of this premise [31, 32].

A Clinical Trial of IntensiVE dialysis (ACTIVE) was a multicentre, open-label trial designed to evaluate the effect of long haemodialysis regimens on quality of life (≥ 24 h/week) over 12 months, compared with standard regimens (≥ 12 h and ≤ 18 h/week) [31]. Unlike the FHN Trial group, the ACTIVE group successfully randomized (1:1) the planned 200 prevalent patients. The primary outcome was the difference in quality of life at the study end, adjusted for baseline, measured with the EuroQol 5 dimension instrument (EQ-5D). Most of the participants had thrice-weekly haemodialysis sessions, with a mean duration of 24 and 12 h/week, respectively. Five deaths occurred in the extended hours group and two in the standard hours group (P = 0.44). Changes in EQ-5D score did not differ between the two groups (mean difference, 0.04; 95% CI − 0.03 to 0.11; P = 0.29). It was concluded that extension of the weekly haemodialysis hours did not alter the quality of life.

The Time to Reduce Mortality in ESKD (TiME) Trial was designed as a pragmatic trial to test the effects of longer sessions compared to the standard ones usually prescribed in the US [32]. It was a cluster randomized, parallel group trial in outpatient dialysis units operated by DaVita and Fresenius Medical Care. Dialysis facilities randomized to the intervention arm adopted a session duration ≥ 255 min for incident patients; those randomized to the usual care arm had no trial-driven approach to session duration. Although the trial enrolled 7,035 incident patients from 266 dialysis units, it was discontinued at a median follow-up of 1.1 years because of inadequate between-group difference in session duration (216 min for the intervention group and 207 min

for the usual care group). Therefore, patient compliance with longer dialysis treatments was insufficient and no differences were found in mortality reduction or hospitalization rate for the intervention arm.

Does increasing convective transport improve clinical outcomes?

The convective clearance provided by haemodiafiltration (HDF) improves the removal of medium molecules [33]. Indeed, the REIN Registry reported that patients treated with HDF had lower mortality than those treated with haemodialysis [34]. But what did the RCTs show?

Five prospective RCTs have been conducted in recent years to compare survival on prevalent haemodialysis patients [7–11]. Patients were randomized to conventional haemodialysis or online post-dilution HDF. The Italian Trial included 146 patients (70 low-flux haemodialysis, 40 HDF, and 36 haemofiltration) [7]; the CONTRAST Trial (Netherlands, Norway, and Canada) included 714 patients (356 low-flux haemodialysis and 358 HDF) [8]; the Turkish Trial included 782 patients, (391 high-flux haemodialysis and 391 HDF) [9]; the ESHOL Trial (Spain) included 906 patients (450 high-flux haemodialysis and 456 HDF) [10]; and the FRENCHIE Trial included 381 patients (191 high-flux haemodialysis and 190 HDF) [11]. Two RCTs had previously been published: the first one enrolled 44 patients (21 on low-flux haemodialysis and 23 on HDF) [12]; the second one enrolled 76 patients (38 on high-flux haemodialysis and 38 on HDF) [13]. Six RCTs could not show a higher survival rate in patients treated with online post-dilution HDF compared to those treated with conventional haemodialysis. The incidence of all-cause mortality was not affected by the treatment [7–9, 11–13]. In contrast, the ESHOL Trial is the only RCT demonstrating a statistically significant reduction in all-cause mortality (30%) with online post-dilution HDF [10]. However, the Working Group of the NKF-KDOQI clinical practice guidelines found these results difficult to interpret due to the severe methodological limitations of this trial [22].

Hopefully, the ongoing CONVINCE study, a multicentre multinational RCT [35], and other planned trials will provide definitive results on the effects of high-volume online post-dilution HDF.

Does starting thrice-weekly haemodialysis improve clinical outcomes?

A multicentre feasibility RCT to assess the impact of incremental *vs.* conventional initiation of haemodialysis on residual kidney function (RKF) was recently conducted in the UK [36]: 29 incident patients were enrolled into the incremental haemodialysis arm (twice a week sessions, $KrU > 3$ mL/min/1.73m^2), increasing the dialysis dose as the RKF decreased, to maintain a total $stKt/V \geq 2$; 26 patients were enrolled into the control arm (three times a week sessions lasting 3.5–4 h) to obtain the same total stKt/V. At six months, 75% of the patients in the control arm and 92% of the patients in the incremental arm had a $KrU > 2$ mL/min/1.73 m^2 (primary outcome). Hospitalisation rate was higher in the control arm (HR 0.31; 95% CI 0.17–0.59; $P < 0.001$, events/person/year). In addition, median costs of the 12-month trial were £ 26,125 (95% CI £ 23,025–£ 29,224) in the standard care arm and £ 19,875 (95% CI £ 17,941–£ 21,810) in the incremental arm that benefited from reduced transport, session and adverse event costs. According to the results of this feasibility RCT, incremental haemodialysis appears safe and cost-saving in incident patients with adequate RKF, justifying a definitive trial [36].

Table 1 summarizes the results of the RCTs included in this review.

Discussion

By and large, the RCTs reviewed herein did not achieve the stated goal. The investigators have already presented specific explanations for the results obtained in their respective manuscripts [2–15, 31, 32, 36]. The limitations and biases of each study are reported in Table 2. We propose some explanations that could justify, at least in part, the observed results:

1. Methodological aspects inherent in the study design may explain the differences in the outcomes observed between RCTs and observational studies. Overall, the RCTs included relatively small cohorts (for example, NCDS published in the New England Journal of Medicine in 1981 enrolled only 151 patients) and short follow-ups, thus producing low event rates and limited statistical power. On the other hand, observational studies, although larger in size and follow-up, hide confounding variables [37].
2. Factors inherent in haemodialysis itself may affect the results obtained in some RCTs. Repeated contact of the blood with the artificial tube surfaces, dialyzer membranes and/or non-native vascular accesses activate the innate immune system, which can lead to excessive activation of platelets, leukocytes, complement and the coagulation cascade [38]. These pro-atherogenic inflammatory reactions, also described in other mechanical circulatory support systems such as extracorporeal membrane oxygenation [39], together with uraemia may contribute to the acceleration of arteriosclerosis [40] and

Table 1 Summary of randomized controlled trials (RCTs) included in this review

Study, authors, (year), (reference number)	Setting and country	Design intervention and control group	Primary outcome	Results (intervention *vs.* control)
RCTs that evaluated early dialysis initiation				
IDEAL, Cooper et al. (2010) [2]	32 clinical centres, Australia and New Zealand	Randomized 1:1 Early dialysis initiation (n = 404): eGFR 10–14 mL/min/1.73m^2 Late dialysis initiation (n = 424): eGFR 5 to 7 mL/min/1.73m^2 or urgent medical indications	All-cause mortality	Early dialysis initiation not associated with higher survival (HR 1.04, 95% CI 0.83–1.30)
RCTs that evaluated higher dialysis dose and/or higher clearance of solutes				
NCDS, Lowrie et al. (1981) [3]	4 clinical centres, US	Two-by-two factorial design (n = 151) Dialysis treatment time [long (4.5–5 h) *vs.* short (3 ± 0.5 h)] Urea nitrogen averaged with respect to time (TAC_{urea}) [high (100 mg/dL) *vs.* low (50 mg/dL)]	All-cause mortality	No difference in mortality at mean follow-up of 12 months
HEMO, Eknoyan et al. (2002) [4]	15 clinical centres (72 dialysis units, US)	Two-by-two factorial design Standard dialysis dose (n = 926): 1.05 eKt/V High dialysis dose (n = 920): 1.45 eKt/V High-flux (n = 921): β^2-microglobulin clearance < 10 mL/min Low-flux (n = 925): β^2-microglobulin clearance > 20 mL/min	All-cause mortality	No survival difference by dialysis dose (HR 0.96, 95% CI 0.84–1.10) or dialyzer flux (HR 0.92, 95% CI 0.81–1.05)
MPO, Locatelli et al. (2009) [5]	59 clinical centres, Europe	Randomized 1:1 High-permeability dialyzer membrane (n = 318) Low-permeability dialyzer membrane (n = 329)	All-cause mortality	No difference in survival (HR 0.76; 95% CI 0.56–1.04)
EGE, Asci et al. (2013) [6]	8 clinical centres, Turkey	Two-by-two factorial design High (n = 352) or low (n = 352) flow dialyzer Utrapure (n = 352) or standard (n = 352) dialysate	Primary Composite fatal and non-fatal cardiovascular events	No difference in primary outcome between high-flux and low-flux dialyzer membrane (HR = 0.73, 95% CI 0.49–1.08) and between standard and ultrapure dialysate (HR 0.90, 95% CI 0.61–1.32)
RCTs that evaluated more frequent or longer dialysis treatments				
FHN daily trial, Chertow et al. (2010) [14]	65 dialysis units, North America	Randomized 1:1 Frequent dialysis (6 days/week) (n = 125) Conventional dialysis (3 days/week) (n = 120)	Two co-primary outcomes; composite: (1) death or change in LVM; (2) death or change in SF-36 RAND PHC score	Frequent dialysis associated with favourable outcomes (1) HR 0.61; 95% CI 0.46–0.82 (2) HR 0.70; 95% CI 0.53–0.92

Table 1 (continued)

Study, authors, (year), (reference number)	Setting and country	Design intervention and control group	Primary outcome	Results (intervention *vs.* control)
FHN Nocturnal Trial, Rocco et al. (2011) [15]	19 clinical centres, US and Canada	Randomized 1:1 Frequent nocturnal home dialysis (6 sessions/week) (n = 45) Conventional home dialysis (3 sessions/week) (n = 42)	Same as in the FHN Daily Trial	The trial did not meet the criteria for statistical significance for either the co-primary composite outcome of death or LVM (HR 0.68; 95% Cl 0.44–1.07; P = 0.095), or of death or change in Physical Health Score (HR 0.91; 95% Cl 0.58–1.43; P = 0.68)
ACTIVE, Jardine et al. (2017) [31]	40 centres in China, Australia, New Zealand and Canada	Randomized 1:1 Longer dialysis sessions (≥ 24 h/week) (n = 100) Conventional dialysis sessions (12 to 18 h/week) (n = 100)	Quality of life (EuroQol 5D)	No difference in quality of life (mean difference, 0.04 (95% confidence interval, − 0.03 to 0.11); P = 0.29)
TiME, Dember et al. (2019) [32]	266 clinical centres, US	Cluster randomization by dialysis facility n = 7,035 patients Longer dialysis sessions (mean session duration, 216 min) Usual care dialysis (mean session duration, 207 min)	All-cause mortality	No differences in mortality or hospitalization rate

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR hazard ratio; PHC, Physical Health Composite; SF-36, Short Form 36; TAC_{urea}, time-averaged urea concentration

Table 2 Limitations and biases of the randomized controlled trials (RCTs) included in this review

Study, author (year) (reference number)	Limitations	Biases
RCTs that evaluated early dialysis initiation		
IDEAL, Cooper et al. (2010) [2]	Assessment of the estimated GFR (eGFR) based on the Cockcroft-Gault equation, corrected for body surface area Not uniform method for creatinine assessment	Most of the patients assigned to the late-start arm did not start dialysis at the eGFR level defined in the protocol The confidence intervals did not exclude a clinically relevant benefit of early initiation of dialysis
RCTs that evaluated higher dialysis dose and/or higher clearance of solutes		
NCDS, Lowrie et al. (1981) [3]	No clear recommendations for the management of patients with low protein catabolic rate (PCR)	Since no patients with PCR < 0.80 were treated with higher Kt/V values, the relative importance of dialysis dose and nutrition in patients with low PCR could not be inferred
HEMO, Eknoyan et al. (2002) [4]	The possible effect the dialysis dose on body size not considered in this RCT	Risk of false positive results from multiple subgroup analyses 60% of patients treated with high-flux dialysis before enrolment into the study Dialyzer reuse, predominance of African Americans, high prevalence of cardiovascular diseases (CVD) (80.1%)
MPO, Locatelli et al. (2009) [5]	Mortality rate lower than that reported in registries (8.2%): thus, lower comorbidity profile than that observed in the routine clinical practice?	Effect of the membrane flow significantly higher in patients with diabetes than in those without diabetes in the group with serum albumin ≤ 4 g/dL: thus, could the risk reduction with high-flux dialysis in this group be related to the diabetes status? The different and, in part, small sample sizes of the subgroups may preclude definitive conclusions
EGE, Asci et al. (2013) [6]	Better outcomes with high-flux dialysis and ultrapure dialysate in some subgroups: however, these were not pre-specified subgroup analyses	A substantial percentage of the study population already treated with high-flux dialysis at the time of randomization Relatively healthy study population (low prevalence of diabetes, hypertension, and CVD history), yielding a quite lower annual mortality rate of 8.32 per 100 patient-years (results not applicable to the general dialysis population)
RCTs that evaluated more frequent or longer dialysis treatments		
FHN Daily Trial, Chertow et al. (2010) [14]	Sample size insufficient to determine the effects of frequent in-centre dialysis on death, cause-specific death, hospitalization, or other events	The rate of death was low in both groups The bulk of the treatment effect seen in intermediate outcomes
FHN Nocturnal Trial, Rocco et al. (2011) [15]	Relatively small sample size Lower adherence to the dialysis prescription in the frequent nocturnal arm Patients enrolled in the trial: younger, presence of residual kidney function, less likely to be African American	Only 87.3% of the randomized patients completed 12 months of follow-up and had measures of both co-primary outcomes 25% of patients in the frequent nocturnal arm had less than five haemodialysis sessions per week
ACTIVE, Jardine et al. (2017) [31]	Small sample size Lack of feasibility for blinding participants and investigators	Not complete adherence, especially in the long-term dialysis group
TiME, Dember et al. (2019) [32]	Inadequate uptake of the interventions	Stop of the trial (mean follow-up of 1.1 years), due to inadequate difference in session length between the groups (216 min in the intervention group and 207 min in the usual care group)

haemodialysis-induced cardiovascular disease [41]. It could be hypothesized that the greater the intensity of haemodialysis (greater contact between surfaces), the greater the pro-atherosclerotic environment. In this direction, frequent haemodialysis has been observed to accelerate the loss of RKF, with 52% of patients being anuric at 4 months, compared to 18% of those treated with conventional haemodialysis [15]. It is important to remember that RKF, which is present in many patients at the start of dialysis, is associated with improved patient survival [42–44].

3. Solutes other than urea play an important role in clinical outcomes. Protein-bound uraemic toxins have been shown to have a toxic effect on endothelial cells and have been associated with increased risk of mortality in haemodialysis patients [45]. However, studies have shown that neither online HDF [46] nor frequent haemodialysis [47] significantly increase clearance of these toxins. Conversely, small degrees of RKF, even those considered "clinically insignificant", provide a clearance of these solutes greater than that provided by dialytic therapies [48]. Thus, it is conceivable that benefits that should be obtained by intensive haemodialysis therapies, in particular with more frequent haemodialysis, are counteracted by the loss of RKF. Therefore, the NKF-KDOQI guidelines recommend that incident patients with substantial RKF be informed about the risks of intensive haemodialysis therapies [22].
4. The inability of many RCTs to demonstrate the expected benefits is mainly based on the fact that ESKD does not result from a single disease entity: it is a collection of different diseases and subtypes of kidney dysfunction. Patients with kidney dysfunction requiring dialysis (KDRD) differ on a multitude of levels including RKF, biochemical parameters (e.g., acid base balance, serum electrolytes, mineral and bone disorder) and volume overload [49].

Registry data show that patients are diagnosed with ESKD when their GFR is anywhere between 4 and 15 mL/min/1.73 m^2; when dialysis is started, half have a GFR > 9 mL/min/1.73 m^2, and > 90% have eGFR ≥ 5 mL/min/1.73 m^2 [50]. In many countries, conventional haemodialysis prescription consists of thrice-weekly haemodialysis targeting urea clearance metrics of spKt/V ≥ 1.20 and urea reduction ratio ≥ 65% [22]. Indeed, conventional haemodialysis therapy has been validated in clinical trials involving only prevalent haemodialysis patients with dialysis vintage > 2 years and virtually no RKF (patients were excluded if residual KrU was > 1.5 mL/min/35 L of urea distribution volume) [3, 4]; this was then extrapolated as the "optimal" dialysis dose to all dialysis patients, including those found at the beginning of need for dialysis therapy and who had RKF. Thus, while conventional haemodialysis therapy may provide vital replacement of kidney function in those who have lost RKF, some patients, at least temporarily, would do well with less intensive dialytic therapy in the form of assistance therapy to complement underlying levels of ongoing RKF.

This raises the question as to whether clinical trials should be designed to include a better defined sub-category of KDRD patients who would most benefit from the intervention. For a clinical trial to be successful, the right patients need to be matched to the therapies they are most likely to benefit from. However, while targeting trials to specific phenotypes postulated to respond to the tested intervention may increase the ability to identify efficacy, this approach may also limit ability to enrol enough patients for a sufficiently powered trial [51]. Adaptive clinical trials hold the potential to increase the efficiency of RCTs in dialysis by identifying the patient population most likely to benefit from alternative haemodialysis treatment models, helping with sample size re-estimation in potential scenarios when fewer patients may be required overall to ensure the same high chance of getting the right answer, or preventing an underpowered trial, which would mean a waste of resources [52, 53].

Future directions

It is important to acknowledge the lack of reliable data to support a stage-based approach to treatment of advanced stages of kidney failure with dialysis. A prerequisite for KDRD phenotyping is longitudinal data acquisition in large, well characterized cohorts [54]. This will enable characterization of distinct KDRD phenotypes, categorized by sociodemographic and clinical data, by using consensus clustering analysis [55]. Future clinical trials of KDRD should account for the heterogeneity of patients when considering inclusion/exclusion criteria and study design, and should a priori consider subgroup analyses to highlight specific KDRD subgroups that may derive greater benefit from a particular intervention. Furthermore, it will be interesting to identify degrees of KDRD clustering or endotypes in different KDRD stages and determinants of stage transition [51]. Such studies can identify subpopulations of patients with KDRD that have different risks of KDRD stage progression, cardiovascular events and death. Of paramount importance in clinical trials is to test whether tailoring haemodialysis prescription based on levels of RKF and clinical symptoms is an effective and well-tolerated approach [51].

The thought behind "incremental" is that the start of standard dialysis often happens abruptly, ignoring a longer and insidious process of declining kidney function over months or years. Also, it has been argued that the rather fast loss of RKF often experienced after initiating standard thrice-weekly

haemodialysis could contribute to the high early mortality rate [42, 56–58]. The slope of kidney function decline can be heterogeneous. Especially among older adults a large fraction exhibits slower progression of RKF [59] potentially making them good candidates for incremental haemodialysis. An incremental, stepped haemodialysis regimen with a scheduled transition from twice- to thrice-weekly is believed to offer the body more time to adapt to the new treatment compared to the sudden start of standard haemodialysis, the prescription of which is fundamentally empirical [60].

Of note, several ongoing clinical trials are currently using thresholds of residual KrU to establish the clinical effectiveness of less frequent haemodialysis in the form of once- or twice-weekly haemodialysis *vs.* thrice-weekly haemodialysis [61–64].

Exploring non-dialysis options within the frame of avoiding overtreatment, one question arises: does conservative kidney management offer a quantity or quality of life benefit compared to dialysis? A recently published systematic review identified twenty-five primary studies, all observational, which reported increased mortality in patients treated with conservative kidney management (pooled HR 0.47, 95% CI 0.34–0.65). In patients ≥ 80 years of age, and in elderly individuals with comorbidities, the survival benefits of dialysis seem to be lost. In most studies, conservative kidney management seemed advantageous for quality of life secondary outcomes. The results were limited by the heterogeneity of the studies and the biased outcomes favouring dialysis [65].

Conclusions

The different intervention strategies of the RCTs reviewed herein were not able to improve the clinical outcomes of ESKD patients. Higher quality studies are needed to guide patients and clinicians in the decision-making process. Future RCTs should account for the heterogeneity of patients when considering inclusion/exclusion criteria and study design; and should a priori consider subgroup analyses to highlight specific subgroups that can benefit most from a particular intervention.

Funding No funding agency granted the present study.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals Statement of human rights, statement on the welfare of animals: this article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No verbal and written informed consent was necessary for this study.

References

1. Chan CT, Covic A, Craig JC, Davenport A, Kasiske BL, Kuhlmann MK, Levin NW, Li PK, Locatelli F, Rocco MV, Wheeler DC (2013) Novel techniques and innovation in blood purification: a clinical update from Kidney Disease: Improving Global Outcomes. Kidney Int 83:359–371. https://doi.org/10.1038/ki.2012.450
2. Cooper BA, Branley P, Bulfone L, Collins JF, Craig JC, Fraenkel MB, Harris A, Johnson DW, Kesselhut J, Li JJ, Luxton G, Pilmore A, Tiller DJ, Harris DC, Pollock CA, IDEAL Study (2010) A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med 363:609–619. https://doi.org/10.1056/NEJMoa1000552
3. Lowrie EG, Laird NM, Parker TF, Sargent JA (1981) Effect of the hemodialysis prescription of patient morbidity: report from the National Cooperative Dialysis Study. N Engl J Med 305:1176–1181. https://doi.org/10.1056/NEJM198111123052003
4. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R, Hemodialysis (HEMO) Study Group (2002) Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 347:2010–2019. https://doi.org/10.1056/NEJMoa021583
5. Locatelli F, Martin-Malo A, Hannedouche T, Loureiro A, Papadimitriou M, Wizemann V, Jacobson SH, Czekalski S, Ronco C, Vanholder R, Membrane Permeability Outcome (MPO) Study Group (2009) Effect of membrane permeability on survival of hemodialysis patients. J Am Soc Nephrol 20:645–654. https://doi.org/10.1681/ASN.2008060590
6. Asci G, Tz H, Ozkahya M, Duman S, Demirci MS, Cirit M, Sipahi S, Dheir H, Bozkurt D, Kircelli F, Ok ES, Erten S, Ertilav M, Kose T, Basci A, Raimann JG, Levin NW, Ok E, EGE Study Group (2013) The impact of membrane permeability and dialysate purity on cardiovascular outcomes. J Am Soc Nephrol 24:1014–1023. https://doi.org/10.1681/ASN.2012090908
7. Locatelli F, Altieri P, Andrulli S, Bolasco P, Sau G, Pedrini LA, Basile C, David S, Feriani M, Montagna G, Di Iorio BR, Memoli B, Cravero R, Battaglia G, Zoccali C (2010) Hemofiltration and hemodiafiltration reduce intradialytic hypotension in ESRD. J Am Soc Nephrol 21:1798–1807. https://doi.org/10.1681/ASN.2010030280
8. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, den Hoedt CH, van der Tweel I, Lévesque R, Nubé MJ, ter Wee PM, Blankestijn PJ, CONTRAST Investigators (2012) Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. J Am Soc Nephrol 23:1087–1096. https://doi.org/10.1681/ASN.2011121140
9. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, Hur E, Demirci MS, Demirci C, Duman S, Basci A, Adam SM, Isik IO, Zengin M, Suleymanlar G, Yilmaz ME, Ozkahya M, Turkish Online Haemodiafiltration Study (2013) Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant 28:192–202. https://doi.org/10.1093/ndt/gfs407
10. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macià J, Carreras J, Soler J, Torres F, Campistol JM, Martinez-Castelao A, ESHOL Study Group (2013) High-efficiency postdilution online

hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol 24:487–497. https://doi.org/10.1681/ASN.2012080875
11. Morena M, Jaussent A, Chalabi L, Leray-Moragues H, Chenine L, Debure A, Thibaudin D, Azzouz L, Patrier L, Maurice F, Nicoud P, Durand C, Seigneuric B, Dupuy AM, Picot MC, Cristol JP, Canaud B, FRENCHIE Study Investigators (2017) Treatment tolerance and patient-reported outcomes favor online hemodiafiltration compared to high-flux hemodialysis in the elderly. Kidney Int 91:1495–1509. https://doi.org/10.1016/j.kint.2017.01.013
12. Wizemann V, Lotz C, Techert F, Uthoff S (2000) On-line haemodiafiltration versus low-flux haemodialysis. A prospective randomized study. Nephrol Dial Transplant 15(Suppl 1):43–48. https://doi.org/10.1093/oxfordjournals.ndt.a027963
13. Schiffl H (2007) Prospective randomized cross-over long-term comparison of online haemodiafiltration and ultrapure high-flux haemodialysis. Eur J Med Res 12:26–33 (**PMID: 17363355**)
14. FHN Trial Group, Chertow GM, Levin NW, Beck GJ, Depner TA, Eggers PW, Gassman JJ, Gorodetskaya I, Greene T, James S, Larive B, Lindsay RM, Mehta RL, Miller B, Ornt DB, Rajagopalan S, Rastogi A, Rocco MV, Schiller B, Sergeyeva O, Schulman G, Ting GO, Unruh ML, Star RA, Kliger AS (2010) In-center hemodialysis six times per week versus three times per week. N Engl J Med 363:2287–2300. https://doi.org/10.1056/NEJMoa1001593
15. Rocco MV, Lockridge RS Jr, Beck GJ, Eggers PW, Gassman JJ, Greene T et al (2011) Frequent Hemodialysis Network (FHN) Trial Group. The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. Kidney Int 80:1080–1091. https://doi.org/10.1038/ki.2011.213
16. Wang C, Lv LS, Huang H, Guan J, Ye Z, Li S, Wang Y, Lou T, Liu X (2017) Initiation time of renal replacement therapy on patients with acute kidney injury: a systematic review and meta-analysis of 8179 participants. Nephrology (Carlton) 22:7–18. https://doi.org/10.1111/nep.12890
17. STARRT-AKI Investigators; Canadian Critical Care Trials Group; Australian and New Zealand Intensive Care Society Clinical Trials Group; United Kingdom Critical Care Research Group; Canadian Nephrology Trials Network; Irish Critical Care Trials Group, Bagshaw SM, Wald R, Adhikari NKJ, Bellomo R, da Costa BR, Dreyfuss D et al (2020) Timing of initiation of renal-replacement therapy in acute kidney injury. N Engl J Med 383:240–251. https://doi.org/10.1056/NEJMoa2000741
18. Hakim RM, Lazarus JM (1995) Initiation of dialysis. J Am Soc Nephrol 6:1319–1328. https://doi.org/10.1681/ASN.V651319
19. Bonomini V, Feletti C, Stefoni S, Vangelista A (1986) Early dialysis and renal transplantation. Nephron 44:267–271. https://doi.org/10.1159/000184004
20. Tattersall J, Greenwood R, Farrington K (1995) Urea kinetics and when to commence dialysis. Am J Nephrol 15:283–289. https://doi.org/10.1159/000168850
21. O'Hare AM, Choi AI, Boscardin WJ, Clinton WL, Zawadzki I, Hebert PL, Kurella Tamura M, Taylor L, Larson EB (2011) Trends in timing of initiation of chronic dialysis in the United States. Arch Intern Med 10(171):1663–1669. https://doi.org/10.1001/archinternmed.2011.436
22. National Kidney Foundation (2015) KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update. Am J Kidney Dis 66:884–930. https://doi.org/10.1053/j.ajkd.2015.07.015
23. Rivara MB, Mehrotra R (2017) Timing of dialysis initiation: what has changed since IDEAL? Semin Nephrol 37:181–193. https://doi.org/10.1016/j.semnephrol.2016.12.008
24. Fu EL, Evans M, Carrero J-J, Putter H, Clase CM, Caskey FJ, Szymczak M, Torino C, Chesnaye NC, Jager KJ, Wanner C, Dekker FW, van Diepen M (2021) Timing of dialysis initiation to reduce mortality and cardiovascular events in advanced chronic kidney disease: nationwide cohort study. BMJ 375:e066306. https://doi.org/10.1136/bmj-2021-066306
25. Port FK, Orzol SM, Held PJ, Wolfe RA (1998) Trends in treatment and survival for hemodialysis patients in the United States. Am J Kidney Dis 32(6 Suppl 4):S34–S38. https://doi.org/10.1016/s0272-6386(98)70159-3
26. Kraus MA, Kansal S, Copland M, Komenda P, Weinhandl ED, Bakris GL, Chan CT, Fluck RJ, Burkart JM (2016) Intensive hemodialysis and potential risks with increasing treatment. Am J Kidney Dis 68(5S1):S51–S58. https://doi.org/10.1053/j.ajkd.2016.05.020
27. Fluck RJ, Fouque D, Lockridge RS Jr (2014) Nephrologists' perspectives on dialysis treatment: results of an international survey. BMC Nephrol 15:16. https://doi.org/10.1186/1471-2369-15-16
28. Foley RN, Gilbertson DT, Murray T, Collins AJ (2011) Long interdialytic interval and mortality among patients receiving hemodialysis. N Engl J Med 365:1099–1107. https://doi.org/10.1056/NEJMoa1103313
29. Chertow GM, Levin NW, Beck GJ, Daugirdas JT, Eggers PW, Kliger AS, Larive B, Rocco MV, Greene T, Frequent Hemodialysis Network (FHN) Trials Group (2016) Long-term effects of frequent in-center hemodialysis. J Am Soc Nephrol 27:1830–1836. https://doi.org/10.1681/ASN.2015040426
30. Rocco MV, Daugirdas JT, Greene T, Lockridge RS, Chan C, Pierratos A, Lindsay R, Larive B, Chertow GM, Beck GJ, Eggers PW, Kliger AS, FHN Trial Group (2015) Long-term effects of frequent nocturnal hemodialysis on mortality: the frequent hemodialysis network (FHN) nocturnal trial. Am J Kidney Dis 66:459–468. https://doi.org/10.1053/j.ajkd.2015.02.331
31. Jardine MJ, Zuo L, Gray NA, de Zoysa JR, Chan CT, Gallagher MP, Monaghan H, Grieve SM, Puranik R, Lin H, Eris JM, Zhang L, Xu J, Howard K, Lo S, Cass A, Perkovic V, ACTIVE Dialysis Steering Committee; Paul (2017) A trial of extending hemodialysis hours and quality of life. J Am Soc Nephrol 28:1898–1911. https://doi.org/10.1681/ASN.2015111225
32. Dember LM, Lacson E Jr, Brunelli SM, Hsu JY, Cheung AK, Daugirdas JT, Greene T, Kovesdy CP, Miskulin DC, Thadhani RI, Winkelmayer WC, Ellenberg SS, Cifelli D, Madigan R, Young A, Angeletti M, Wingard RL, Kahn C, Nissenson AR, Maddux FW, Abbott KC, Landis JR (2019) The TiME trial: a fully embedded, cluster-randomized, pragmatic trial of hemodialysis session duration. J Am Soc Nephrol 30:890–903. https://doi.org/10.1681/ASN.2018090945
33. Tattersall JE, Ward RA, EUDIAL Group (2013) Online haemodiafiltration: definition, dose quantification and safety revisited. Nephrol Dial Transplant 28:542–550. https://doi.org/10.1093/ndt/gfs530
34. Mercadal L, Franck JE, Metzger M, Urena Torres P, de Cornelissen F, Edet S, Béchade C, Vigneau C, Drüeke T, Jacquelinet C, Stengel B, Registry REIN (2016) Hemodiafiltration versus hemodialysis and survival in patients with ESRD: The French Renal Epidemiology and Information Network (REIN) Registry. Am J Kidney Dis 68:247–255. https://doi.org/10.1053/j.ajkd.2015.11.016
35. Blankestijn PJ, Fischer KI, Barth C, Cromm K, Canaud B, Davenport A, Grobbee DE, Hegbrant J, Roes KC, Rose M, Strippoli GF, Vernooij RW, Woodward M, de Wit GA, Bots ML (2020) Benefits and harms of high-dose haemodiafiltration versus high-flux haemodialysis: the comparison of high-dose haemodiafiltration with high-flux haemodialysis (CONVINCE) trial protocol. BMJ Open 10:e033228. https://doi.org/10.1136/bmjopen-2019-033228
36. Vilar E, Kaja Kamal RM, Fotheringham J, Busby A, Berdeprado J, Kislowska E, Wellsted D, Alchi B, Burton JO, Davenport A, Farrington K (2021) A multicenter feasibility randomized controlled trial to assess the impact of incremental versus conventional initiation of hemodialysis on residual kidney function. Kidney Int. https://doi.org/10.1016/j.kint.2021.07.025

37. Grimes DA, Schulz KF (2002) An overview of clinical research: the lay of the land. Lancet 359:57–61. https://doi.org/10.1016/S0140-6736(02)07283-5
38. Ekdahl KN, Soveri I, Hilborn J, Fellström B, Nilsson B (2017) Cardiovascular disease in haemodialysis: role of the intravascular innate immune system. Nat Rev Nephrol 13:285–296. https://doi.org/10.1038/nrneph.2017.17
39. Ostermann M, Lumlertgul N (2021) Acute kidney injury in ECMO patients. Crit Care 25(1):313. https://doi.org/10.1186/s13054-021-03676-5
40. Williams J, Gilchrist M, Strain D, Fraser D, Shore A (2020) The systemic microcirculation in dialysis populations. Microcirculation 27:e12613. https://doi.org/10.1111/micc.12613
41. Ahmadmehrabi S, Tang WHW (2018) Hemodialysis-induced cardiovascular disease. Semin Dial 31:258–267. https://doi.org/10.1111/sdi.12694
42. Obi Y, Rhee CM, Mathew AT, Shah G, Streja E, Brunelli SM, Kovesdy CP, Mehrotra R, Kalantar-Zadeh K (2016) Residual kidney function decline and mortality in incident hemodialysis patients. J Am Soc Nephrol 27:3758–3768. https://doi.org/10.1681/ASN.2015101142
43. Lee MJ, Park JT, Park KS, Kwon YE, Oh HJ, Yoo TH, Kim YL, Kim YS, Yang CW, Kim NH, Kang SW, Han SH (2017) Prognostic value of residual urine volume, GFR by 24-hour urine collection, and egfr in patients receiving dialysis. Clin J Am Soc Nephrol 12:426–434. https://doi.org/10.2215/CJN.05520516
44. Krediet RT (2017) Preservation of residual kidney function and urine volume in patients on dialysis. Clin J Am Soc Nephrol 12:377–379. https://doi.org/10.2215/CJN.00330117
45. Mair RD, Sirich TL, Meyer TW (2018) Uremic toxin clearance and cardiovascular toxicities. Toxins (Basel) 10:226. https://doi.org/10.3390/toxins10060226
46. Kandouz S, Mohamed AS, Zheng Y, Sandeman S, Davenport A (2016) Reduced protein bound uraemic toxins in vegetarian kidney failure patients treated by haemodiafiltration. Hemodial Int 20:610–617. https://doi.org/10.1111/hdi.12414
47. Sirich TL, Fong K, Larive B, Beck GJ, Chertow GM, Levin NW, Kliger AS, Plummer NS, Meyer TW, Frequent Hemodialysis Network (FHN) Trial Group (2017) Limited reduction in uremic solute concentrations with increased dialysis frequency and time in the Frequent Hemodialysis Network Daily Trial. Kidney Int 91:1186–1192. https://doi.org/10.1016/j.kint.2016.11.002
48. Toth-Manikowski SM, Sirich TL, Meyer TW, Hostetter TH, Hwang S, Plummer NS, Hai X, Coresh J, Powe NR, Shafi T (2020) Contribution of "clinically negligible" residual kidney function to clearance of uremic solutes. Nephrol Dial Transplant 35:846–853. https://doi.org/10.1093/ndt/gfz042
49. Murea M, Deira J, Kalantar-Zadeh K, Casino FG, Basile C (2021) The spectrum of kidney dysfunction requiring chronic dialysis therapy: Implications for clinical practice and future clinical trial. Semin Dial. https://doi.org/10.1111/sdi.13027
50. United States Renal Data System Annual Data Report 2020 (2021) Chronic kidney disease (CKD) in the United States: chapter 8: transition of care in chronic kidney disease. https://adr.usrds.org/2020/chronic-kidney-disease/8-transition-of-care-in-chronic-kidneydisease. Accessed 30 Nov 2021
51. Murea M, Flythe JE, Anjay R, Emaad AM, Gupta N, Kovach C, Vachharajani TJ, Kalantar-Zadeh K, Casino FG, Basile C (2022) Kidney dysfunction requiring dialysis is a heterogeneous syndrome: we should treat it like one. Curr Opin Nephrol Hypertens 31:92–99. https://doi.org/10.1097/MNH.0000000000000754
52. Judge C, Murphy RP, Cormican S, Smyth A, O'Halloran M, O'Donnell M (2020) Adaptive design methods in dialysis clinical trials: a systematic review protocol. BMJ Open 10:e036755. https://doi.org/10.1136/bmjopen-2019-036755
53. Pallmann P, Bedding AW, Choodari-Oskooei B, Dimairo M, Flight L, Hampson LV, Holmes J, Mander AP, Odondi L, Sydes MR, Villar SS, Wason JMS, Weir CJ, Wheeler GM, Yap C, Jaki T (2018) Adaptive designs in clinical trials: why use them, and how to run and report them. BMC Med 16:29. https://doi.org/10.1186/s12916-018-1017-7
54. Murea M (2021) Precision medicine approach to dialysis including incremental and decremental dialysis regimens. Curr Opin Nephrol Hypertens 30:85–92. https://doi.org/10.1097/MNH.0000000000000667
55. Monti S, Tamayo P, Mesirov J, Golub T (2003) Consensus clustering: a resampling-based method for class discovery and visualization of gene expression microarray data. Mach Learn 52:91–118. https://doi.org/10.1023/A:1023949509487
56. Perl J, Bargman JM (2009) The importance of residual kidney function for patients on dialysis: a critical review. Am J Kidney Dis 53:1068–1081. https://doi.org/10.1053/j.ajkd.2009.02.012
57. Vilar E, Farrington K (2011) Emerging importance of residual renal function in end-stage renal failure. Semin Dial 24:487–494. https://doi.org/10.1111/j.1525-139X.2011.00968.x
58. Shafi T, Jaar BG, Plantinga LC, Fink NE, Sadler JH, Parekh RS, Powe NR, Coresh J (2010) Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. Am J Kidney Dis 56:348–358. https://doi.org/10.1053/j.ajkd.2010.03.020
59. Tótoli C, Carvalho AB, Ammirati AL, Draibe SA, Canziani MEF (2019) Associated factors related to chronic kidney disease progression in elderly patients. PLoS ONE 14:e0219956. https://doi.org/10.1371/journal.pone.0219956
60. Murea M, Moossavi S, Garneata L, Kalantar-Zadeh K (2019) Narrative review of incremental hemodialysis. Kidney Int Rep 5:135–148. https://doi.org/10.1016/j.ekir.2019.11.014
61. Deira J, Suárez MA, López F, García-Cabrera E, Gascón A, Torregrosa E, García GE, Huertas J, de la Flor JC, Puello S, Gómez-Raja J, Grande J, Lerma JL, Corradino C, Musso C, Ramos M, Martín J, Basile C, Casino FG (2019) IHDIP: a controlled randomized trial to assess the security and effectiveness of the incremental hemodialysis in incident patients. BMC Nephrol 20:8. https://doi.org/10.1186/s12882-018-1189-6
62. Fernández Lucas M, Ruíz-Roso G, Merino JL, Sánchez R, Bouarich H, Herrero JA, Muriel A, Zamora J, Collado A (2020) Initiating renal replacement therapy through incremental haemodialysis: protocol for a randomized multicentre clinical trial. Trials 21:206. https://doi.org/10.1186/s13063-020-4058-0
63. Casino FG, Basile C, Kirmizis D, Kanbay M, van der Sande F, Schneditz D, Mitra S, Davenport A, Gesuldo L, Eudial Working Group of ERA-EDTA (2020) The reasons for a clinical trial on incremental haemodialysis. Nephrol Dial Transplant 35:2015–2019. https://doi.org/10.1093/ndt/gfaa220
64. Murea M, Moossavi S, Fletcher AJ, Jones DN, Sheikh HI, Russell G, Kalantar-Zadeh K (2021) Renal replacement treatment initiation with twice-weekly versus thrice-weekly haemodialysis in patients with incident dialysis-dependent kidney disease: rationale and design of the TWOPLUS pilot clinical trial. BMJ Open 11:e047596. https://doi.org/10.1136/bmjopen-2020-047596
65. Engelbrecht BL, Kristian MJ, Inge E, Elizabeth K, Guldager LT, Helbo TL, Jeanette F (2021) Does conservative kidney management offer a quantity or quality of life benefit compared to dialysis? A systematic review. BMC Nephrol 22:307. https://doi.org/10.1186/s12882-021-02516-6