Nephrology Dialysis Transplantation (2023) 38: 435–446
https://doi.org/10.1093/ndt/gfac274
Advance Access publication date 20 September 2022

ORIGINAL ARTICLE

Impact of incremental initiation of haemodialysis on mortality: a systematic review and meta-analysis

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ABSTRACT

Background. Incremental haemodialysis initiation entails lower sessional duration and/or frequency than the standard 4 h thrice-weekly approach. Dialysis dose is increased as residual kidney function (RKF) declines. This systematic review evaluates its safety, efficacy and cost-effectiveness.

Methods. We searched MEDLINE, EMBASE, CINAHL and the Cochrane Library databases from inception to 27 February 2022. Eligible studies compared incremental haemodialysis (sessions either fewer than three times weekly or of duration <3.5 h) with standard treatment. The primary outcome was mortality. Secondary outcomes included treatment-emergent adverse events, loss of RKF, quality of life and cost effectiveness. The study protocol was prospectively registered. Risk of bias assessment used the Newcastle-Ottawa Scale and the revised Cochrane risk of bias tool, as appropriate. Meta-analyses were undertaken in Review Manager, Version 5.4.

Results. A total of 644 records were identified. Twenty-six met the inclusion criteria, including 22 cohort studies and two randomized controlled trials (RCTs). Sample size ranged from 48 to 50 596 participants (total 101 476). We found no mortality differences (hazard ratio = 0.99; 95% CI 0.80–1.24). Cohort studies suggested similar hospitalization rates though the two small RCTs suggested less hospitalization after incremental initiation (relative risk = 0.31; 95% CI 0.18–0.54). Data on other treatment-emergent adverse events and quality of life was limited. Observational studies suggested reduced loss of RKF in incremental haemodialysis. This was not supported by RCT data. Four studies reported reduced costs of incremental treatments.

Conclusions. Incremental initiation of haemodialysis does not confer greater risk of mortality compared with standard treatment. Hospitalization may be reduced and costs are lower.

Keywords: hospitalization, incremental haemodialysis, meta-analysis, mortality, safety

INTRODUCTION

Haemodialysis (HD) has long been established as a life-sustaining treatment for patients with end-stage kidney disease (ESKD). Despite this, mortality rates are disproportionately high, especially within the first few months following the initiation of treatment [1]. Researchers have speculated that this may be due to difficulties in patients adjusting to the sudden intensity of haemodialysis, which is conventionally prescribed three times a week [2].

It has been suggested that some patients may benefit from a gentler start to dialysis treatment. In line with this, incremental HD has been proposed as an alternative to conventional HD whereby dialysis dosage can be tailored to the individual according to their level of residual kidney function (RKF). This would allow some patients to start haemodialysis at a lower intensity (e.g. twice weekly) and gradually increase the amount of dialysis they receive as their natural kidney function declines [3]. To achieve this, dialysis and RKF clearance are usually combined into a composite measure, and dialysis dose adjusted to ensure this total clearance remains above accepted minimum levels. Safe performance of incremental HD therefore requires frequent measurement of RKF and adjustment of dialysis prescription. Among potential benefits there are suggestions that incremental HD may help preserve both RKF and vascular access function, reduce treatment burden and even improve survival [4–7].

The Standardised Outcomes in Nephrology-Haemodialysis (SONG-HD) initiative, which aims to establish core outcomes of HD research, have listed 'dialysis-free time' as a factor that is considered 'critically important' by a large proportion of HD patients [8]. Thus, incremental HD is a treatment method that is likely to appeal to the HD population as well as having potential cost benefits for the healthcare service.

The notion of considering RKF to prescribe dialysis dosage is often used in peritoneal dialysis, which has been associated with greater RKF preservation and patient survival [9]. Thus, in recent years, research has also focused on how an

KEY LEARNING POINTS

What is already known about this subject?

- Incremental-start haemodialysis is an alternative to conventional initiation, though not widely adopted.
- Most, but not all, studies take account of residual kidney function in determining the suitability for and prescription of incremental initiation.
- Limited data are available regarding mortality, hospitalization and vascular access complications, although retrospective studies suggest possible benefit of incremental-start haemodialysis on preserving residual kidney function.

What this study adds?

- Evidence suggests no significant difference in mortality between incremental-start and conventional-start haemodialysis where residual kidney function is accounted for in determining suitability of and prescription for incremental treatment.
- There is little comparative evidence on differences in treatment-emergent adverse events and quality of life, though evidence from two small randomized controlled trials suggests that there may be a reduced risk of hospitalization in patients initiated on incremental haemodialysis.
- There are few health-economic data, though a cost benefit of incremental haemodialysis initiation has been reported.

What impact this may have on practice or policy?

- Current evidence suggests equipoise in relation to the safety of incremental and conventional-start haemodialysis in patients with sufficient residual kidney function.
- Confirmation of the safety of incremental haemodialysis initiation in a large randomized controlled study would support its widespread adoption, particularly given the apparent cost benefit.

incremental approach to dialysis may be applied to the HD population. Whilst several observational and experimental studies have been conducted, previous reviews have only included observational data and there is currently contrasting evidence as to whether incremental HD is a safe and effective method in relation to standard care. This systematic review is relevant due to the recent publication of randomized controlled trial (RCT) evidence. This review aimed to evaluate available evidence as to whether incremental HD is a safe and efficacious alternative to conventional HD. In doing so, it also aimed to highlight any gaps in evidence that could support future developments in care delivery aligned to the priorities of patients [8].

The objectives of this study were to evaluate the safety, efficacy and cost-effectiveness of incremental HD in comparison with conventional HD methods.

MATERIALS AND METHODS

Protocol and registration

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. The study protocol was developed and methods were pre-registered with an international prospective register of systematic reviews (PROSPERO: CRD42022309971).

Search strategy

Studies were identified through the MEDLINE, EMBASE, CINAHL and Cochrane Library databases. Additionally, lateral search techniques were used to check the reference lists of included studies and previous scoping and systematic reviews to identify any additional primary studies. The initial search was conducted on 27 February 2022 and was re-run on 10 August 2022, to ensure eligible studies published during this period were included in the review.

Key words for the electronic database search were developed using the PICO Framework and generated around the concepts of 'Incremental Haemodialysis' (e.g. 'incremental dialysis' or 'incremental haemodialysis' or 'once weekly haemodialysis' or 'twice weekly haemodialysis') and 'Safety Outcomes' (e.g. 'mortality' or 'fatality' or 'survival' or 'death' or 'adverse event' or 'serious adverse event' or 'complication' or 'safety'). The search was limited to published articles written in the English language and those involving human participants. The full search strategy can be found in Supplementary Materials S1.

Study selection and data extraction

To be eligible for inclusion in the review, studies needed to compare incremental HD (defined as HD prescribed either fewer than three times a week or three times a week for a duration of <3.5 h per session) with conventional HD in adult patients receiving treatment for ESKD. The primary outcome of interest was mortality. Secondary outcomes included treatment-emergent adverse events (i.e. hospitalization, vascular access complications, fluid overload, hyperkalaemia and acidosis), rate of loss of RKF, symptom scores, quality of life and health-economic analysis. Studies needed to address the primary outcome for inclusion in the review. A full overview of the inclusion and exclusion criteria can be found in Table 1.

Search results were extracted into the systematic review tool Rayyan [11] and duplicate articles were removed. The first author (E.C.) screened the title and abstract of each article and removed those that did not meet the eligibility criteria. Remaining articles underwent a full-text screen to determine

Table 1: Inclusion and exclusion criteria.

	Inclusion	Exclusion
Population	Adults (>18 years old) receiving haemodialysis treatment for ESKD	Children (<18 years old) Patients receiving peritoneal dialysis treatment for ESKD
Intervention	Incremental haemodialysis	Incremental peritoneal dialysis Palliative care dialysis
Comparator	Conventional haemodialysis	Conventional peritoneal dialysis Incremental peritoneal dialysis
Outcome	Mortality	Studies that do not report mortality data for incremental and conventional haemodialysis.
Study design	Observational studies Experimental studies (including feasibility studies)	Case reports Case series Qualitative studies

their eligibility for inclusion in the review. A subsection of articles (20%) were independently assessed by two authors (E.V. and K.F.) and any conflicts were discussed and resolved within the research team.

Data extraction was conducted by a single author (E.C.) and at least 20% checked by second authors (E.V. and K.F.). The data extracted included study characteristics (e.g. study title, study authors, year of publication, country of origin, study design sample size), participant characteristics (e.g. age, sex, ethnicity, primary cause of ESKD, comorbidities, levels of RKF, urine volume), intervention characteristics (e.g. frequency and duration of dialysis sessions), mortality data (e.g. numbers of deaths, risk estimates, significance values) and where reported, data pertaining to secondary outcomes of interest.

Risk of bias assessment

The quality of observational and non-randomized studies were assessed using the Newcastle-Ottawa Scale (NOS) [12] which assesses the risk of bias across three main domains: (i) selection of the study groups, (ii) comparability of the study groups and (iii) ascertainment of the outcome of interest. Each study received a score between 0 and 9, with lower scores indicating a greater risk of bias.

The quality of randomized studies was assessed using the revised Cochrane risk of bias tool for randomized trials (RoB-2) [13]. The RoB-2 tool assess bias across five domains: (i) bias arising from the randomization process, (ii) bias due to deviations from intended interventions, (iii) bias due to missing outcome data, (iv) bias in measurement of the outcomes and (v) bias in the selection of the reported results. For each domain, the studies were categorized as either 'high risk of bias', 'some concerns' or 'low risk of bias' and, using the algorithm provided, a judgement as to the overall risk of bias for each study was made.

Data synthesis and statistical analysis

Study characteristics were summarized narratively. The primary outcome of interest for this systematic review was mortality. Risk estimates [relative risk (RR) and hazard ratio (HR)] and 95% confidence intervals (95% CIs) for mortality were extracted and included in a random-effects meta-analysis. Results are presented as HRs, despite relative risk estimates also being included in the model. Different variations of the analysis were performed by removing the studies that did not report HR and removing studies whereby patients may not have had sufficient renal function to support an incremental regimen (i.e. receiving less frequent dialysis as a result of socio-economic pressures). Hospitalization data from the two RCTs were combined in a random-effects meta-analysis. Heterogeneity was measured using the I^2 statistic. I^2 values of 25%, 50% and 75% were considered the cut-off for 'low heterogeneity', 'moderate heterogeneity' and 'high heterogeneity', respectively, as proposed by Higgins *et al.* [14]. Analyses were performed using Review Manager, Version 5.4 (RevMan 5) [15] and STATA, Version 17 [16]. For the other outcomes, data were either too limited or too heterogenous to justify a meta-analysis, so results were summarized narratively.

RESULTS

Study selection

A total of 644 records were identified. A PRISMA flow diagram outlining the full study selection process can be found in Fig. 1. Full-text screening was performed on 51 articles. Of those, 11 were excluded due to being conference abstracts, eight were excluded because they did not include data pertaining to the primary outcome, two were excluded for including participants under 18 years old, two had no comparator group, one was a case series and one reported on the same dataset as another included article (most recent paper retained). Overall, a total of 26 studies were identified for inclusion in the review [4, 6, 17–40].

Study characteristics

Of the 26 included studies, 22 were observational cohort studies [4, 6, 19–30, 32–37, 39, 40], two were RCTs [31, 38], one was a non-RCT [18] and one employed a pre-post study design [17]. Ten studies were performed in Europe [4, 6, 18, 19, 22, 25, 28, 36, 37, 38], nine in Asia [17, 21, 24, 26, 27, 30, 34, 35, 40], five in North America [23, 29, 31–33], one in North Africa [20] and one in Oceania [39]. The majority of studies ($n = 16$) were multicentre studies [18, 22–24, 26, 28, 29, 31–36, 38–40], including those utilizing national cohort data.

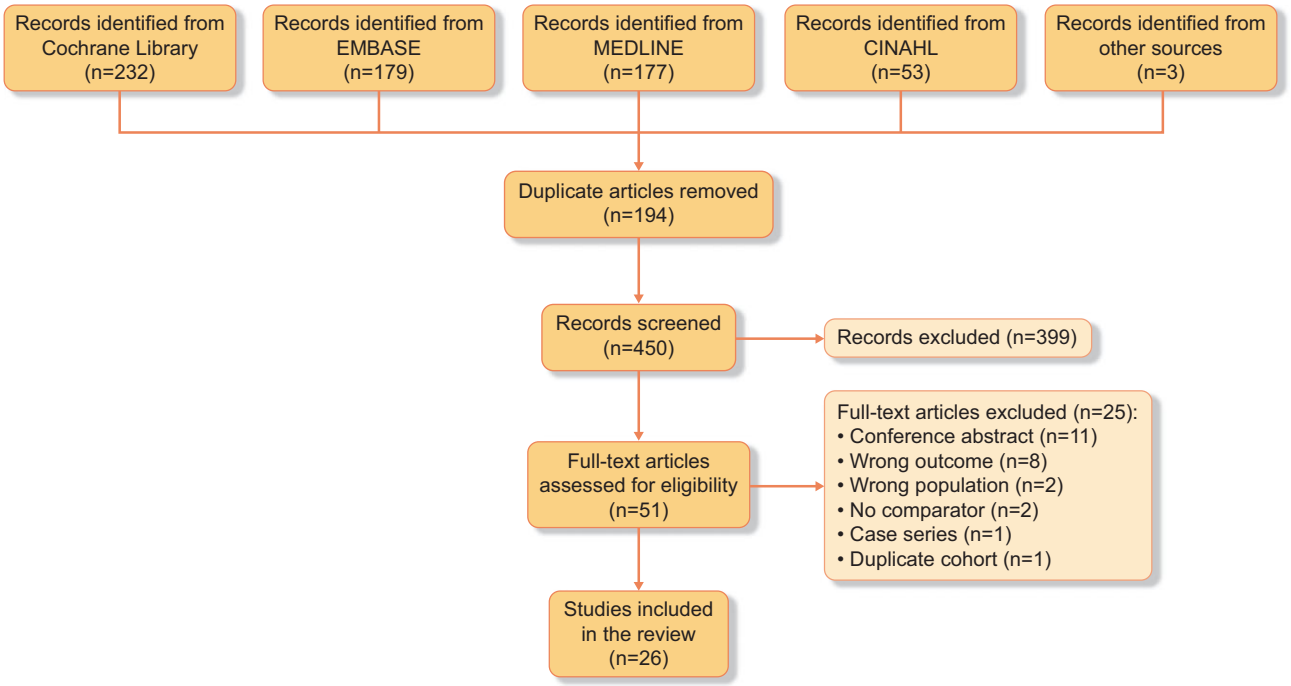

Figure 1: Study selection PRISMA flow diagram.

Sample size ranged from 48 to 50 596 participants, with the total number of participants across all studies being 101 476. Mean age of participants ranged from 54 to 69 years old in the incremental group and 53 to 68 years old in the conventional group. The proportion of male participants ranged from 43% to 70% and 39% to 78% in the incremental and conventional groups, respectively. Full details of participant characteristics can be found in Table 2.

All studies included in the review defined conventional HD as a prescription of at least three sessions of HD per week, with two studies also including patients receiving more than three sessions per week [37, 39]. In 19 studies, incremental HD referred to a prescription of two HD session per week [4, 6, 17, 20, 22–28, 30–35, 38, 40]. Six studies defined incremental dialysis as receiving either one or two sessions [19, 21, 29, 36, 37, 39], and in Caria *et al.* [18], the intervention group received one session of HD per week in combination with a very low protein diet.

In the majority of studies (n = 18) the decision to initiate patients on incremental HD was determined by clinical parameters and in circumstances whereby it was deemed appropriate by the treating physician [4, 6, 17–19, 21–25, 28, 29, 31, 33, 37–40]. In eight studies, less frequent dialysis was prescribed for socio-economic reasons such as the financial limitations or insurance coverage of patients or the lack of available of dialysis services [20, 26, 27, 30, 32, 34–36].

Risk of bias assessment

The quality of the non-randomized and observational studies included in the review ranged from moderate to high quality (NOS scores ranged from 5 to 8; see Supplementary Materials S2). Both RCTs [31, 38] had a 'low' risk of bias (see Supplementary Materials S3). Risk of bias for all articles was assessed by the first author, with any uncertainty being discussed within the research team.

Mortality

Twenty-six studies compared mortality between incremental and conventional HD. Of these, 18 studies had appropriate risk estimate data (HR and RR) and were included in a meta-analysis [6, 21, 22, 24–26, 29–40]. We found no significant difference in mortality between the incremental and conventional HD regimens (HR = 0.99; 95% CI 0.80–1.24; I^2 = 82%; Fig. 2). These results remained the same both when only including the articles reporting HRs (HR = 0.94; 95% CI 0.79–1.31), and when we removed studies in which the decision to initiate patients on incremental dialysis was determined by socio-economic factors rather than clinical or laboratory data (HR = 0.90; 95% CI 0.77–1.06), although heterogeneity reduced (59% and 51%, respectively).

Treatment-emergent adverse events

Hospitalization

Thirteen studies examined the impact of incremental versus conventional HD on hospitalization [4, 18, 21, 24, 25, 28, 30–32, 34, 37, 38, 40]. Of the observational studies, seven found no significant difference in hospitalization between the two groups [21, 24, 28, 30, 34, 37, 40], two found hospitalization rates to be significantly lower in the incremental group [4, 25] and one suggested incremental HD posed an increased risk of hospitalization [32].

Results from the non-RCT conducted by Caria *et al.* [18] suggest that once-weekly HD, in combination with strict

Table 2: Participants' characteristics.

Author (year), country of origin [Ref]	Study design	HD regimen	Number of participants	Mean age (years)	Male gender (%)	Top three causes of ESKD (%)	Measurement of RKF	Baseline RKF	Baseline urine volume (mL/day)
Aoun (2022), Lebanon [17]	Pre–post	Incremental	19	76[a]	57.9	NR	NR	NR	NR
		Conventional	57	70[a]	61.4	NR		NR	NR
Caria (2014), Italy [18]	Non-RCT	Incremental	38	64.5 ± 13.2	65.8	NR	GFR (mL/min/1.73 m^2 BSA)	7.8 ± 1.9	1983 ± 651
		Conventional	30	65.2 ± 11.0	63.3	NR		9.2 ± 4.2	1472.6 ± 433
Casino (2022), Italy [19]	Observational	Incremental	163	66.91 ± 14.63	64.4	DN: 19.6 HN: 28.2 GN: 19.0 Other/unknown: 33.2	KRU (mL/min/1.73m^2)	4.63 ± 1.42	1875 ± 659
		Conventional	39	62.15 ± 16.96	38.5	DN: 25.6 HN: 15.3 GN: 23.0 Other/unknown: 36.1		3.76 ± 1.94	1357 ± 816
Chaker (2020), Tunisia [20]	Observational	Incremental	30	53.9 ± 20.0	NR	NR	NR	NR	NR
		Conventional	58	58.1 ± 16.4	NR	NR		NR	NR
Chen (2021), China [21]	Observational	Incremental	45	56.3 ± 14.3	48.9	GN: 55.6 PKD: 13.3 HN; 11.1 Other/unknown: 20.0	eGFR (mL/min/1.73 m^2)	6.71[a] (IQR 5.11–8.97)	1566.2 ± 533.9
		Conventional	68	61.9 ± 13.8	60.3	DN: 36.8 GN: 30.9 HN: 10.3 Other/unknown: 22.0		6.39[a] (IQR 4.72–9.45)	1129.4 ± 521.9
Davenport (2019), UK [22]	Observational	Incremental	254	63 ± 16	65	NR	NR	NR	NR
		Conventional	455	65 ± 16	62	NR		NR	NR
Fernández-Lucas (2014), Spain [4]	Observational	Incremental	70	62.2 ± 15.1	70	DN: 20.0 IN: 20.0 GN: 17.1 Other/unknown: 42.8	GFR (mL/min/1.73 m^2)	6.35 ± 2.35	1618 ± 832
		Conventional	64	62.6 ± 11.9	78	DN: 20.3 IN: 15.6 RVD: 15.6 Other/unknown: 48.4		5.22 ± 2.74	1153 ± 676
Hanson (1999), USA [23]	Observational	Incremental	296	64.5	42.9	DN: 36.5 HN: 29.4 GN: 10.1 Other/unknown: 24.0	NR	NR	NR
		Conventional	4592	60.6	52.2	DN: 39.0 HN: 29.1 GN: 10.5 Other/unknown: 21.0		NR	NR
Hwang (2016), Korea [24]	Observational	Incremental	113	61.0 ± 14.2	58.4	DN: 46 HN: 27.4 GN: 16.8 Other/unknown: 9.8	KRU (mL/min/1.73 m^2 BSA)	10.2 ± 23.9	1003 ± 595
		Conventional	137	59.7 ± 11.6	60.6	DN: 50.4 HN: 21.9 GN: 11.7 Other/unknown: 16.0		4.4 ± 14.5	630 ± 557

Table 2: Continued.

Author (year), country of origin [Ref]	Study design	HD regimen	Number of partici-pants	Mean age (years)	Male gender (%)	Top three causes of ESKD (%)	Measurement of RKF	Baseline RKF	Baseline urine volume (mL/day)
Jaques (2022), Switzerland [25]	Observational	Incremental	68	59.7 ± 16.9	67.6	DN/HN: 39.7 GN: 23.5 Other/unknown: 36.8	KRU (mL/min)	3.1 ± 2.1	1851 ± 759
		Conventional	166	62.8 ± 15.7	68.0	DN/HN: 53.3 GN: 10.9 Other/unknown: 35.8		2.2 ± 1.9	1220 ± 717
Kamal (2019), UK [6]	Observational	Incremental	154	59 ± 15	66	DN: 19.0 GN: 14.0 PKD: 10.0 Other/unknown: 57.0	KRU (mL/min)	5.3 ± 2.4	NR
		Conventional	411	62 ± 15	73	DN: 24.0 HN: 13.0 GN: 13.0 Other/unknown: 49.0		5.1 ± 2.8	NR
Lin (2012), China [26]	Observational	Incremental	1041	56.6 ± 15.3	51.1	DN: 7.6 HN: 13.2 GN: 50.4 Other/unknown: 28.8	NR	NR	NR
		Conventional	1531	58.8 ± 13.8	56.9	DN: 11.7 HN: 14.0 GN: 51.5 Other/unknown: 22.8		NR	NR
Lin (2018), China [27]	Observational	Incremental	38	61.8 ± 13.6	50.0	NR	NR	NR	NR
		Conventional	68	59.1 ± 11.8	54.4	NR		NR	NR
Lodge (2020), UK [28]	Observational	Incremental	166	65.0	64.5	DN: 30.7 HN/RVD: 16.3 GN: 12.7 Other/unknown: 40.2	NR	NR	NR
		Conventional	236	59.0	65.3	DN: 34.3 HN/RVD: 12.7 GN: 13.1 Other/unknown: 39.9		NR	NR
Mathew (2016), USA [29]	Observational	Incremental	434	64 ± 13	65	DN: 43.0 HN: 29.0 GN: 11.0 Other: 17.0	Renal urea clearance (mL/min/1.73 m^2)	5.4[a] (IQR 3.1–3)	NR
		Conventional	50 162	63 ± 13	65	DN: 49.0 HN: 28.0 GN: 8.0 Other: 14.0		3.1[a] (IQR1.8–4.8)	NR
Mukherjee (2017), India [30]	Observational	Incremental	35	54 ± 14	54	NR	NR	NR	NR
		Conventional	82	60 ± 13	61	NR		NR	NR
Murea (2021), USA [31]	RCT	Incremental	23	59.1 ± 15.0	66	DN: 35.0 GN: 4.0 Other/unknown: 61.0	Averaged renal urea and creatine clearance (mL/min/1.73 m^2)	6.1 (95% CI 4.1–8.1)	914 (95% CI 654–1174)
		Conventional	25	63.3 ± 12.8	66	DN: 52.0 Other/unknown: 48.0		7.2 (95% CI 5.3–9.1)	1424 (95% CI 976–1872)
Nieves-Anaya (2021), Mexico [32]	Observational	Incremental	44	55.0 ± 17.4	55	DN: 28.0 Hypoplasia: 49.0 PKD: 8.0 Other: 15.0	NR	NR	NR

Table 2: Continued.

Author (year), country of origin [Ref]	Study design	HD regimen	Number of participants	Mean age (years)	Male gender (%)	Top three causes of ESKD (%)	Measurement of RKF	Baseline RKF	Baseline urine volume (mL/day)
		Conventional	44	55.5 ± 14.8	66	DN: 46.0 HN: 23.0 PKD: 9.0 Other: 22.0		NR	NR
Obi (2016), USA [33]	Observational	Incremental	351	69	60	NR	Renal urea clearance (mL/min/1.73 m^2)	4.8[a] (IQR 3.2–6.7)	1150[a] (IQR 800–1650)
		Conventional	8068	68	60	NR		4.6[a] (IQR 3.2–6.5)	1150[a] (IQR 775–1650)
Panaput (2014), Thailand [34]	Observational	Incremental	504	55.6 ± 13.9	57.5	DN: 31.7 HN: 19.4 GN: 6.3 Other/unknown: 42.6	NR	NR	263.4 ± 317.2
		Conventional	169	57.8 ± 12.5	62.1	DN: 52.1 HN: 24.3 GN: 4.7 Other/unknown: 19		NR	271.9 ± 383.2
Park (2017), Korea [35]	Observational	Incremental	105	60.2 ± 13.3	58.1	DN: 42.8 HN: 12.4 GN: 18.1 Other/unknown: 26.7	eGFR (mL/min/1.73 m^2)	7.5 ± 3.4	NR
		Conventional	822	57.3 ± 14.4	62.3	DN: 60.5 HN: 13.4 GN: 14.7 Other/unknown: 11.4		7.3 ± 6.5	NR
Stankuvienė (2010), Lithuania [36]	Observational	Incremental	856	NR	NR	NR	NR	NR	NR
		Conventional	1207	53.1 ± 16.3	56.2	NR		NR	NR
Torreggiani (2022), France [37]	Observational	Incremental	90	69[a]	61.5	DN/HN: 57.1 GN: 13.2 Other: 29.7	eGFR (mL/min/1.73 m^2)	7[a] (IQR 5–9)	1500[a] (IQR 1100–2000)
		Conventional	67	67[a]	56.7	DN/HN: 49.1 GN: 15.1 Other: 35.9		6[a] (IQR 4–7)	900[a] (IQR 400–1475)
Vilar (2022), UK [38]	RCT	Incremental	29	61.4 ± 15.2	69.1	DN: 48.3 GN: 13.8 PKD: 20.7 Other: 17.1	Urea clearance (mL/min per 1.73 m^2 BSA)	4.41[a] (IQR 4.00–5.69)	NR
		Conventional	26	63.1 ± 12.3	73.1	DN: 26.9 GN: 7.7 PKD: 11.5 Other: 53.8		4.21[a] (IQR 3.65–5.17)	NR
Wolley (2019), Australia/New Zealand [39]	Observational	Incremental	850	67	54.9	NR	eGFR (mL/min/1.73 m^2)	7.59[a] (IQR 5.59–10.4)	NR
		Conventional	26 663	62	62.1	NR		6.66[a] (IQR 4.83–8.98)	NR
Yan (2018), China [40]	Observational	Incremental	123	61.3 ± 15.6	57	NR	NR	NR	NR
		Conventional	290	58.2 ± 15.1	60	NR		NR	NR

[a]Median value.

DN: diabetic nephropathy; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate; GN: glomerulonephritis; HN: hypertensive nephropathy; IN: interstitial nephropathy; IQR: interquartile range; NR: not reported; PKD: polycystic kidney disease; RVD: renal vascular disease; BSA: body surface area.

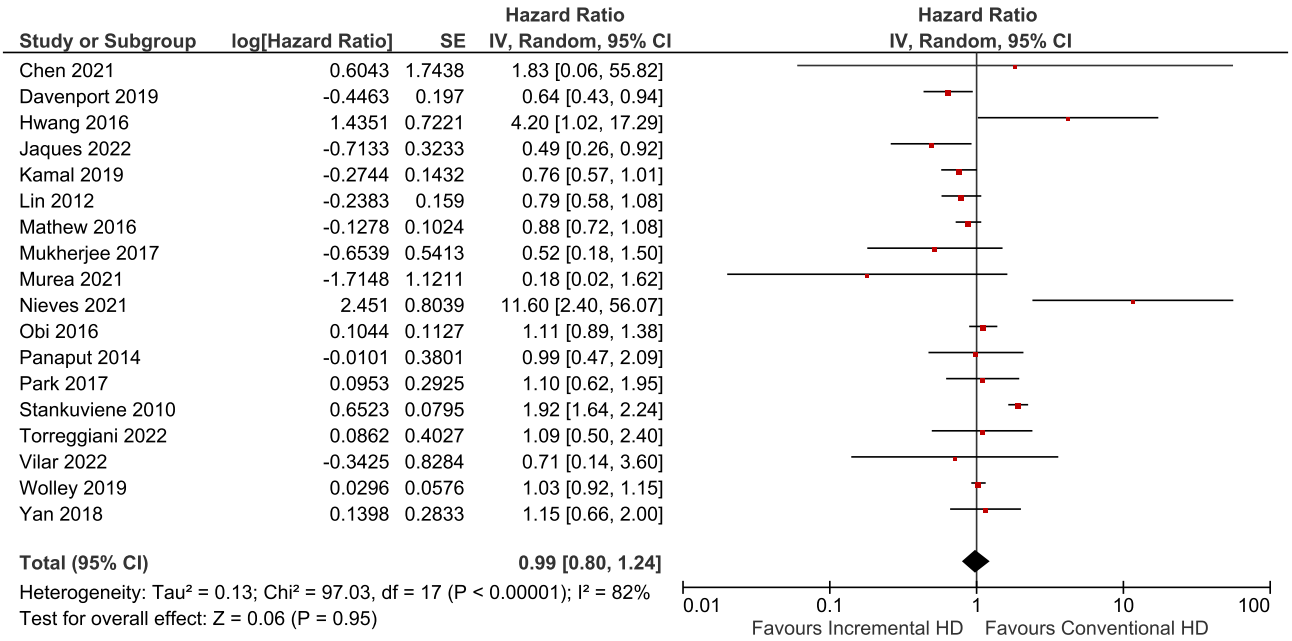

Figure 2: Mortality forest plot.

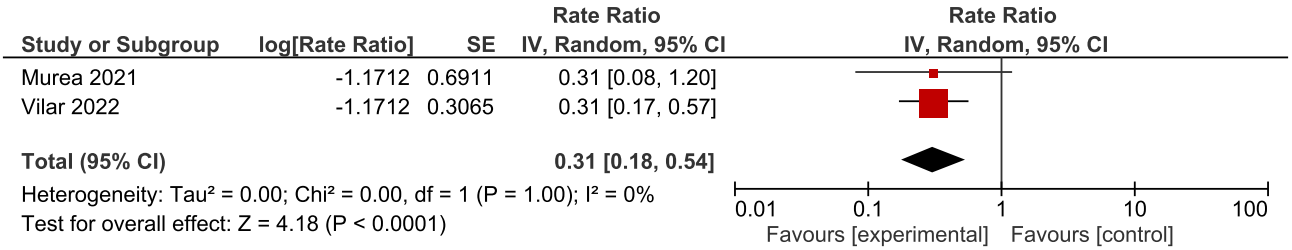

Figure 3: Hospitalization forest plot.

dietary restrictions, was associated with a lower hospitalization rate compared with conventional HD methods. Data from the two RCTs included in the review [31, 38] were included in a meta-analysis which suggests that patients receiving incremental HD have a reduced risk of hospitalization compared with those on a conventional HD regimen (RR = 0.31; 95% CI 0.18–0.54; $I^2 = 0\%$; Fig. 3).

Vascular access complications

Five studies reported data on vascular access complications [4, 21, 31, 34, 38]. Murea *et al.* [31] and Panaput *et al.* [34] both reported greater vascular access complication in the incremental arm compared with the conventional arm, although insufficient data were presented to determine whether there was a significant difference between the groups.

Fernández-Lucas *et al.* [4] and Vilar *et al.* [38] found no significant difference in vascular access complication between the incremental and conventional regimens. On the other hand, Chen *et al.* [21] suggest that patients on incremental HD have significantly less vascular access complications than patients receiving conventional HD (HR = 0.26; 95% CI 0.08–0.82; $P = .02$).

Fluid overload

Of all the included studies, only Vilar *et al.* [38] reported on fluid overload. Episodes of fluid overload did not significantly differ between the incremental and conventional HD regimens [incidence rate ratio (IRR) 0.48; 95% CI 0.08–2.85; $P = .49$].

Hyperkalaemia

Only one study compared the rate of events for hyperkalaemia between incremental and conventional HD [38]. Vilar *et al.* [38] found no significant difference in hyperkalaemia events between the two groups (IRR 0.18; 95% CI 0.02–1.60; $P = .11$).

Acidosis

Three studies monitored bicarbonate levels throughout their study periods [18, 24, 38]. Caria *et al.* [18] and Hwang *et al.* [24] both found no significant difference in bicarbonate between the incremental and conventional HD groups. In contrast, data from Vilar *et al.* [38] suggest that bicarbonate levels were significantly lower in incremental patients compared with patients receiving conventional HD.

Rate of loss of residual kidney function

Eight studies observed levels of RKF throughout the duration of the study periods [4, 6, 18, 21, 24, 31, 33, 38]. Due to the wide variability in the measures of RKF employed, data could not be combined into a meta-analysis. Nevertheless, results from the observational studies and the non-RCT suggest that

Table 3: RKF data from included studies.

Author (year) [Ref]	Study design	Number of participants (incremental/ conventional)	Measure of RKF	Observation of RKF	Results	Significant difference in favour of incremental HD?
Caria *et al.* (2014) [18]	Non-RCT	38/30	GFR	Rate of loss (mL/min/month)	Rate of loss lower in the I-HD group compared to the standard HD group (−0.13 vs −1.53)	Not reported
Chen *et al.* (2021) [21]	Observational	45/68	Urine output	RKF loss (defined as a urine output <200 mL/day)	I-HD reduced the risks of RKF loss (HR = 0.33)	Yes
Fernánadez-Lucas *et al.* (2014) [4]	Observational	70/64	Urea and creatinine clearance	Rate of loss (mL/min/month)	Rate of loss lower in the I-HD group compared with the standard arm (0.2 vs 0.5; median)	Yes
Hwang *et al.* (2015) [24]	Observational	113/137	KRU	Levels of RKF at 12, 24 and 36 month follow-up (mL/min/1.73 m^2 BSA)	I-HD patients had greater RKF at 12, 24 and 36 month follow-up compared with the standard group	Yes
Kamal *et al.* (2019) [6]	Observational	154/411	KRU	Rate of loss	Rate of loss lower in the I-HD group compared with the standard arm	Yes
Murea *et al.* (2021) [31]	RCT	23/25	UV and averaged renal urea and creatinine clearance	RKF parameters at 6, 12 and 24 week follow-up	I-HD patients had lower declines in UV and averaged urea and creatinine clearance at week 24 compared with the standard group	Not reported
Obi *et al.* (2016) [33]	Observational	351/8068	KRU and UV	Rate of loss	Rate of loss of KRU and UV was lower for the I-HD group compared with the standard arm	Yes
Vilar *et al.* (2022) [38]	RCT	29/26	KRU	Rate of loss (mL/min/1.73 m^2/month)	No significant difference between the rate of loss in the I-HD group compared with the standard group	No

GFR: glomerular filtration rate; I-HD: incremental haemodialysis; KRU: residual renal urea clearance; RKF: residual kidney function; UV: urine volume; BSA: body surface area.

incremental HD may better preserve RKF than conventional HD methods, although these findings were not replicated in the two RCTs that have been conducted so far (see Table 3).

Symptoms scores

No studies reported data for symptom scores.

Quality of life

Health-related quality of life was assessed in two studies [35, 38]. Vilar *et al.* [38] found no significant difference in quality of life (measured using the EQ-5D-5 L) between the two groups at baseline, or at 6-month or 12-month follow-up. Similarly, Park *et al.* [35] found no significant difference in KDQOL-SF scores between the incremental and conventional HD group at 12 months.

Health economics

Four studies considered the health-economic impact of implementing incremental HD as a treatment method for ESKD [18, 19, 37, 38]. Torreggiani *et al.* [37] reported that 5419 of 12 199 sessions were 'saved' by providing patients with non-conventional HD regimens rather than thrice weekly dialysis. This 44% reduction in sessions resulted in an estimated cost-saving of over €1 896 000 in dialysis costs and €270 950 in transportation. Similarly, Casino *et al.* [19] found that initiating patients on incremental HD saved 22 045 (49.5%) of the 47 988 sessions, with an estimated cost reduction of €3.64 million.

Caria *et al.* [18] estimated that the costs of incremental HD could potentially be >60% less than the cost of conventional HD, due to anticipated reductions in hospitalizations and medication use as well as reduced HD sessions. Vilar *et al.* [38] conducted a comprehensive health-economic analysis and concluded that, despite increased costs for medication (e.g. anti-hypertensives, phosphate binders, erythrocyte stimulating agent) and patient monitoring (e.g. urine collection), incremental HD cost less than conventional HD methods (within-trial median annual costs: £19 875 versus £26 125, respectively). Cost savings were made as a result of reduced transport fees, fewer HD sessions and reduced costs from adverse events.

Publication bias

Publication biases were assessed by examining funnel plot asymmetry (see Fig. 4) and using Egger's regression test. There was no evidence of publication bias across the studies reporting mortality data ($P = .68$).

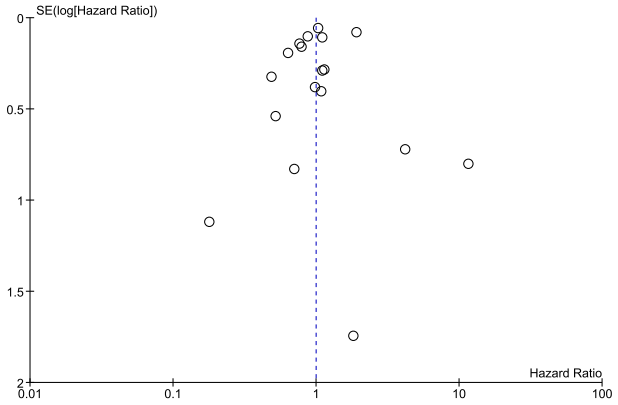

Figure 4: Publication bias funnel plot.

DISCUSSION

This systematic review aimed to evaluate the safety, efficacy and cost-effectiveness of incremental HD in comparison with conventional HD methods. Data were pooled from across 26 studies, the majority of which were observational cohort studies. Findings from our meta-analysis showed no significant difference in mortality between incremental and conventional HD, supporting the notion that incremental HD is a safe and appropriate alternative to standard care. Furthermore, data from the two RCTs included in the review [31, 38] suggest that incremental HD can reduce the risk of hospitalization by 69%. Several observational studies also highlighted that incremental HD may be better at preserving RKF than conventional HD methods. Residual kidney function has been identified as an important factor associated with improved outcomes for patients receiving HD, including being a strong predictor of patient survival [41].

Whilst the findings reported in the current review suggest incremental HD may be a more favourable treatment method for the preservation of RKF, it is important to note that this finding has not been replicated in the limited number of RCTs conducted so far [31, 38]. In addition, the wide variability in the way RKF was assessed across studies prevented us from combining the data for meta-analysis, thus caution should be exercised when making inferences based on these findings. Indeed, conducting this systematic review has demonstrated a need for a standardized measure of RKF to allow for greater interpretation and comparison between studies assessing this outcome in the future.

Too few studies have reported data on other HD-related treatment-emergent adverse events to assess the impact of dialysis frequency on these outcomes. Nevertheless, findings from the RCT conducted by Vilar *et al.* [38] suggest that there was no increased risk of fluid overload or hyperkalaemia in incremental HD patients compared with those receiving conventional HD. Findings from Vilar *et al.* [38] did suggest, however, that patients receiving incremental HD may experience a decrease in bicarbonate levels, highlighting the potential need to supplement bicarbonate in these patients.

All of the studies included in the review had a moderate to low risk of bias, implying strength in the validity and reliability of the results obtained from each study. Despite this, it is important to consider the circumstances in which patients were prescribed incremental HD before drawing conclusions about the safety and efficacy of incremental methods. For example, in several studies in this review, some patients did not have fair or equal access to dialysis treatment and were initiated on less frequent HD as a result of financial pressures or a lack of adequate healthcare services. The Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Haemodialysis [42] state that twice-weekly HD is not appropriate for patients with residual kidney urea clearance <2 mL/min/1.73 m^2. As such, the decision to reduce frequency of dialysis in patients who lack such levels of RKF may result in underdialysis and have a substantial negative impact on patient outcomes.

Findings from the current review suggest that, despite incremental HD providing patients with more dialysis-free time (a factor considered 'critically important' by HD patients) [8], there was no significant difference in health-related quality of life between the incremental and conventional HD groups. Whilst tools such as the KDQOL-SF assess quality of life in patients with kidney diseases, very few items have focused on the specific experiences associated with HD treatment. Thus, this systematic review has demonstrated a potential need for more sensitive tools to measure quality of life in HD patients.

Incremental HD may also be a cost-effective alternative to conventional HD. In the current review, four studies highlighted the benefit of providing fewer HD sessions on reducing treatment costs [18, 19, 37, 38], including those associated with treatment-emergent adverse events. Whilst there is potential for increased costs to incur from enhanced patient monitoring and greater medication usage, incremental HD was still a substantially cheaper treatment option compared with standard care.

One limitation of this systematic review is the non-inclusion of studies that did not report on the primary outcome of mortality, the main proxy for safety. This may have introduced bias, with some studies potentially being overlooked despite reporting other outcomes associated with the safety and efficacy of incremental HD. These outcomes may warrant review in their own right. Other limitations include the exclusion of publications in languages other than English and non-peer-reviewed literature.

Many dialysis professionals are understandably hesitant to sanction reductions in dialysis frequency, fearing underdialysis. Further evidence of the safety and efficacy of incremental approaches would help to allay such fears. RCTs are considered the gold standard method for providing such evidence but present practical difficulties, including recruitment and retention to studies which, in this case, require significant alterations to dialysis regimes and regular monitoring of RKF which is not common practice in most dialysis units. Alternative approaches include pragmatic trials focused on providing evidence of safety and efficacy within normal practice settings, patient preference trials, prospective comparative cohort studies with propensity matching and registry follow-up, and effectiveness–implementation hybrid trials [43]. Having said that both the small RCTs reported in

this review advocate and provide evidence of feasibility for larger RCTs.

Overall, the findings from this review lend support to the safety of incremental HD as a treatment for ESKD and highlight the potential for this method to be implemented as an alternative to standard care in patients with sufficient RKF. Whilst results are promising, further RCTs need to be conducted to fully determine the safety, efficacy, impact of quality of life and cost-effectiveness of incremental HD in comparison with conventional dialysis regimens.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

FUNDING

None declared.

AUTHORS' CONTRIBUTIONS

E.V. and K.F. conceptualized the study. E.C., S.S., E.V. and K.F. designed the systematic review. Data collection, extraction and analysis was conducted by E.C., E.V. and K.F. Data were interpreted by E.C., S.S., E.V. and K.F. All authors contributed to and approved the final manuscript.

DATA AVAILABILITY STATEMENT

All relevant data are included within the manuscript.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this manuscript have not previously been published in whole or part.

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Received: 7.7.2022; Editorial decision: 9.9.2022