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Original Investigation

Convective Versus Diffusive Dialysis Therapies for Chronic Kidney Failure: An Updated Systematic Review of Randomized Controlled Trials

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Background: Convective dialysis therapies (hemofiltration or hemodiafiltration) are associated with lower mortality compared to hemodialysis in observational studies. A previous meta-analysis of randomized trials comparing convective modalities with hemodialysis in 2006 was inconclusive due to insufficient data. Additional randomized trials recently have reported conflicting results.

Study Design: Systematic review and meta-analysis of randomized trials to February 27, 2013.

Setting & Population: Patients with chronic kidney failure treated by hemodialysis, hemodiafiltration, hemofiltration, or biofiltration.

Selection Criteria for Studies: Randomized controlled trials.

Intervention: Convective therapies (hemodiafiltration, hemofiltration, and acetate-free biofiltration) compared with hemodialysis.

Outcomes: All-cause and cardiovascular mortality, nonfatal cardiovascular events, hospitalization, change in dialysis modality, health-related quality of life, adverse events, blood pressure, and clearances of urea and β_2-microglobulin.

Results: 35 trials (4,039 participants) were included. In low-quality evidence, convective dialysis had little or no effect on all-cause mortality (relative risk [RR], 0.87; 95% CI, 0.70-1.07) and may reduce cardiovascular mortality (RR, 0.75; 95% CI, 0.58-0.97) and hypotension (RR, 0.72; 95% CI, 0.66-0.80) during dialysis, but had uncertain effects on nonfatal cardiovascular events (RR, 1.14; 95% CI, 0.85-1.52) and hospitalization (RR, 1.21; 95% CI, 0.12-12.05). Adverse events were not reported systematically and health-related quality-of-life outcomes were sparse. Convective therapies reduced predialysis levels of β_2-microglobulin (mean difference, −5.77 [95% CI, −10.97 to −0.56] mg/dL) and increased dialysis dose (Kt/V_{urea} mean difference, 0.10; 95% CI, 0.02-0.19), but these effects were very heterogeneous. Sensitivity analyses limited to trials comparing hemodiafiltration with hemodialysis showed similar results.

Limitations: Studies had important risks of bias leading to low confidence in the summary estimates and generally were limited to patients who had adequate dialysis vascular access.

Conclusions: Treatment effects of convective dialysis are unreliable due to limitations in trial methods and reporting. Convective dialysis may reduce cardiovascular but not all-cause mortality, and effects on nonfatal cardiovascular events and hospitalization are inconclusive.

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INDEX WORDS: End-stage kidney disease; systematic review; meta-analysis; dialysis; hemodiafiltration.

Editorial, p. 888

Despite sufficient removal of unwanted accumulated solutes and water by dialysis to avoid acute life-threatening complications, long-term dialysis patients report markedly impaired quality of life and severe symptoms.[1,2] In addition, survival remains poor; 10%-20% of adults treated with long-term dialysis die each year.[3] While conventional hemodialysis clears smaller water-soluble metabolites efficiently by diffusion, poor outcomes might be explained in part by

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inadequate removal of middle- and larger size waste products of metabolism, which are implicated in the pathogenesis of atherosclerosis.[4] To support this hypothesis, higher circulating levels of middle molecules (such as vitamin B_{12} or β_2-microglobulin) in dialysis patients are associated with cardiovascular and infection-related mortality in nonrandomized studies.[5] Removal of larger metabolites by newer hemodialysis strategies is a potential approach to improve dialysis outcomes.[6,7]

Convective dialysis therapies (hemofiltration [HF], hemodiafiltration [HDF], or acetate-free biofiltration) clear water across the dialysis membrane using positive pressure to drag small, middle, and larger size protein-bound solutes into the dialysate waste more efficiently than hemodialysis. In uncontrolled studies, convective dialysis therapies were shown to lower mortality.[8-10] In addition, HDF is associated with reduced intradialytic hypotension,[9] and enhanced biocompatibility of ultrapure dialysate fluids used in convective technologies may reduce inflammation, oxidative stress, and infection.[11,12]

In our previous meta-analysis of 17 randomized trials (600 participants) comparing convective with diffusive dialysis,[13] convective modalities had uncertain effects on mortality in low-quality evidence, and data for adverse events were sparse. Since 2006, an additional 18 randomized trials (3,439 participants) have been published, but results have been inconsistent and consequently there has been variable uptake of HDF and HF into clinical practice. For instance, in 2010, the proportion of incident dialysis patients treated with HDF in Europe varied between 0.7% in Finland and 18.9% in the Catalonian region of Spain.[14] In Australia and New Zealand, the proportions of dialysis patients treated with hemodiafiltration in 2011 were 21.5% and 10.9%, respectively.[15] The European Best Practice Guidelines, published in 2007, suggested that HDF is a suitable treatment strategy to delay complications of end-stage kidney disease and that exchange volumes should be as high as possible.[16] Given the apparent uncertainty in the clinical community regarding the place of convective dialysis therapies, variability in use, and recent trial data, the aim of our study was to summarize the treatment benefits and harms for convective versus diffusive dialysis therapies for people with end-stage kidney disease.

METHODS

Protocol

We have conducted an updated systematic review and meta-analysis according to a previously published protocol[17] and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[18]

Inclusion Criteria

We included published and unpublished data from randomized controlled trials (RCTs) and quasi-RCTs that evaluated convective dialysis therapies (HDF, HF, or acetate-free biofiltration) compared with diffusive dialysis therapy (hemodialysis) for the treatment of end-stage kidney disease.

Search Strategies

In the initial published review, we searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the American College of Physicians database, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) electronically without language restriction through May 2006.[13] In this review update, we searched the Cochrane Renal Group's specialized register (through February 27, 2013). The specialized register contains studies identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group, as well as hand-searched journals, conference proceedings, and current awareness alerts. Details of search terms are provided in table *a* of Item S1 (provided as online supplementary material). Two independent reviewers (I.N. and V.S.) screened the electronic search results by title and abstract to identify potentially relevant RCTs, which then were examined in full text detail to identify eligible RCTs for inclusion in the review (Fig 1). Disagreements in the screening process were resolved by discussion.

Data Extraction and Risk of Bias

Two independent reviewers (I.N. and V.S.) extracted data for the following outcomes: all-cause mortality, cardiovascular mortality, nonfatal cardiovascular events, hospitalization, change of dialysis modality, hypotension, predialysis systolic and diastolic blood pressure, predialysis serum β_2-microglobulin levels, and Kt/V. Risk of bias was assessed using standard domains.[19] We considered the RCT to be at high risk of selective outcome reporting when investigators did not report data for all-cause and cardiovascular mortality and adverse events or patient symptoms. We contacted investigators of included trials to obtain any missing or incomplete data for key outcomes.

Statistical Analysis

We summarized treatment effects using random-effects meta-analysis and expressed results as relative risks (RRs) or rate ratios for binary outcomes (mortality, rate of nonfatal cardiovascular events, rate of hospitalization, change in dialysis modality, and rate of hypotension during dialysis) or mean difference for continuous outcomes (serum β_2-microglobulin, blood pressure, and Kt/V) together with 95% confidence intervals (CIs). We used the method suggested by Knapp and Hartung[20] to generate CIs for summary treatment effect estimates. We assessed for heterogeneity in treatment estimates using the Cochran Q test and I^2 statistic. Planned metaregression analyses were conducted to explore potential sources of heterogeneity in treatment estimates for mortality and change in dialysis modality considering the following trial-level characteristics: hemodialysis membrane flux, age, duration of follow-up, and convection volume. Metaregression analyses to explore the effects of trial-level characteristics on other treatment estimates for clinical outcomes or the effect of residual kidney function on treatment effectiveness were not performed because statistical heterogeneity in summary treatment estimates was not observed or insufficient data were available. We conducted sensitivity analyses for mortality, nonfatal cardiovascular events, hospitalization, and change in dialysis modality, limiting data to studies evaluating HDF. We were not able to limit analyses to studies at low risk of bias from allocation concealment or selective reporting of outcomes because insufficient studies at low risk for these quality domains provided extractable data.

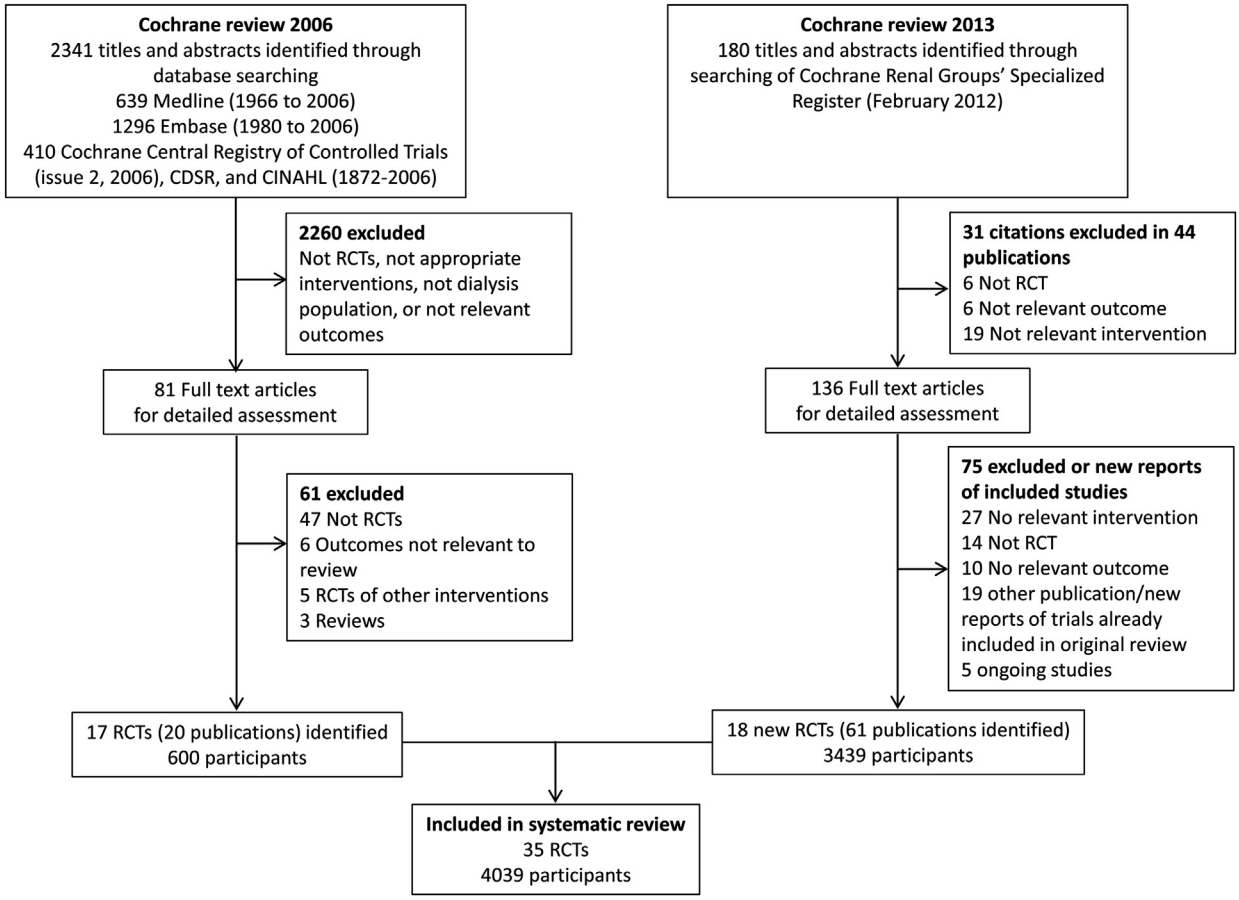

Figure 1. Flow chart for process of screening electronic databases and inclusion of trials in the review. Abbreviation: RCT, randomized controlled trial.

We rated the quality of the evidence using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system for the clinical outcomes of quality of all-cause and cardiovascular mortality, nonfatal cardiovascular events, and health-related quality of life.[21] To assess for potential bias from small-study effects, we constructed funnel plots and formally assessed for plot asymmetry by using the Egger regression test.[22] To estimate the absolute numbers of participants who had mortality or nonfatal cardiovascular events avoided or incurred, we used the risk estimate and 95% CI obtained from the corresponding meta-analysis together with the absolute population risk derived from previously published registry data[3] or from the control group of available RCTs. We did analyses using Stata, release 12 (StataCorp LP).

RESULTS

Literature Search

In the initial Cochrane review to May 2006,[13] 17 RCTs (600 participants) that compared convective with diffusive dialysis therapy were included. Electronic searching in February 2013 identified 180 additional citations, of which 44 citations were excluded on initial screening (Fig 1). Of the 136 citations reviewed in detail, 75 were excluded because they were additional reports of studies included in the previous review, were not an RCT, did not include eligible appropriate interventions, or were ongoing. We included an additional 18 trials, bringing the total number of trials in the updated review to 35 (4,039 participants).[23-57] We received additional unpublished data from the investigators of 10 trials that were considered for inclusion in meta-analyses (Item S2).[23-32]

Trial Characteristics

Table 1 describes in detail the characteristics of the 35 included trials. Table *b* of Item S1 reports details of the dialysis therapies used. We included 21 studies comprising 3,787 participants in meta-analyses.[23-27,31-46] Overall, 22 trials (3,217 participants) compared HDF with hemodialysis,[23,26-30,32,34,36-40,42,44-51] one trial (146 participants) compared HF or HDF in 2 separate arms with hemodialysis,[24] 5 trials (191 participants) compared HF with hemodialysis,[25,33,41,52,53] and 7 trials (485 participants) compared acetate-free biofiltration with hemodialysis.[31,35,43,54-57] Of the 23 trials evaluating HDF, all except 3[39,50,51] reported convection methods using fluid generated online (online HDF). Twelve trials (34%) used high-flux

Table 1. Studies Evaluating Convective Dialysis Therapies Versus HD

Study[a]	N	Intervention[b] vs Comparison	Follow-up Duration	Design	Age (y)	Male Sex	Diabetes	Dialysis Vintage (mo)	Residual Kidney Function	Dialysis Vascular Access	Primary Outcome(s)
HDF Versus HD											
Teo[50] (1987, CA)	9	HDF vs low-flux HD	4 mo	Crossover	36.5 ± 9	90%	NR	NR	NR	NR	Cardiac function
Locatelli[39] (1996, IT)	205	HDF vs low- or high-flux HD	24 mo	Parallel	53.2 ± 12.9	72.2%	5.4%	NR	"Very low"; median CCr, 0.0 mL/min	NR	Treatment tolerance, nutritional parameters, and B2M
Lornoy[49] (2000, BE)	8	Online HDF vs high-flux HD	1 dialysis session	Crossover	68 ± 60-75	NR	NR	NR	Anuric	NR	Solute clearance (B2M, BUN, Cr, and phosphorus)
Ward[45] (2000, DE)	44	Online HDF vs high-flux HD	12 mo	Parallel	61 ± 15 vs 52 ± 14	59%	21% vs 14%	47 ± 44 vs 68 ± 73	9% had average CCr of 3.1 mL/min; remainder had urine volume < 150 mL/d	Permanent blood access capable of delivering Qb > 250 mL/min	Solute removal
Wizemann[46] (2000, DE)	44	Online HDF vs low-flux HD	24 mo	Parallel	60 ± 12 vs 61 ± 11	52% vs 62%	22% vs 14%	NR	NR	NR	"Clinical impact"
Lin[38] (2001, TW)	67	Online HDF vs high-flux HD	NR	Parallel	55 ± 11 vs 53.7 ± 11.4	63% vs 62%	11% vs 14%	117.8 ± 69.1 vs 108.0 ± 52.6	Anuric	Native AV access or Gortex shunt	"Biochemical, hemodynamic, and clinical effects"
Tucillo[51] (2002, IT)	12	HDF vs HD	3 mo	Parallel	NR	NR	NR	NR	NR	NR	Phosphorus clearance
Bammens[47] (2004, DE)	14	Online HDF vs high-flux HD	0.5 mo	Crossover	66.6 ± 11.6	71%	NR	24.8 ± 37.4	50% anuric; 50% had interdialytic urine volume 737 ± 299 mL	Native AVF enabling 2-needle access and Qb > 250 mL/min	*p*-Cresol clearance
Cristofano[23] (2004, IT)	12	Online HDF vs low-flux HD	1 dialysis session	Parallel	NR	50%	NR	NR	NR	NR	Solute clearance (cystatin C, B2M, and CRP)
Selby[29] (2006, UK)	12	Online HDF vs low-flux HD	2 wk	Crossover	68 ± 11.2	83%	NR	39.5 ± 18.7	All but 1 anuric	83% native AVF, 17% tunneled internal jugular catheter	Systemic hemodynamics and troponin T
Vaslaki[44] (2006, HU)	129	Online HDF vs low-flux HD	6 mo	Crossover	62.3 ± 12.4	34.3%	24.5%	NR	37% anuric; residual diuresis 740 ± 385 mL/d	NR	CV stability and anemia management
Karamperis[48] (2007, DK)	13	Online HDF vs low-flux HD	1 dialysis session	Crossover	Mean, 49 (range, 26-76)	77%	Exclusion criterion	Mean, 46.8 (range, 3.6-216)	NR	Stable AVF	Hemodynamics
Schiffl[42] (2007, DE)	76	Online HDF vs high-flux HD	24 mo	Crossover	62 ± 10	55%	20%	Median, 26 (range, 9-280)	68% anuric at end of follow-up	Permanent blood access capable of delivering Qb > 250 mL/min	"Benefits and risks"

(Continued)

Table 1 (Cont'd). Studies Evaluating Convective Dialysis Therapies Versus HD

Study[a]	N	Intervention[b] vs Comparison	Follow-up Duration	Design	Age (y)	Male Sex	Diabetes	Dialysis Vintage (mo)	Residual Kidney Function	Dialysis Vascular Access	Primary Outcome(s)
Mandolfo[26] (2008, IT)	8	Online HDF vs high-flux HD	2 wk	Crossover	72.2 ± 4.8	63%	NR	NR	<1 mL/min	50% AVF, 50% permanent CVC	Small- and medium-molecular-weight solute removal
Locatelli[24,c] (2010, IT)	110	Online HDF vs low-flux HD	18 mo	Parallel	66.8 [54.6-74.3] vs 65.2 [58.1-70.8]	55% vs 61.4%	27.5% vs 17.1%	37.2 [18-73.2] vs 30 [14.4-108]	Diuresis > 200 mL/d exclusion criterion	Dysfunction of vascular access with Qb rate < 300 mL/min was exclusion criterion	Intradialytic hypotension
Righetti[28] (2010, IT)	24	Online HDF vs low-flux HD	6 mo	Crossover	61.4 ± 14.2	67%	NR	48.7 ± 48.5	Residual kidney function was exclusion criterion	NR	"Long-term efficacy"
Pedrini[27] (2011, IT)	69	Online HDF vs low-flux HD	6 mo	Crossover	59.6 ± 12.9	70%	Diabetes was exclusion criterion	76 (73)	16% had residual CCr of 2.34 ± 1.21 mL/min	Native or prosthetic AVF capable of Qb > 300 mL/min	Solute clearances
Grooteman[34] (2012, CONTRAST Study [multiregion])	714	Online HDF vs low-flux HD	36 mo	Parallel	64.1 ± 14.0 vs 64.0 ± 13.4	65% vs 60%	22% vs 26%	36 ± 33.6 vs 33.6 ± 34.8	Residual kidney function in 52% of HDF, 53% of HD	79% AVF, 14% graft, 7% central catheter	All-cause mortality
Ohtake[40] (2012, JP)	22	Online HDF vs high-flux HD	12 mo	Parallel	58.6 ± 11.3 vs 62.4 ± 7.7	77% vs 55%	NR	64.5 ± 38.2 vs 58.8 ± 64.4	NR	Functional failure of AVF with <5 mL/kg/min Qb was exclusion criterion	Atherosclerotic and cardiac functional markers
Stefansson[30] (2012, SE)	25	Online HDF vs low-flux HD	2 mo	Crossover	60.6 ± 13.6	70%	NR	NR	NR	40% AVF, 60% CVC	Dialysis-related symptoms, complications, and QoL, plus use of heparin and anemia management
Kantartzi[37] (2013, GR)	24	Online HDF vs low-flux HD	3 mo	Crossover	62 ± 13.34	21%	4%	3.67 ± 2.78 vs 2.53 ± 1.71	Anuric	Native AVF or synthetic graft	Health-related QoL
Maduell[36] (2013, ESHOL Study [ES])	906	Online HDF vs low- or high-flux HD	22.9 ± 13.2 mo	Parallel	64.5 ± 14.4 vs 66.3 ± 14.3	69.5% vs 64.2%	22.8% vs 27.1%	28.5 [12-60] vs 27.0 [12-58]	NR	86.0% AVF, 3.8% graft, 10.3% catheter	All-cause mortality
Ok[32] (2013; Turkish Online HDF Study [TR])	782	Online HDF vs high-flux HD	24 mo	Parallel	56.4 ± 13 vs 56.5 ± 14.9	59.6% vs 58.1%	33.2% vs 36.3%	58.7 ± 46.1 vs 57.1 ± 43.2	Presence of urine output > 250 mL/d was exclusion criterion	Insufficient vascular access was exclusion criterion; 95.5% AVF	Composite of death from any cause and nonfatal CV events
HF Versus HD											
Schiffl[53] (1992, DE)	30	HF vs low- or high flux HD	48 mo	Parallel	Range, 28-69	40%	NR	NR	NR	NR	B2M removal
Fox & Henderson[52] (1993, US)	9	Online HF vs high-flux HD	1 dialysis session	Crossover	63 ± 12	100%	11%	54 ± 72	NR	NR	Hemodynamic response

Beerenhout[33] (2005, NL)	40	HF vs low-flux HD	12 mo	Parallel	59 ± 13 vs 58 ± 12	80% vs 52%	15% vs 20%	24 ± 24 vs 33 ± 19	NR	"Adequate vascular access" was inclusion criterion	CV and nutritional parameters, QoL, and uremic toxicity profile
Santoro[25] (2008, IT)	64	HF vs high-flux HD	36 mo	Parallel	69 ± 11 vs 66.4 ± 10.2	44% vs 56%	13% vs 0%	70.3 ± 11.3 vs 59.9 ± 10.9	< 2 mL/min/1.73 m^2 was inclusion criterion	Vascular access dysfunction was exclusion criterion	All-cause mortality
Locatelli[24] (2010, IT)	106[c]	HF vs low-flux HD	18 mo	Parallel	71.3 [60.6-74.4] vs 65.2 [58.1-70.8]	53% vs 61.4%	8.3% vs 17.1%	49.2 [16.8-92.3] vs 30 [14.4-108]	Diuresis > 200 mL/d exclusion criterion	Dysfunction of vascular access with Qb rate < 300 mL/min was exclusion criterion	Intradialytic hypotension
Alvestrand[41] (2011, ProFil Study [Scandinavia])	34	HF vs low-flux HD	48 mo	Parallel	62 ± 11 vs 64 ± 13	75% vs 72%	22% vs 25%	NR	2.9 ± 1.9 vs 1.6 ± 1.6 mL/min	Expected need for CVC > 3 mo was exclusion criterion	Left ventricular hypertrophy
AFB Versus HD											
Noris[55] (1998, IT)	5	AFB vs high-flux HD	1 wk	Crossover	57.6 ± 9.2	60%	NR	NR	NR	AVF	Nitric oxide synthesis, IL-1β, and hemodynamic parameters
Verzetti[57] (1998, IT)	41	AFB vs HD	6 mo	Crossover	60 ± 10	59%	100%	25 ± 22	NR	NR	Intra- and interdialytic symptoms, acid-base balance, nutrition, and carbohydrate metabolism
Schrander-vd Meer[43] (1999, NL)	20	AFB vs HD	12 mo	Parallel	NR	NR	NR	NR	NR	NR	Dialysis efficiency and metabolic control
Eiselt[35] (2000, CZ)	10	AFB vs low-flux HD	12 mo	Parallel	38 ± 9 vs 47 ± 10	NR	NR	54 ± 40 vs 41 ± 20	Anuric or negligible kidney function	NR	Anemia
Basile[54] (2001, IT)	15	AFB vs low-flux HD	6 mo	Crossover	59.9 ± 7.2	60%	NR	53.2 ± 21.0	Negligible kidney function was inclusion criterion	NR	Anemia
Todeschini[56] (2002, IT)	9	AFB vs high-flux HD	3 dialysis sessions	Crossover	63.6 ± 7.2	33%	NR	Range, 24-60	NR	AVF	Polymorphonuclear cell function
Tessitore[31] (2012, IT)	371	AFB vs low- or high-flux HD	36 mo	Parallel	66.9 ± 8.8 vs 67.1 ± 8.8	60% vs 58%	37.1% vs 41.1%	NR	NR	90% AVF, 3% graft, 7% CVC	Intradialytic CV stability

Note: Unless otherwise indicated, values are given as mean ± standard deviation or median [interquartile range].

Abbreviations: AFB, acetate-free biofiltration; AV, arteriovenous; AVF, arteriovenous fistula; B2M, β_2-microglobulin; BE, Belgium; BUN, blood urea nitrogen; CA, Canada; CCr, creatinine clearance; CONTRAST, Convective Transport; Cr, creatinine; CRP, C-reactive protein; CV, cardiovascular; CVC, central venous catheter; CZ, Czech Republic; DE, Germany; DK, Denmark; ES, Spain; ESHOL, Estudio de Supervivencia de Hemodiafiltracion On-Line; GR, Greece; HD, hemodialysis; HDF, hemodiafiltration; HF, hemofiltration; HU, Hungary; IL, interleukin; IT, Italy; JP, Japan; NL, Netherlands; NR, not reported; Qb, blood flow rate; QoL, quality of life; SE, Sweden; TR, Turkey; TW, Taiwan; UK, United Kingdom; US, United States.

[a]Year of publication and setting (country or region) provided in parentheses.

[b]Details of the interventions and comparisons are provided in detail in table *b* of Item S1.

[c]The study by Locatelli et al[24] reported data for HDF or HF versus HD.

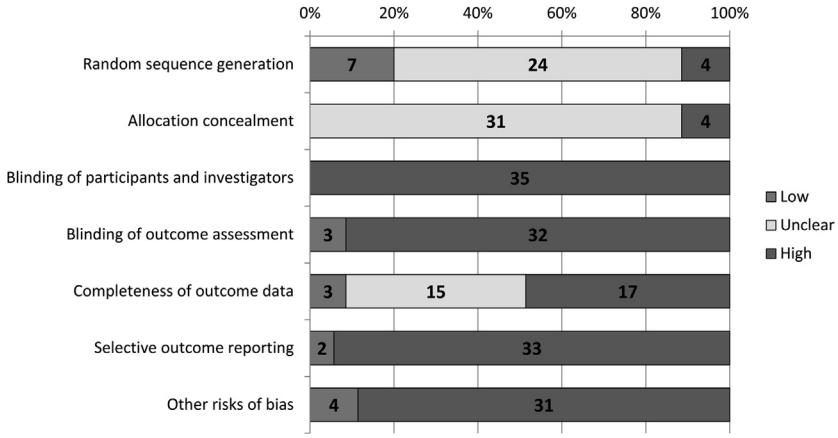

Figure 2. Summary risks of bias in included studies (n = 35).

membranes for hemodialysis, 16 trials (46%) used low-flux membranes, 4 trials (11%) used either low- or high-flux membranes, and in 3 trials (9%), membrane flux was unclear. Convection strategies were highly heterogeneous and no trial randomly assigned participants to specific targeted convection volumes. In 16 (46%) studies, adequate vascular access for high-volume dialysis was required. Most RCTs included patients who were anuric or had minimal residual kidney function.

Thirty trials (86%) were conducted in Europe and Scandinavia, 2 (6%) were conducted in Asia, 2 (6%) were conducted in North America, and there was one multiregional study. Ten trials evaluated short-term

Table 2. GRADE Evidence Profile for Effects of Convective Versus Dialysis Treatment for End-Stage Kidney Disease From Meta-Analyses of RCTs *(continued on following page)*

	Quality Assessment				
No. of RCTs	Study Limitations[a]	Consistency[b]	Directness of Evidence	Precision	Publication Bias
		All-Cause Mortality			
11	Very serious limitations: allocation concealment 0%, completeness of outcome reporting 18%, matched dialysis flux 27%	No serious inconsistency	Some indirectness; studies generally enrolled patients with adequate vascular access	No serious imprecision	Undetected
6	Very serious limitations: allocation concealment 0%, completeness of outcome reporting 33%, blinding of outcome assessment 17%, matched dialysis flux 33%	No inconsistency	Some indirectness; studies generally enrolled patients with adequate vascular access	No serious imprecision	Undetected
		Nonfatal CV Events			
1	Very serious limitations: allocation concealment 0%, completeness of outcome reporting 100%, blinding of outcome assessment 100%, matched dialysis flux 0%	Not applicable	Single study	Some imprecision	Not estimable
		Quality of Life			
8	Very serious limitations: crossover effects 50%, blinding in outcome assessment 0%, selective reporting of outcomes 88%, matching of dialysis flux 63%	Important inconsistency	Some indirectness; studies generally enrolled patients with adequate vascular access	Serious imprecision	Not estimable

Abbreviations: AFB, acetate-free biofiltration; CI, confidence interval; CV, cardiovascular; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HD, hemodialysis; HDF, hemodiafiltration; HF, hemofiltration; RCT, randomized controlled trial; RR, relative risk.

[a]Percentage of studies at low risk of bias.

[b]Decrease in quality score, I^2, and P value for heterogeneity.

[c]Values given as n/N.

[d]Derived from data within dialysis registries for all-cause mortality and CV mortality.[3]

[e]Approximate absolute events rate of outcomes per year. *(continued on following page)*

outcomes conducted over follow-up that varied between one dialysis session and 2 weeks of treatment.[23,26,29,47-49,51,52,55,56] The remaining 24 trials evaluated outcomes during treatment of 2-48 (median, 12) months except for one, in which treatment duration was unclear.[38] Sample sizes varied between 5 and 906 (median, 24) participants. Of the overall 4,039 participants, 2,402 (59%) were derived from 3 large RCTs evaluating online HDF.[32,34,36]

Risks of Bias

Risks of bias in individual studies are shown in Fig S1 and a summary of overall risks of bias are provided in Fig 2. Trials generally had very serious limitations due to risks of bias in most domains leading to downgrading of overall evidence quality. Risks of bias were high or unclear for sequence generation (80% of RCTs) and allocation concealment (all RCTs). Blinding of both participants and investigators was not clearly reported in any trial and blinding of outcome assessment for cardiovascular mortality, quality of life, and withdrawal of treatment was not reported in 32 trials (91%). There was selective reporting of outcomes in all except 2 trials (94%). A key risk of bias present in all except 3 studies (9%) was attrition from follow-up of at least 90% of randomly assigned patients and/or loss of patients to follow-up was not similar between treatment groups for reasons potentially related to the outcomes of interest. Of the 3 largest trials contributing to meta-analyses, ESHOL (Estudio de Supervivencia de Hemodiafiltracion On-Line) did not include 39.1% of randomly assigned patients in analyses,[36] and in the Turkish Online HDF study, 20.5% of participants left the study for reasons other than death, including 10% of participants allocated to HDF due to vascular access problems.[32] Other potential sources of bias included data not being extractable for meta-analysis, involvement of a commercial sponsor on authorship and/or data management, lack of matching of interventions (eg, membrane flux or dialysis dose), lack of or unclear matching of baseline patient characteristics, early trial termination, and an abstract-only publication (table *c* of Item S1). Adverse-event reporting was

Table 2 (Cont'd). GRADE Evidence Profile for Effects of Convective Versus Dialysis Treatment for End-Stage Kidney Disease From Meta-Analyses of RCTs

Summary of Findings						
HDF, HF, or AFB[c]	HD[c]	RR (95% CI)	Control Group Absolute Risk[d,e]	Absolute Effect per 1,000 Treated (95% CI)[f]	Quality of Evidence[g]	Overall Judgment
			All-Cause Mortality			
368/1,648	437/1,748	0.87 (0.70-1.07)	200/1000[d]	Not significant	Low ++	Convective therapy may have little or no effect on all-cause mortality
143/1,440	196/1,449	0.75 (0.58-0.97)	100/1000[d]	25 (3-42) fewer	Low ++	Convective therapy may reduce CV mortality
			Nonfatal CV Events			
Not estimable		1.14 (0.85-1.53)	130/1000[h]	Not significant	Very low +	Convective therapy has uncertain effects on rates of nonfatal CV events
			Quality of Life			
Not estimable		Not estimable	Not estimable	No summary effect possible	Very low +	Convective therapy has uncertain effects on quality of life

[f]Absolute numbers of men and women with end-stage kidney disease who had mortality or CV events avoided per 1,000 treated were calculated from the risk estimate for the outcome (and associated 95% CI) obtained from meta-analysis of RCTs together with the absolute population risk estimated from the previously published registry or trial data.

[g]Low indicates that our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect. Very low indicates that we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[h]Derived from the reported event rate in the available trial for nonfatal CV events.[34]

conducted at prespecified points during follow-up in 6 (17%) RCTs and serious adverse events were not reported in any study (table *d* of Item S1).

Outcomes

All-Cause and Cardiovascular Mortality

In 11 trials (3,396 participants), low-quality evidence indicated that convective dialysis treatment had little or no effect on all-cause mortality (RR, 0.87; 95% CI, 0.70-1.07; Table 2; Fig 3). Data for cardiovascular mortality were available in 6 RCTs comprising 2,889 participants. In low-quality evidence, convective therapy may reduce death from cardiovascular causes compared with hemodialysis (RR, 0.75; 95% CI, 0.58-0.97; Table 2; Fig 4). In absolute terms, convective therapy might prevent 25 cardiovascular deaths for every 1,000 patients treated for 1 year, but has no significant effect on death overall.

Nonfatal Cardiovascular Events and Hospitalization

In studies that reported events per person-years, convective dialysis had uncertain effects on rates of hospitalization (2 trials; 1,688 participants; rate ratio, 1.21; 95% CI, 0.12-12.05)[32,36] and nonfatal cardiovascular events (1 trial; 714 participants; rate ratio, 1.14; 95% CI, 0.85-1.52).[34]

Change in Dialysis Treatment Modality

The relative proportion of participants who crossed over to another form of dialysis was uncertain (5 RCTs; 2,919 participants; RR, 0.87; 95% CI, 0.30-2.52; Fig 5), with moderate heterogeneity in the analysis ($I^2 = 47\%$).

Quality of Life

Data for quality of life were extractable from 8 trials (988 participants), including 6 evaluating HDF and one each evaluating HF or acetate-free biofiltration.[30,33,34,37,38,42,45,57] In very low-quality evidence, data for quality of life were inconsistent (Table 2; table *e* of Item S1). Data from the 4 parallel-group trials reporting this outcome showed that there was no difference in the change in quality of life (any domain) comparing HDF with hemodialysis in one trial,[34] both HDF and hemodialysis patients reported significant improvement in physical symptoms during the RCT irrespective of treatment allocation in a second trial,[45] hemodialysis patients had lower physical well-being scores than patients on HDF but treatment effects on work tolerance and mental alertness were not available in a third trial,[38] or directly comparative data for HF compared with hemodialysis were not available in a fourth trial.[33]

Clearances of Urea and β_2-Microglobulin

In 12 RCTs comprising 1,813 participants, convective dialysis therapy reduced predialysis serum β_2-microglobulin levels (mean difference, −5.77 [95% CI, −10.97 to −0.56] mg/dL), but results were very heterogeneous ($I^2 = 94\%$; table *f* of Item S1). All the included studies in this analysis compared either HDF or HF with hemodialysis. Convective dialysis treatment increased Kt/V (14 RCTs; 2,115 participants; mean difference, 0.10; 95% CI, 0.02-0.19), but there was considerable heterogeneity among the studies reporting this outcome ($I^2 = 85\%$; table *f* of Item S1).

Blood Pressure

In one trial reporting number of hypotensive events per person-years of follow-up, convective dialysis reduced hypotension during dialysis (906 participants; rate ratio, 0.72; 95% CI, 0.66-0.80).[36] Convective dialysis therapy had little or no effect on predialysis systolic (7 RCTs; 1,876 participants; mean difference, 1.13 [95% CI, −2.34 to 4.60] mm Hg) or diastolic (6 RCTs; 1,154 participants; mean difference, −0.23 [95% CI, −1.28 to 0.81] mm Hg) blood pressure.

Publication Bias, Sensitivity Analyses, and Metaregression

For patient-level outcomes with sufficient extractable data (all-cause mortality, cardiovascular mortality, and change in dialysis modality), there was no evidence of funnel plot asymmetry suggesting any bias from small-study effects (Fig S2). When we limited analyses to studies comparing HDF with hemodialysis, we found very similar treatment effects. Compared to hemodialysis, HDF had uncertain effects on all-cause mortality (7 trials; 2,837 participants; RR, 0.85; 95% CI, 0.58-1.24),[24,32,34,36,39,42,46] albeit with moderate heterogeneity ($I^2 = 53\%$); cardiovascular mortality (4 RCTs; 2,478 participants; RR, 0.72; 95% CI, 0.49-1.06)[32,34,36,42]; and change in dialysis modality (4 trials; 2,512 participants; RR, 0.99; 95% CI, 0.32-3.10).[24,32,34,36] Data for rates of nonfatal cardiovascular events, hospitalization, and hypotension during dialysis already were limited to trials comparing HDF with hemodialysis.

In univariate metaregression analysis, achieved convection volume did not modify risk of all-cause mortality ($P = 0.2$) or change in dialysis modality ($P = 0.9$). In other metaregression analyses, age, membrane flux, and duration of follow-up were not significant effect modifiers of treatment effects for mortality or change in modality ($P > 0.05$ for all).

DISCUSSION

In this study, we compared the effects of convective dialysis treatment (HDF, HF, or acetate-free

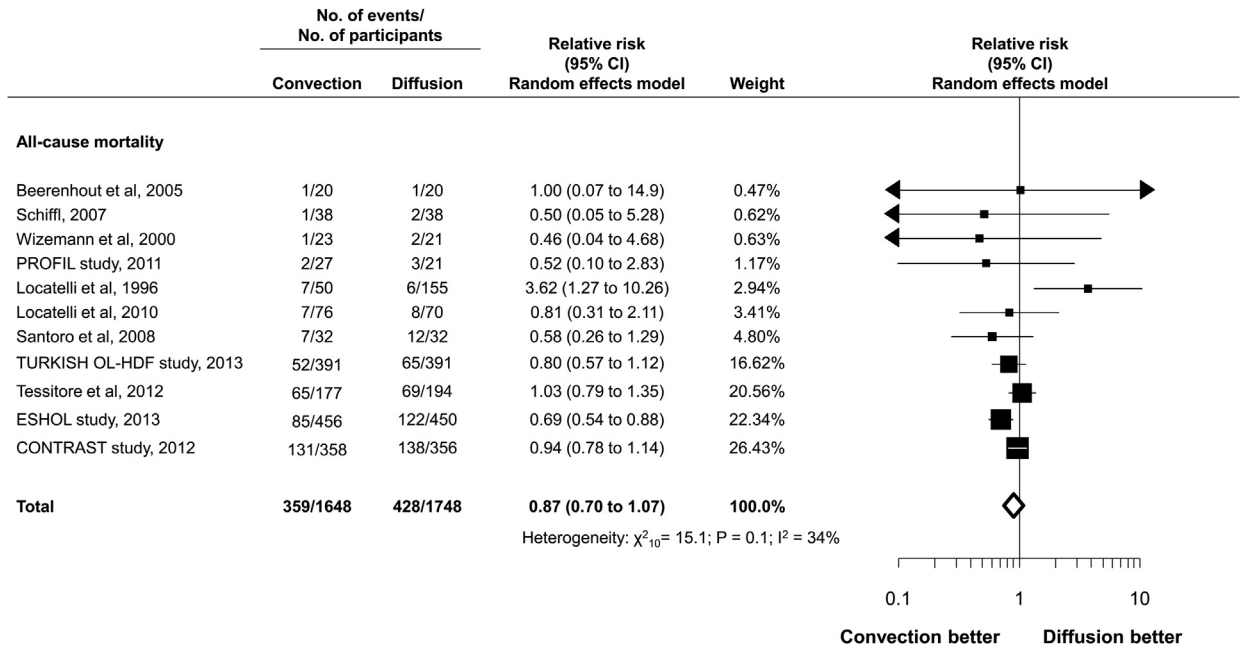

Figure 3. Effects of hemofiltration, hemodiafiltration (HDF), or acetate-free biofiltration versus hemodialysis on all-cause mortality. Abbreviations: CI, confidence interval; CONTRAST, Convective Transport; ESHOL, Estudio de Supervivencia de Hemodiafiltracion On-Line; OL, online.

biofiltration) with hemodialysis in 35 trials involving 4,039 dialysis patients. Convective dialysis modalities had little or no effect on all-cause mortality and may reduce cardiovascular death and hypotension during dialysis, but had uncertain effects on rates of nonfatal cardiovascular events and hospitalization. In absolute terms, 25 cardiovascular deaths might be prevented for every 1,000 patients treated for 1 year with convective dialysis. The comparative risks of changing dialysis modality were uncertain and treatment effects on clearances of urea and β_2-microglobulin were markedly inconsistent. Treatment effects of convective dialysis potentially are unreliable due to very serious limitations in methodology and reporting in available randomized trials. Allocation concealment, blinding of outcome assessment, complete reporting of patient-relevant outcomes, and inclusion of patients in outcome analyses were inadequate in most studies and therefore the evidence quality for clinical outcomes was downgraded to low or very

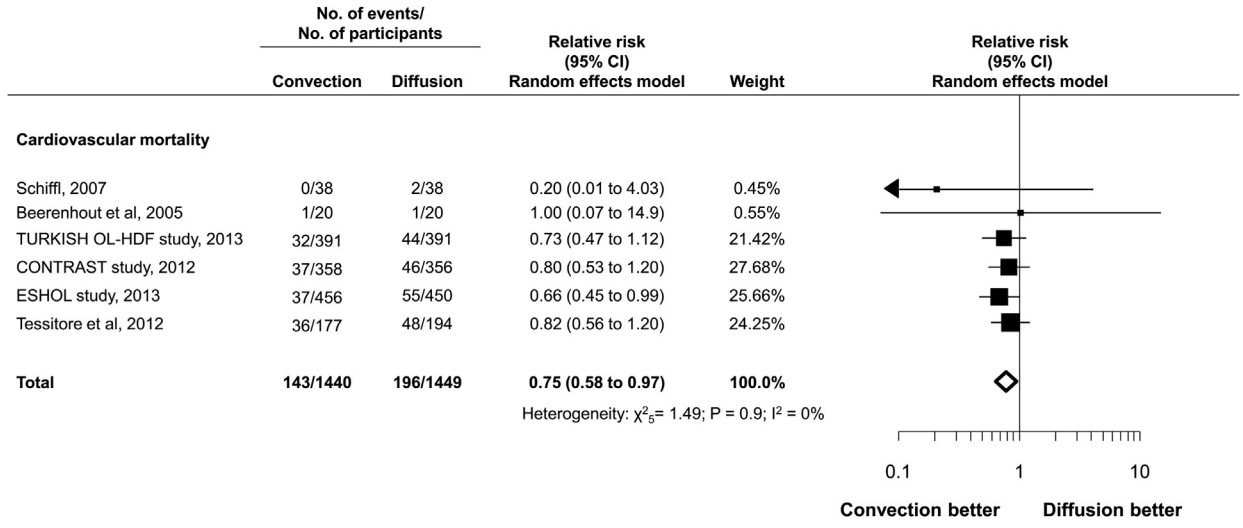

Figure 4. Effects of hemofiltration, hemodiafiltration (HDF), or acetate-free biofiltration versus hemodialysis on cardiovascular mortality. Abbreviations: CI, confidence interval; CONTRAST, Convective Transport; ESHOL, Estudio de Supervivencia de Hemodiafiltracion On-Line; OL, online.

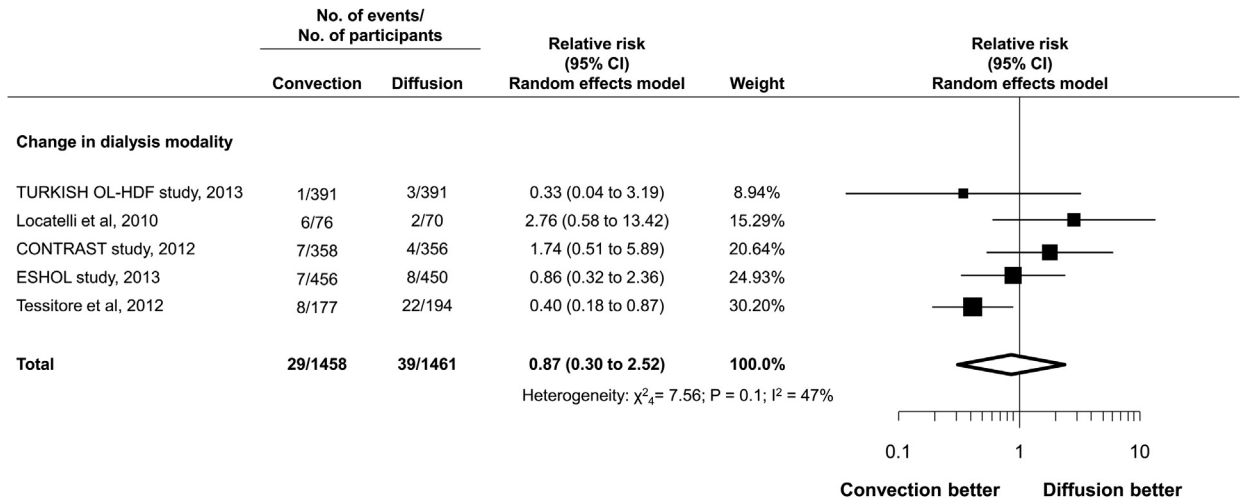

Figure 5. Effects of hemofiltration, hemodiafiltration (HDF), or acetate-free biofiltration versus hemodialysis on change of dialysis modality. Abbreviations: CI, confidence interval; CONTRAST, Convective Transport; ESHOL, Estudio de Supervivencia de Hemodiafiltracion On-Line; OL, online.

low. Data for adverse events and quality of life were insufficient to draw clinically meaningful conclusions. Due to the limitations of existing data, the confidence in estimated effects of convective dialysis is low and the true effects of treatment might be substantially different from those summarized from existing studies.

The European best practice guidelines on hemodialysis suggest that online HDF or HF should be considered to delay long-term complications of dialysis therapy and that exchange volumes should be as high as possible.[16] Current use of HDF varies widely. The prevalence of HDF ranges from 0.3-232 per million of population within countries and regions of Europe,[14] and the proportion of HDF as the treatment modality for patients in Australasia ranges from 0.8%-23%.[15] This review suggests that the benefits of HDF or HF from contemporaneous RCTs are limited to cardiovascular mortality and hypotension during dialysis and that evidence limitations lead to low or very low confidence in these treatment benefits.

None of the available studies randomly assigned participants to specific targeted convection volumes. Accordingly, robust evidence supportive of higher convection volumes to improve dialysis outcomes is not available. This review, in showing no strong evidence for a reduction in all-cause mortality with convective dialysis, diverges from the conclusions of the largest HDF trial to date (ESHOL), which reported a 30% relative reduction in death during 36 months of follow-up and suggested that 8 patients needed to be switched from hemodialysis to HDF therapy to prevent one death each year.[36] We suggest that the consistent findings across all studies in the meta-analysis for mortality in this review indicate that the overall summary estimate from meta-analysis is robust, even accounting for the findings in ESHOL. Notably, in that study, patients were withdrawn and not included in analyses if they did not receive the allocated treatment modality for 2 months or more, including those who did not achieve the minimum requested replacement volume (18 L per session). Because it is probable that these participants might have had poorer outcomes (such as poorer vascular access due to other comorbid conditions, including vascular disease or diabetes) and may have been preferentially excluded from follow-up, ESHOL might unreliably estimate mortality risk. It would be informative to re-evaluate mortality data from ESHOL using intention-to-treat analyses that include mortality outcome data for all randomly assigned patients according to their original treatment assignment.

The strengths of this review include the searching of conference proceedings and inclusion of unpublished data to provide a comprehensive analysis of all available evidence and the rigorous assessment of evidence quality that has been incorporated into review conclusions using the methods of the GRADE guidelines.[21]

However, potential limitations in primary studies contributing to this review limit confidence in the conclusions that might be drawn from the available evidence for convective and diffusive dialysis modalities.

First, due to risks of bias in the primary studies, particularly from selective reporting of outcomes and attrition from follow-up, the confidence in treatment estimates is low and estimated treatment effects may be unreliable. As such, the low-quality evidence for convective dialysis in existing trials suggests that robust information is not available to support good decision making about the relative benefits and harms of HDF to alter patient outcomes.

Second, higher achieved convection volumes for HDF were associated with lower mortality in post hoc nonrandomized analyses within the Convective Transport (CONTRAST),[34] Turkish Online HDF,[32] and ESHOL[36] studies. However, caution is needed before concluding that this is evidence for the need to deliver high convection volumes to reduce all-cause mortality with HDF. Convection volumes were not randomized treatment targets in any RCT (ie, patients at randomization were not equally likely to be assigned to specific convection volume targets) and as such, the relationship observed between convection volume and mortality also is likely to be strongly confounded in important ways. Participants with insufficient vascular access and those with lower achieved blood flows (both known to be linked to comorbid conditions and poorer outcomes[58,59]) would have been less likely to achieve higher convection volumes and those with longer treatment times would have been more likely to achieve convection targets. It is known that these specific patient and treatment characteristics independently predict mortality and may, as such, offer viable and alternative explanations for the association between convection volume and risk of death.

Third, there was considerable heterogeneity in the dialysis interventions across RCTs, including differences in flux, vascular access requirements, blood flows, and treatment times, as well as convection volumes, resulting in uncertainty about which specific aspects of the convection process might be responsible for lower cardiovascular mortality. Future standardization of therapy patterns might improve our understanding of the features of convective dialysis care that might lead to improved outcomes and patient acceptability.

Fourth, data for adverse events were sparse and none evaluated serious adverse events. Understanding hazards of treatment is essential to balancing desirable and undesirable outcomes when considering new therapies, and questions about potential harms from convection therapy cannot be answered with confidence using the existing RCT evidence.

Fifth, the generalizability of the findings from RCTs to wider dialysis populations, including those in regions other than Europe, might be limited. The absolute treatment benefits of convection on cardiovascular mortality might not be applicable to many dialysis patients because data frequently were limited to participants who had vascular access sufficient to sustain high convection volumes.

Finally, it was not possible to assess the effects of residual kidney function on treatment effects for mortality and cardiovascular mortality because insufficient studies reported residual kidney function sufficiently to conduct subgroup or sensitivity analyses.

The key implications of the present data are for planning future research. Additional trials with low risks of bias from attrition, or analysis of data that includes all patients randomly assigned in existing trials could strengthen the conclusions that might be drawn from future and existing evidence, particularly to answer whether convective dialysis lowers adverse cardiovascular end points. Future trials need to consider standardization of convective dialysis approaches to improve data synthesis and our understanding of the relative contributions of different aspects of convective strategies to clinical outcomes. Strengthened registry capture of adverse events and specific randomization of patients to different convection volumes might enhance our understanding of the acceptability of convective dialysis and whether outcomes depend on convective volumes, respectively. In addition, there are relatively few data from regions outside Europe, and collaborative approaches to future trials that include other global regions could be considered.

Due to limitations in trial methodology and reporting, the effects of convective dialysis on cardiovascular outcome and survival are unclear. Thus, widespread uptake of convective dialysis care is not supported by available evidence. Additional multiregional trials that use robust methodology, standardized interventions, and randomized convection volumes are needed to better understand the effects of convective modalities on clinically relevant outcomes in this population.

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SUPPLEMENTARY MATERIAL

Figure S1: Risks of bias in individual trials.

Figure S2: Funnel plots evaluating small-study effects for patient-level outcomes.

Item S1: Search strategies and other material.
Item S2: Authors supplying unpublished data.
Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2013.12.004) is available at www.ajkd.org

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