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Haemodiafiltration, haemofiltration and haemodialysis for end-stage kidney disease (Review)

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TABLE OF CONTENTS

[Intervention Review]

Haemodiafiltration, haemofiltration and haemodialysis for end-stage kidney disease

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ABSTRACT

Background

Convective dialysis modalities (haemofiltration (HF), haemodiafiltration (HDF), and acetate-free biofiltration (AFB)) removed excess body fluid across the dialysis membrane with positive pressure and accumulated middle- and larger-size accumulated solutes more efficiently than haemodialysis (HD). This increased larger solute removal combined with use of ultra-pure dialysis fluid in convective dialysis is hypothesised to reduce the frequency and severity of symptoms during dialysis as well as improve clinical outcomes. Convective dialysis therapies (HDF and HF) are associated with lower mortality compared to diffusive therapy (HD) in observational studies. This is an update of a review first published in 2006.

Objectives

To compare convective (HF, HDF, or AFB) with diffusive (HD) dialysis modalities on clinical outcomes (mortality, major cardiovascular events, hospitalisation and treatment-related adverse events) in men and women with end-stage kidney disease (ESKD).

Search methods

We searched the Cochrane Renal Group's Specialised Register (to 18 February 2015) through contact with a Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

We included randomised controlled trials comparing convective therapy (HF, HDF, AFB) with another convective therapy or diffusive therapy (HD) for treatment of ESKD.

Data collection and analysis

Two independent authors identified studies, extracted data and assessed study risk of bias. We summarised treatment effects using the random effects model. We reported results as a risk ratio (RR) for dichotomous outcomes and mean difference (MD) for continuous data together with 95% confidence intervals (CI). We assessed for heterogeneity using the Chi^2 test and explored the amount of variation in treatment estimates beyond that expected by chance using the I^2 statistic.

Main results

Twenty studies comprising 667 participants were included in the 2006 review. In that review, there was insufficient evidence of treatment effects on major clinical outcomes to draw clinically meaningful conclusions. Searching to February 2015 identified 40 eligible studies comprising 3483 participants overall. In total, 35 studies (4039 participants) compared HF, HDF or AFB with HD, three studies (54 participants) compared AFB with HDF, and three studies (129 participants) compared HDF with HF.

Risks of bias in all studies were generally high resulting in low confidence in estimated treatment effects. Convective dialysis had no significant effect on all-cause mortality (11 studies, 3396 participants: RR 0.87, 95% CI 0.72 to 1.05; I^2 = 34%), but significantly reduced cardiovascular mortality (6 studies, 2889 participants: RR 0.75, 95% CI 0.61 to 0.92; I^2 = 0%). One study reported no significant effect on rates of nonfatal cardiovascular events (714 participants: RR 1.14, 95% CI 0.86 to 1.50) and two studies showed no significant difference in hospitalisation (2 studies, 1688 participants: RR 1.23, 95% CI 0.93 to 1.63; I^2 = 0%). One study reported rates of hypotension during dialysis were significantly reduced with convective therapy (906 participants: RR 0.72, 95% CI 0.66 to 0.80). Adverse events were not systematically evaluated in most studies and data for health-related quality of life were sparse. Convective therapies significantly reduced predialysis levels of B_2 microglobulin (12 studies, 1813 participants: MD -5.55 mg/dL, 95% CI -9.11 to -1.98; I^2 = 94%) and increased dialysis dose (Kt/V urea) (14 studies, 2022 participants: MD 0.07, 95% CI -0.00 to 0.14; I^2 = 90%) compared to diffusive therapy, but results across studies were very heterogeneous. Sensitivity analyses limited to studies comparing HDF with HD showed very similar results. Directly comparative data for differing types of convective dialysis were insufficient to draw conclusions.

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

Authors' conclusions

Convective dialysis may reduce cardiovascular but not all-cause mortality and effects on nonfatal cardiovascular events and hospitalisation are inconclusive. However, any treatment benefits of convective dialysis on all patient outcomes including cardiovascular death are unreliable due to limitations in study methods and reporting. Future studies which assess treatment effects of convection dose on patient outcomes including mortality and cardiovascular events would be informative.

PLAIN LANGUAGE SUMMARY

Haemodiafiltration, haemofiltration and haemodialysis for end-stage kidney disease

People who have severe loss of kidney function are treated with dialysis or a kidney transplant to remove toxins and fluid. Dialysis removes waste products and fluid by filtering these across a membrane in the dialysis machine (for haemodialysis) or within the body (for peritoneal dialysis). Toxins that build-up in the body when the kidneys fail vary in size and larger molecules are removed less well by standard haemodialysis. Newer dialysis types 'push' water across the dialysis membrane which allows the removal of unwanted molecules more efficiently. Larger molecules are removed better and the dialysis fluid has fewer impurities, leading to the potential for convective dialysis to improve the ways patients feel and survive on dialysis. The three types of convective dialysis therapy are haemodiafiltration, haemofiltration, and acetate-free biofiltration. Use of convective therapy for dialysis is higher in Europe and lower in the USA. Given the difference between regions for uptake of this treatment and the potential benefits on patient outcomes, we have updated this Cochrane review to new additional studies available in 2015.

We identified 40 studies enrolling 4137 adult participants. Of these, 35 studies in 4039 adults compared convective dialysis with standard haemodialysis. Overall the evidence in the studies was low or very low quality due to limitations in the methods used in the research leading to low confidence in the results. Overall, there was no evidence convective dialysis lowered risk of death from any cause but may reduce death due to heart or vascular disease. Overall treating 1000 men and women who have end-stage kidney disease with convective dialysis rather than standard haemodialysis may prevent 25 dying from heart disease. Convective therapy may reduce blood pressure falls during dialysis but there was no evidence that convective dialysis influenced chances of hospital admission or other side-effects, or improved quality of life.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Convective compared with diffusive dialysis modalities for men and women with end-stage kidney disease

Patient or population: men and women with end-stage kidney disease

Intervention: convective dialysis

Comparison: diffusive dialysis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Diffusion	Convection				
All-cause mortality	200 per 1000	Not significant	RR 0.87 (0.72 to 1.05)	11 (3396)	⊕⊕⊝⊝ **low**	Convective therapy has little or no effect on all-cause mortality
Cardiovascular mortality	100 per 1000	75 per 1000	RR 0.75 (0.81 to 0.92)	6 (2889)	⊕⊕⊝⊝ **low**	Convective therapy may reduce cardiovascular mortality
Nonfatal cardiovascular events	130 per 1000	Not significant	RR 1.23 (0.93-1.63)	2 (1688)	⊕⊝⊝⊝ **very low**	Convective therapy has uncertain effects on non-fatal cardiovascular events
Health-related quality of life	Not estimable	Not estimable	Not estimable	8 (988)	⊕⊕⊝⊝ **very low**	Convective therapy has uncertain effects on health-related quality of life

*The **assumed risk** (e.g. the median control group risk across studies) is derived from data within dialysis registries for all-cause mortality and cardiovascular mortality and the reported event rate in the available study for nonfatal cardiovascular events (CONTRAST (Dutch) Study 2005). The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk Ratio

GRADE (Grading of Recommendations Assessment, Development, and Evaluation) Working Group grades of evidence (Guyatt 2011).
Low quality: Indicates that our confidence in the effect estimate is limited: The true effect may be substantially difference from the estimated effect.
Very low quality: Indicated that we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimated effect.

BACKGROUND

Description of the condition

Dialysis, kidney transplantation or supportive care are available treatment options for end-stage kidney disease (ESKD). Dialysis therapies include peritoneal dialysis as well as standard haemodialysis (HD) or convective dialysis (haemofiltration (HF), haemodiafiltration (HDF), and acetate-free biofiltration (AFB)) to remove accumulated fluid and metabolites from the blood when kidney function is severely impaired. Despite effective removal of solutes and water by standard HD to avoid life-threatening complications, long-term dialysis patients reported markedly impaired quality of life, sleep disturbance, nausea, depressive symptoms, anxiety, thirst, and pain (Murtagh 2007). In addition, survival remains poor; 10 to 20% of men and women treated with long-term dialysis die each year (USRDS 2011).

Description of the intervention

Standard HD removes accumulated metabolites and fluid from the patient's blood by diffusion across a semi-permeable membrane into the dialysate fluid for removal into the dialysis waste. Convective dialysis (HDF, HF and AFB) clears water (convection) using positive pressure across the dialysis membrane for removal. Accumulated solutes follow the movement of water in a phenomenon known as 'solvent drag' (Henderson 2004). Water and electrolytes are replaced as required into the blood circulation. The replacement fluid can be added to the patient's blood before the membrane filter ("pre-dilution") or after the dialysis filter along with the blood returning into the patient's blood circulation ("post-dilution").

Accumulated metabolites have different molecular weights and are cleared differently depending on the type of molecular transport used in dialysis (diffusive versus convective). HF may remove higher molecular weight molecules whereas standard HD may be more effective at removing smaller solutes such as urea (Locatelli 2000). A hybrid system that includes both convection and diffusion, known as HDF combines convection with diffusion (Schmidt 1986). In HD and HDF, the dialysate contains acetate, which buffers circulating acids which cannot be buffered sufficiently by kidney function. Acetate depresses myocardial contractility and may cause haemodynamic instability during dialysis (Daugirdas 1991; Sztajzel 1993). AFB, a HDF technique, uses a hypertonic sodium bicarbonate solution in place of acetate to manage acidosis (Zucchelli 1990).

How the intervention might work

While standard HD clears smaller, water-soluble metabolites efficiently by diffusion, poor clinical outcomes might be explained in part by inadequate removal of middle- and larger-sized waste products of metabolism which are implicated in the pathogenesis of atherosclerosis and dialysis-related amyloidosis (Guerin 2000). In uncontrolled studies, convective dialysis therapies are associated with lower mortality (Locatelli 1999; Vilar 2009) and lower circulating levels of middle-size molecules such as vitamin B12 or B_2 microglobulin in dialysis patients are associated with reduced cardiovascular and infection-related mortality (Liabeuf 2012). In addition, HDF is associated with less frequent hypotension during dialysis (Vilar 2009) and the enhanced biocompatibility of ultrapure dialysate fluids used in convective technologies may reduce inflammation, oxidative stress and infection.(Arizono 2004; Calo 2007) Removal of larger metabolites by newer convective dialysis strategies is therefore a potential strategy to improve dialysis outcomes and greater convection volumes during HDF might be a principal determinant of clinical effectiveness with HDF because of greater clearances of middle and large uraemic solutes during treatment.

Why it is important to do this review

In our previous meta-analysis, published in 2006, that included 17 randomised studies (600 participants) comparing convective with diffusive dialysis (Rabindranath 2006), convective modalities had uncertain effects on mortality in low-quality evidence and data for adverse events were sparse. Since 2006, 18 additional studies (3439 participants) comparing convection with diffusion modalities have been published, but results have been inconsistent, and consequently there has been variable uptake of HDF into clinical practice; 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 (ERA-EDTA Registry 2010). In Australia and New Zealand, the proportion of dialysis patients treated with HDF in 2011 was 21.5% and 10.9%, respectively (ANZDATA 2012). The European Best Practice Guidelines that were published in 2007 suggest that HDF is a suitable treatment strategy to delay complications of ESKD and exchange volumes should be as high as possible (EBPG 2007).

OBJECTIVES

To compare convective (HF, HDF, or AFB) with diffusive (HD) dialysis modalities on clinical outcomes (mortality, major cardiovascular events, hospitalisation and treatment-related adverse events) in men and women with ESKD

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) comparing convective therapies (HF, HDF, AFB) and HD.

Types of participants

Adults with ESKD treated with dialysis.

Types of interventions

1. Convective therapy (HDF/ HF/AFB) compared with diffusive therapy (HD)
2. Direct comparisons of different convective therapies (HDF/HF/AFB)

Types of outcome measures

Primary outcomes

- All-cause mortality.

Secondary outcomes

Clinical outcomes

- Cardiovascular mortality

- Hypotension (symptomatic hypotension, hypotension requiring treatment and post-dialysis hypotension, recorded as number of events/person-years follow-up or number of patients experiencing one or more episodes)
- Hospitalisation (days of hospitalisation, one or more episodes, or number of events/person-years of follow-up)
- Change of dialysis modality (from convective to diffusive dialysis modality or vice versa)
- Symptoms (headaches, nausea, vomiting) occurring during or after dialysis (recorded as number of treatment sessions at which event occurred or number of patients experiencing one or more episodes of headaches, nausea or vomiting)
- "Any adverse symptoms" or number of patients experiencing "Any adverse symptoms" (number of events/person-years of follow-up or patients experiencing one or more events)
- Health-related quality of life (any instrument used)
- Amyloid-related complications (amyloidosis, carpal tunnel syndrome, amyloid-related arthropathy).

Surrogate outcomes

- Adequacy of dialysis (assessed by Kt/V values or by urea reduction ratio (URR))
- End of treatment blood pressure (measured as systolic, diastolic or mean arterial pressure, in mm Hg)
- End of treatment predialysis B_2 microglobulin levels (mg/L).

Dialysis adequacy measures and B_2 microglobulin measures were not regarded as key clinical outcomes in this review. However, they were included to facilitate the determination of their usefulness as secondary outcome measures for the interventions compared.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's Specialised Register (to 18 February 2015) through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's specialised register contains studies identified from the following sources.

1. Quarterly searches of the Cochrane Central Register of Controlled Trials CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals & the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal-journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal & ClinicalTrials.gov

Studies contained in the specialised register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies as well as a list of handsearched journals, conference proceedings and current awareness alerts are available in the 'specialised register' section of information about the Cochrane Renal Group.

See Appendix 1 for search terms used in strategies for this review.

Data collection and analysis

Selection of studies

The search strategies described were used to obtain titles and abstracts of studies that might be relevant to the review. The 2006 review was undertaken by six authors (Rabindranath 2006). Two authors independently assessed and retrieved titles and abstracts. The full text of all potentially relevant studies were retrieved by the same authors and independently assessed in detail. Two authors carried out data extraction independently using standardised data extraction forms. Disagreements were resolved in consultation among the authors.

The review update was undertaken by six authors. Two authors independently assessed and retrieved titles and abstracts. The full text (if published) of all potentially relevant studies were retrieved and independently assessed for inclusion by two authors. Two authors extracted data which was cross-checked by a third author. Discrepancies were resolved by discussion among the authors.

Data extraction and management

Two authors carried out data extraction independently using standard data extraction forms and data were entered into RevMan. We extracted the number of events and participants as risk of events or when these data were not provided, the number of events/person-years of follow-up for dichotomous outcomes and mean (SD) and numbers of participants at risk for continuous outcomes. We translated studies not reported in English before assessment and data extraction. Where more than one publication of a study existed, only the publication with the most complete data was included.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

We considered the study to be at high risk of selective outcome reporting when investigators did not report data for all-cause mortality and cardiovascular mortality and adverse events or patient symptoms.

We rated the quality of the evidence for convection versus diffusion interventions using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system for systematic reviews considering study limitations, precision and consistency of treatment estimates, directness of available evidence and publication bias for the clinical outcomes of quality of all-cause

and cardiovascular mortality, nonfatal cardiovascular events, and health-related quality of life (Guyatt 2011) to generate a Summary of findings for the main comparison. To estimate the absolute number of men and women with ESKD who had mortality or nonfatal cardiovascular events avoided or incurred with convective dialysis therapy, 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 (USRDS 2011) or from the control group of available RCTs.

Measures of treatment effect

We summarised treatment effects using random-effects meta-analysis and expressed results as relative risks (RR) or rate ratios with 95% confidence intervals (CI) for binary outcomes for all studies reporting one or more events (all-cause mortality, cardiovascular mortality, rate of nonfatal cardiovascular events, rate of hospitalisation, rate of hypotension during dialysis, change in dialysis modality) and mean difference (MD) with 95% CI for continuous outcomes (serum B_2 microglobulin, Kt/V, URR, blood pressure).

Data from cross-over studies were included when authors reported results for the first phase of the study (Mandolfo 2008; Schiffl 2007; Vaslaki 2006). The studies of Schiffl 2007 and Vaslaki 2006 presented the results separately for the two phases and we included in our analysis data from the first phase. For Cristofano 2004, the results of first phase of the study were obtained after contacting the authors. For all the other cross-over studies, results were extracted and presented in narrative form in a tabular format when available.

Dealing with missing data

Any additional unpublished information or clarification required from the authors was requested by written or electronic correspondence and relevant data obtained in this manner were included in the review.

Assessment of heterogeneity

Heterogeneity of treatment effects between studies was formally tested using the Cochran Q test. The I^2 statistic was used to determine the proportion of variation in treatment estimates present that was attributable to heterogeneity beyond the level of that expected by chance (Higgins 2003).

Data synthesis

Data were pooled using a random effects model. For each analysis, the fixed effects model was also evaluated to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses to explore how possible sources of heterogeneity (type of treatment (different types of convective therapy (HF, HDF, AFB)); membrane flux (high *versus* low); age; allocation concealment) might modify treatment effects were not conducted as there was either no evidence for heterogeneity in analyses or insufficient numbers of studies available to conduct analysis.

To assess for potential bias from small study effects, we constructed funnel plots for the log risk ratio against its variance (standard error) for individual studies and formally assessed for plot asymmetry by using the Egger regression test.(Egger 1997).

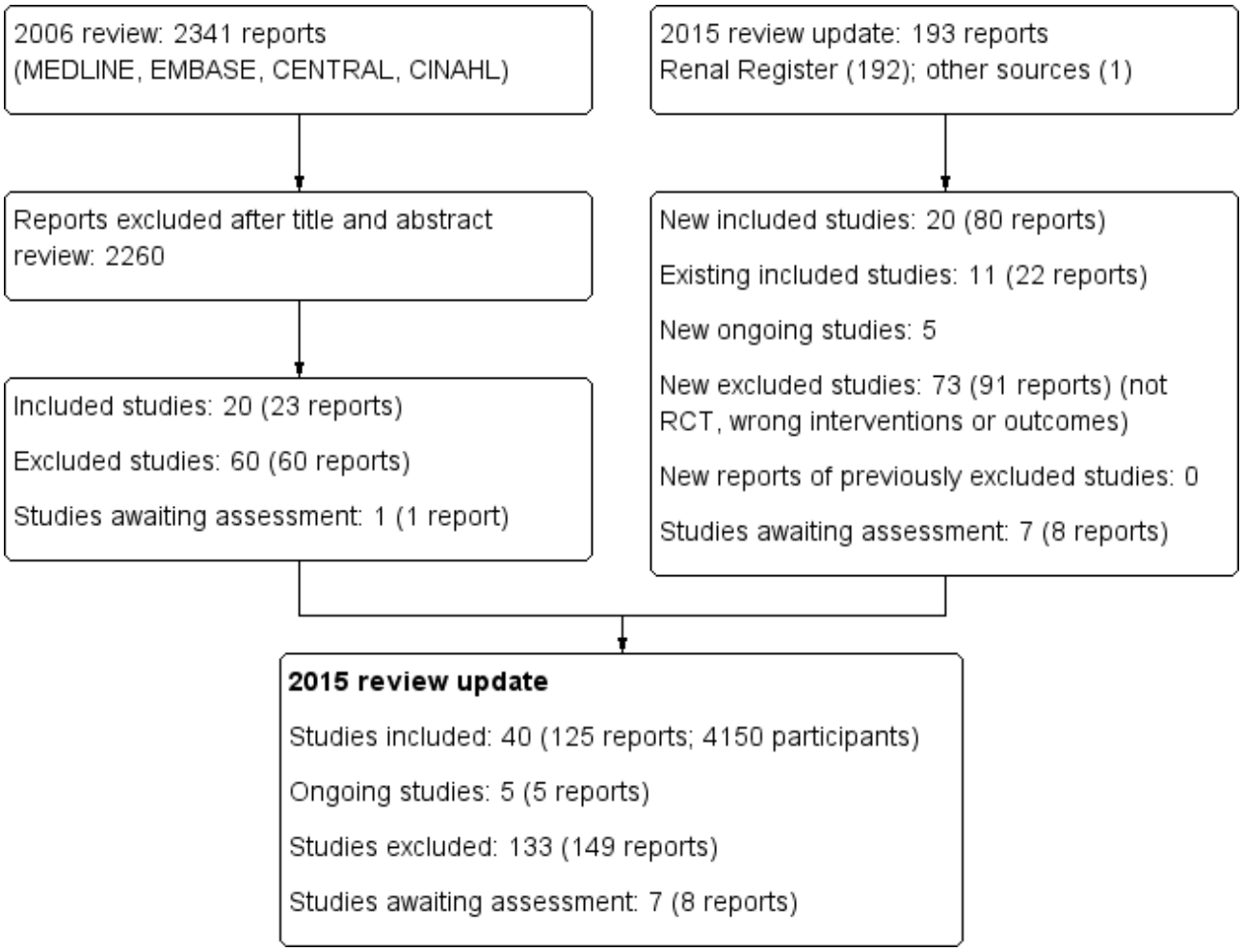
RESULTS

Description of studies

Results of the search

The results of the search processes are shown in Figure 1.

Figure 1. Study flow diagram.



2006 review

The combined search of MEDLINE, EMBASE, CINAHL, CENTRAL, American Journal of Physicians Database, and Database of Abstracts of Reviews of Effectiveness in May 2006 identified 2341 potentially relevant studies. After reviewing titles and abstracts, 2260 studies were excluded. The full text-versions of 81 studies were retrieved, 59 which were excluded and one study (Ohyama 1981) in Japanese was waiting assessment. The major reason for exclusion was that the identified studies were not randomised. In total 20 studies (Altieri 2004; Bammens 2004; Basile 2001; Beerenhout 2005; Ding 2002; Eiselt 2000; Fox 1993; Lin 2001; Locatelli 1994; Lornoy 1998; Movilli 1996; Noris 1998; Schiffl 1992; Schrander vd Meer 1998; Teo 1987; Todeschini 2002; Tuccillo 2002; Verzetti 1998; Ward 2000; Wizemann 2000) reported in 23 publications enrolling 654 participants were included in the first version of this review.

2015 review update

The updated search of the Cochrane Renal Group's Specialised Register (18 February 2015) identified 193 new reports. After review 91 reports (73 studies) were excluded.

Five citations were ongoing studies with protocols available in the on-line clinical studies registries (NCT01098149; NCT01327391; NCT01396863; NCT01445366; NCT02374372. We included 20 additional studies in this update (80 reports; 3483 participants) (Bolasco 2003; Coll 2009; CONTRAST (Dutch) Study 2005; Cristofano 2004; ESHOL Study 2011; Karamperis 2005; Kantartzi 2013; Mandolfo 2008; Meert 2009; Ohtake 2012; Pedrini 2011a; PROFIL Study 2011; Righetti 2010; Santoro 2005a; Schiffl 2007; Selby 2006a; Stefansson 2012; Santoro 1999; TURKISH HDF 2013; Vaslaki 2006).

Forty studies (4137 participants) could be included in the review. Thirty-five studies (4039 participants) compared HF, HDF or AFB with HD, three studies (54 participants) compared AFB with HDF, and three studies (120 participants) compared HDF with HF (Table 1). For the studies that have been reported more than once, only data from the latest versions were used. The characteristics of the populations and interventions in the included studies are reported in the Characteristics of included studies .

Prior to publication of this review update a final search of the Specialised Register identified seven new potential studies (Beerenhout 2004; Bellien 2014; Cornelis 2014; de Sequera 2013; Francisco 2013; Gonzales-Diez 2012; Krieter 2010a). These studies will be assessed for inclusion in a future update of this review.

Included studies

The 40 included studies were grouped into five subsets (Characteristics of included studies; Table 2).

Convective versus diffusive therapy

1. HF versus HD (Beerenhout 2005; Bolasco 2003; Fox 1993; PROFIL Study 2011; Santoro 2005a; Schiffl 1992)
2. HDF versus HD (Bammens 2004; Bolasco 2003; CONTRAST (Dutch) Study 2005; Cristofano 2004; ESHOL Study 2011; Karamperis 2005; Kantartzi 2013; Lin 2001; Locatelli 1994; Lornoy 1998; Mandolfo 2008; Ohtake 2012; Pedrini 2011a; Righetti 2010; Schiffl 2007; Stefansson 2012; Teo 1987; Tuccillo 2002; TURKISH HDF 2013; Vaslaki 2006; Ward 2000; Wizemann 2000)
3. AFB versus HD (Basile 2001; Eiselt 2000; Noris 1998; Schrander vd Meer 1998; Selby 2006a; Santoro 1999; Todeschini 2002; Verzetti 1998)

Study characteristics

Of the 22 studies evaluating HDF, all but three (Locatelli 1994; Teo 1987; Tuccillo 2002) reported convection methods using fluid generated on-line (on-line HDF). In the HD control group, 12 studies (34%) used high-flux membranes, 16 studies (46%) used low-flux membranes, four studies (11%) used either low or high-flux membrane and in three studies (9%) the membrane flux was unclear. Convection strategies were highly heterogeneous and no study randomised participants to specific targeted convection volumes. In 16 (46%) studies, adequate vascular access for high volume dialysis was required. Most studies included patients who were anuric or had minimal kidney function.

Seventeen studies had a parallel study design (Beerenhout 2005; CONTRAST (Dutch) Study 2005; Cristofano 2004; Eiselt 2000; ESHOL Study 2011; Lin 2001; Locatelli 1994; Bolasco 2003; Ohtake 2012; PROFIL Study 2011; Santoro 2005a; Schiffl 1992; Schrander vd Meer 1998; Santoro 1999; TURKISH HDF 2013; Ward 2000; Wizemann 2000). Ten studies evaluated short-term outcomes conducted over follow-up that varied between one dialysis sessions and two weeks of treatment (Bammens 2004; Cristofano 2004; Fox 1993; Karamperis 2005; Lornoy 1998; Mandolfo 2008; Noris 1998; Selby 2006a; Todeschini 2002; Tuccillo 2002). The remaining 24 studies evaluated outcomes during treatment of between two and 48 months (median 12 months) except one in which treatment duration was unclear (Lin 2001). Sample size varied between five and 906 participants (median 24). Of the overall participants, 2402 (59%) were derived from three large studies evaluating on-line HDF (CONTRAST (Dutch) Study 2005; ESHOL Study 2011; TURKISH HDF 2013).

Direct comparisons of different convective therapies

1. HDF versus AFB (Coll 2009; Ding 2002; Movilli 1996)
2. HDF versus HF (Altieri 2004; Bolasco 2003; Meert 2009).

Three studies (Locatelli 1994; Schiffl 1992; Bolasco 2003) had three or more treatment arms. These studies had a parallel study design. In the study by Locatelli 1994, HDF was compared with cuprophane HD, low-flux polysulfone HD and high -flux polysulfone HD. Schiffl 1992 compared HF with both low-flux HD and high-flux polysulfone HD. Bolasco 2003 assigned participants to HF, HDF or HD. When analysing data from these studies for dichotomous outcomes, convective modalities were compared with the combined results of all the HD treatment arms. For continuous data analysis, data for HDF compared with HD were used.

Study characteristics

Of the six studies comparing convection with another convective strategy, five reported convection methods using fluid generated on-line. Two studies used high-flux (33%) membranes for HD, one reported low-flux membranes (17%), and in the remainder the HD flux was unclear. Convection strategies were highly heterogeneous and no study randomised participants to specific targeted convection volumes. In four (66%) studies, adequate vascular access for high volume dialysis was required. Most studies included patients who were anuric or had minimal renal function.

One study had a parallel study design (Bolasco 2003) and the remainder were cross-over studies. Follow-up duration ranged between two and 24 months (median six months) with only one study reporting follow-up for 12 months or more. Study sample sizes were small (12 to 76 participants; median 21).

Excluded studies

In total 133 studies (149 reports) were excluded. The reasons for exclusion were; not randomised (69); wrong population (1); wrong intervention (43); or outcomes not relevant to this review (23).

Risk of bias in included studies

Risk of bias in individual studies is shown in Figure 2 and the summary risk of bias in included studies is shown in Figure 3. According to standard criteria (Appendix 2), studies generally had very serious limitations due to risks of bias in most evaluated domains leading to down-grading of overall evidence quality.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

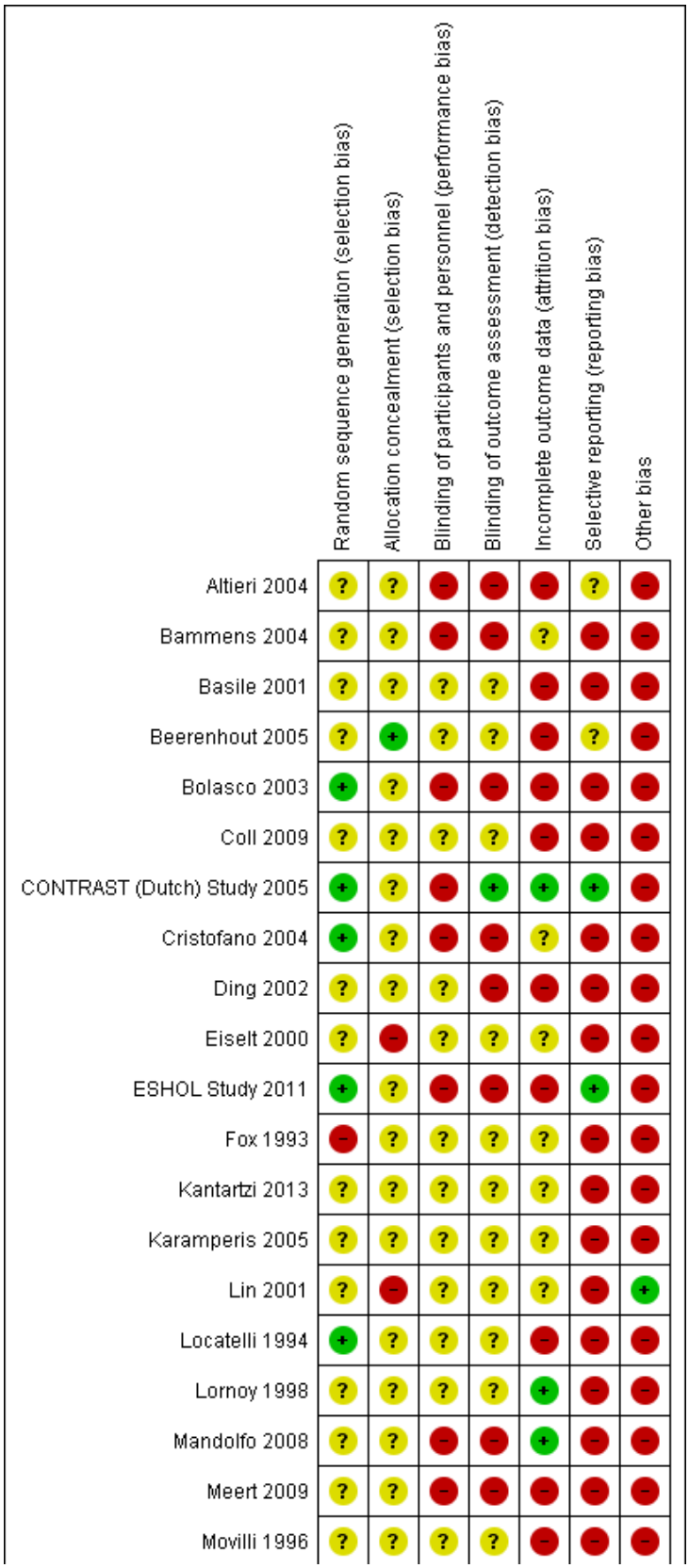


Figure 2. (Continued)

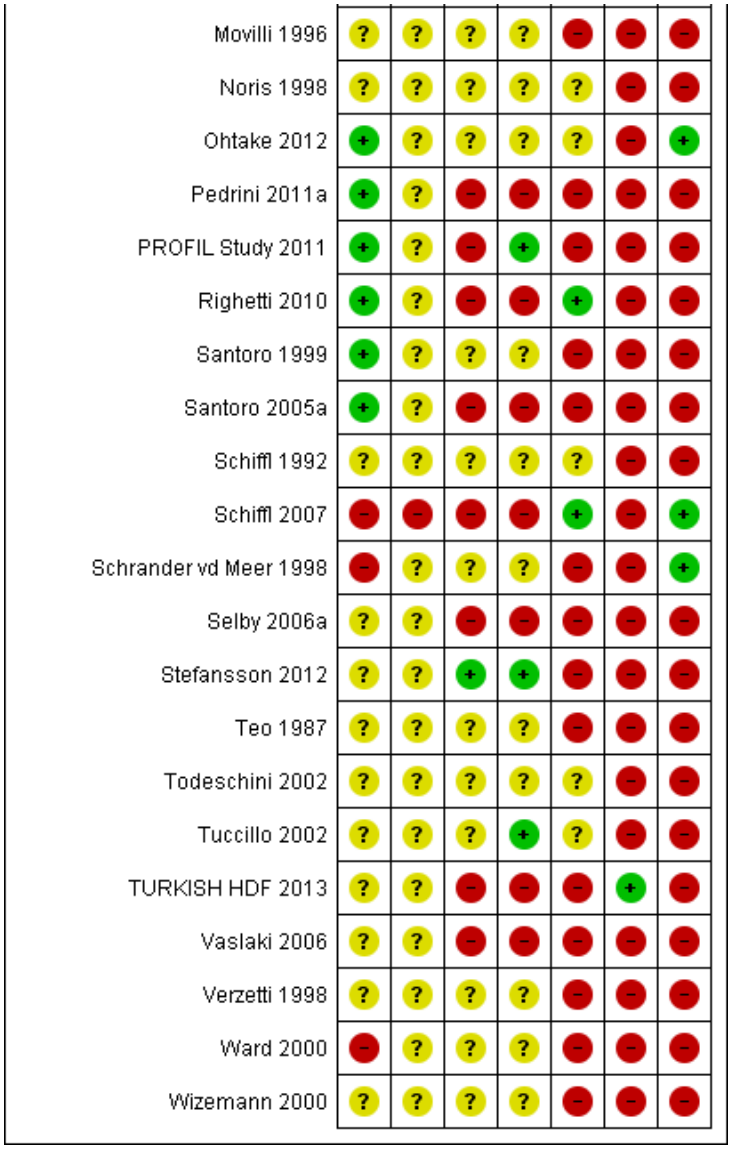
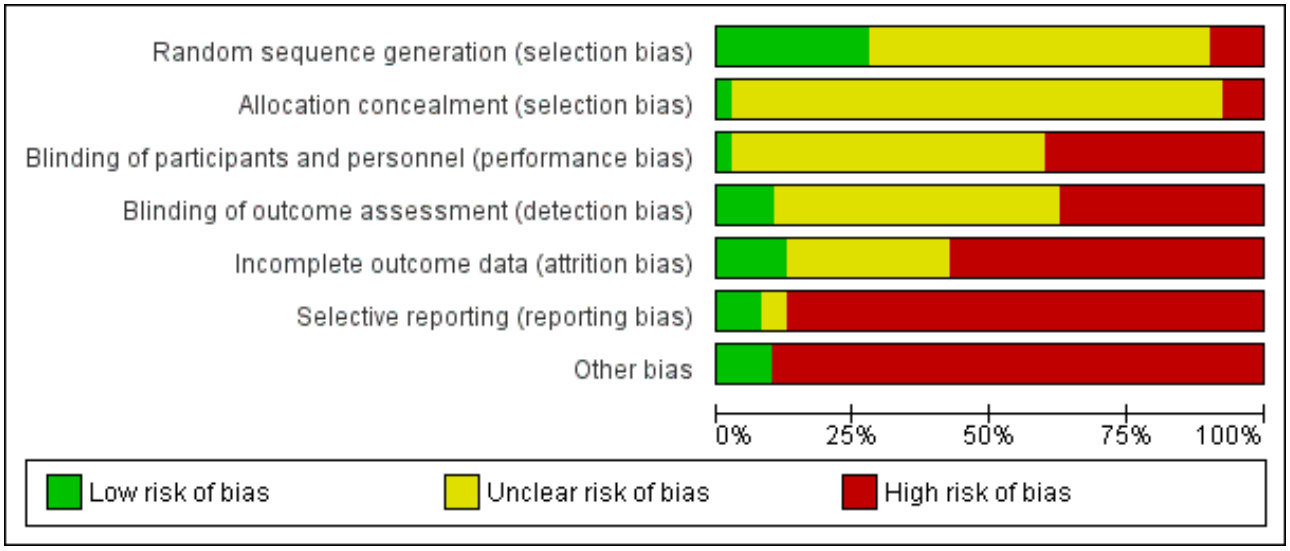


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

All studies stated that patients were randomly allocated to treatment groups. Sequence generation methods were at low risk of bias in 11 studies (Bolasco 2003; CONTRAST (Dutch) Study 2005; Cristofano 2004; ESHOL Study 2011; Locatelli 1994; Ohtake 2012; Pedrini 2011a; PROFIL Study 2011; Righetti 2010; Santoro 1999; Santoro 2005a), high risk in four studies (Fox 1993; Schiffl 2007; Schrander vd Meer 1998; Ward 2000), and unclear in the remainder.

Allocation concealment was at low risk of bias in one study (Beerenhout 2005), high risk in three studies (Eiselt 2000; Lin 2001; Schiffl 2007) and unclear in the remainder.

Blinding

Two studies reported blinding of participants (Karamperis 2005; Stefansson 2012) but not investigators for all outcomes and three (CONTRAST (Dutch) Study 2005; PROFIL Study 2011; Stefansson 2012) reported blinding of outcome assessment. In Tuccillo 2002, we considered that the lack of blinding will not influence the results. In Karamperis 2005, the authors did not blind the investigators but used electronic devices for assessing the outcomes.

Incomplete outcome data

A key risk of bias present in all but five studies (CONTRAST (Dutch) Study 2005; Lornoy 1998; Mandolfo 2008; Righetti 2010; Schiffl 2007) was the lack of complete outcome data for at least 90% of randomised patients and/or loss of patients to follow-up was not similar between treatment groups for reasons unrelated to the outcomes of interest. Of the three largest studies contributing to the meta-analyses, ESHOL Study 2011 did not include 39% of randomised patients in their analyses, and in the TURKISH HDF 2013, 21% of participants left the study for reasons other than death including 10% of the participants allocated to HDF due to vascular access problems. Twenty-three studies were at high risk of incomplete follow-up (Altieri 2004; Basile 2001; Beerenhout 2005; Bolasco 2003; Coll 2009; Ding 2002; ESHOL Study 2011; Locatelli 1994; Meert 2009; Movilli 1996; Pedrini 2011a; PROFIL Study 2011; Santoro 1999; Santoro 2005a; Schrander vd Meer 1998; Selby 2006a; Stefansson 2012; Teo 1987; TURKISH HDF 2013; Vaslaki 2006; Verzetti 1998; Ward 2000; Wizemann 2000) and the risk was unclear in the remainder.

Selective reporting

Three studies were at low risk of bias for selective outcome reporting (CONTRAST (Dutch) Study 2005; ESHOL Study 2011; TURKISH HDF 2013), in two studies it was unclear (Altieri 2004; Beerenhout 2005) and the remainder were at high risk.

Other potential sources of bias

Twenty-one studies (52%) had a cross-over design which was considered as a potential source of bias because of the carry over effect. All but four studies (Lin 2001; Ohtake 2012; Schiffl 2007; Schrander vd Meer 1998) were at high risk of other sources of bias including: commercial sponsor on authorship, or data management, or both; interventions or baseline participant characteristics or both were not matched; data not extractable for meta-analysis; abstract-only publication; or early termination of the study.

Effects of interventions

See: **Summary of findings for the main comparison**

Convective transport (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis

All-cause and cardiovascular mortality

In eleven studies (3396 participants), convective dialysis treatment had no significant effect on all-cause mortality compared to HD (Analysis 1.1 (11 studies, 3396 participants): RR 0.87, 95% CI 0.72 to 1.05; I^2 = 34%). There was a moderate level heterogeneity between the studies.

Convective therapy significantly reduced death from cardiovascular causes compared with HD (Analysis 1.2 (6 studies, 2889 participants): RR 0.75, 95% CI 0.61 to 0.92; I^2 = 0%). In absolute

terms, convective therapy might prevent 25 cardiovascular deaths for every 1000 patients treated for one year, but has no significant effect on death overall.

Nonfatal cardiovascular events and hospitalisation

CONTRAST (Dutch) Study 2005 reported no significant effect on nonfatal cardiovascular events for convective dialysis versus HD (Analysis 1.3 (1 study, 714 participants): RR 1.14, 95% CI 0.86 to 1.50).

Locatelli 1994 reported no significant difference between convective therapy and HD for the number of hospitalisations/year (Analysis 1.4.1 (1 study, 45 participants): MD 0.20 hospitalisations/y, 95% CI -0.07 to 0.47).

There was no significant difference between convective therapy and HD for the number of days spent in hospital (Analysis 1.4.2 (2 studies, 67 participants): MD -1.22 days, 95% CI -7.47 to 5.03; I^2 = 90%), and rate of hospitalisation (Analysis 1.5 (2 studies, 1688 participants): RR 1.23, 95% CI 0.93 to 1.63; I^2 = 0%). Verzetti 1998 (cross-over study) reported less hospitalisation in the convective therapy group compared to the HD group (data presented in Analysis 1.17.1). The substantial level of heterogeneity observed in the analysis of days spent in hospital might be possibly due to the 10 year difference in the date of publication of contributing studies.

Change in dialysis modality

The proportion of participants crossing over to another form of dialysis was not significantly different between treatment modalities (Analysis 1.6 (5 studies, 2919 participants): RR 0.87, 955 CI 0.41 to 1.84; I^2 = 47%). There was a moderate level heterogeneity between the studies.

Blood pressure

ESHOL Study 2011 reported the number of hypotensive events/person-years of follow-up; convective dialysis significantly reduced the rate of hypotension during dialysis (Analysis 1.7 (906 participants): RR 0.72, 95% CI 0.66 to 0.80). In two studies, the percentage of dialysis sessions complicated by hypotension was not significantly different (Analysis 1.8 (2 studies, 42 participants): MD -4.05%, 95% CI -15.39 to 7.30; I^2 = 0%). Seven cross-over studies reported data on number of patients experiencing hypotension, intradialytic hypotensive events or symptomatic intradialytic hypotensive events and reported uncertain effects of convective therapy (data presented in Analysis 1.17.2; Analysis 1.17.3; Analysis 1.17.4)

There was no significant difference between convective therapy and HD on predialysis systolic (Analysis 1.9.1 (7 studies, 1859 participants): MD 1.19 mm Hg, 95% CI -1.46 to 3.84; I^2 = 44%) or diastolic blood pressure (Analysis 1.9.2 (6 studies, 1154 participants): MD -0.25 mm Hg, 95% CI -1.06 to 0.56; I^2 = 0%). There was moderate heterogeneity between studies in treatment effects on predialysis systolic blood pressure.

Lin 2001 reported that the maximal drop in blood pressure during dialysis was significantly less with convection therapy compared to HD (Analysis 1.10 (1 study, 67 participants): MD -28.70 mm Hg, 95% CI -38.60 to -18.80).

In cross-over studies convective therapy was not significantly different from HD for predialysis systolic, diastolic, and mean arterial blood pressure (Analysis 1.17,5; Analysis 1.17.6; Analysis 1.17.7). Similarly, in cross-over studies, convective therapy was not significantly different from HD for postdialysis systolic blood pressure, diastolic blood pressure, fall in systolic blood pressure, and mean arterial blood pressure (Analysis 1.17.8; Analysis 1.17.9; Analysis 1.17.10; Analysis 1.17.11). There was no difference between before- and after-dialysis systolic or diastolic blood pressure in cross-over studies Analysis 1.17.12; Analysis 1.17.13). Blood pressure during dialysis was lower with convective therapy in one cross-over study (Selby 2006a; Analysis 1.17.14; Analysis 1.17.15; Analysis 1.17.16).

Quality of life

Data for health-related outcomes were reported in eight studies (988 participants) (Beerenhout 2005; CONTRAST (Dutch) Study 2005; Kantartzi 2013; Lin 2001; Schiffl 2007; Stefansson 2012; Verzetti 1998; Ward 2000) and described in Table 3. Of these, 50% (four studies) were a parallel group design (Beerenhout 2005; CONTRAST (Dutch) Study 2005; Lin 2001; Ward 2000). In the CONTRAST (Dutch) Study 2005, changes in quality of life scores for all domains assessed were not statistically different between the groups. Lin 2001 reported that participants treated with convective therapy had significantly higher end-of-treatment "patient well-being" scores although results for tolerance and mental alertness were not reported (Analysis 1.11.6 (1 study, 67 patients): MD 0.60, 95% CI 0.30 to 0.90). In the study of Ward 2000, patients in both treatment groups had similar perceptions of quality of life. Patients showed a significant improvement in physical symptoms during the study, irrespective of treatment allocation. There was little or no effect on the quality of life dimensions assessed by the Kidney Diseases Questionnaire including fatigue, depression, relationships, frustration, and between-dialysis patient well-being score (Ward 2000; Analysis 1.11). Similarly, in Beerenhout 2005, physical symptoms improved from baseline in the convection group but no direct comparison in scores comparing convection with diffusion treatment was reported for physical scores and other domains (frustration, depression) did not change significantly. The remaining four studies were cross-over design and disaggregated data for the end of the first phase of treatment were not available.

Urea clearance and B_2 microglobulin

Convective therapy increased Kt/V (Analysis 1.12 (14 studies, 2022 participants): MD 0.07, 95% CI -0.00 to 0.14; I^2 = 90%) and URR (Analysis 1.13 (3 studies, 879 participants): SMD 0.39, 95% CI 0.06 to 0.72; I^2 = 48%). There were moderate to high levels of heterogeneity between studies. Ten cross-over studies reported heterogeneous treatment effects for convective therapy on predialysis Kt/V (Analysis 1.17.17). A single cross-over study reported a higher URR with convective therapy (Analysis 1.17.18).

Convective therapy significantly lowered pre-dialysis serum B_2 microglobulin compared with diffusive therapies (Analysis 1.14 (12 studies, 1813 participants): MD -5.55 mg/L, 95% CI -9.11 to -1.98; I^2 = 94%). Heterogeneity was significant across the studies. There was no significant difference between convective therapy and HD on end of treatment B_2 microglobulin clearance (Analysis 1.15 (3 studies, 65 participants): MD 13.05 mg/L, 95% CI -5.94 to 32.04; I^2 = 85%). Heterogeneity was high between the studies. Schiffl

1992 reported data for dialysate B_2 microglobulin levels and found significantly higher dialysate B_2 microglobulin concentrations in the dialysate with convection therapy (Analysis 1.16 (1 study, 20 patients): MD 133.00 mg/L, 95% CI 71.46 to 194.54). Four cross-over studies (Kantartzi 2013; Pedrini 2011a; Righetti 2010; Stefansson 2012) reported lower levels of predialysis serum B_2 microglobulin levels with convective therapy (Analysis 1.17.19).

Symptoms (headaches, nausea, vomiting) related to dialysis

Symptoms of headaches, nausea/vomiting were not reported in any of the included studies.

Amyloid-related complications

Only Lin 2001 reported this outcome with respect to carpal tunnel syndrome. The authors reported that 8/38 participants in the convective treatment group had carpal tunnel syndrome compared with 3/29 patients in the HD group within 13 dialysis sessions after commencing the study. Details of the number of patients in each treatment arm with carpal tunnel syndrome at baseline were not provided. Considering the long duration needed to develop carpal tunnel syndrome, it is probable that at baseline there may have been more participants in the convective modality group with carpal tunnel syndrome. Due to this potential imbalance in participant characteristics, we did not analyse this outcome based on the results of this study.

Convective therapy versus convective therapy: haemofiltration versus haemodiafiltration

All-cause and cardiovascular mortality

Bolasco 2003 reported no significant difference in all-cause mortality between HF and HDF (Analysis 2.1 (1 study, 76 participants): RR 2.78, 95% CI 0.57 to 13.44).

Cardiovascular mortality was not reported in any of the included studies.

Hospitalisation

No data were available from the parallel RCTs.

Altieri 2004 reported no significant difference between HF and HDF for the number of days spent in hospital (Analysis 2.4.1).

Change in dialysis modality

Data for change in dialysis modality comparing HF with HDF were not available.

Blood pressure

No data were available from the parallel RCTs for hypotension.

Altieri 2004 reported no significant difference in the number of patients experiencing hypotension but the rate of hypotension episodes/patient/month was significantly lower with HF compared to HDF (Analysis 2.4.2).

Bolasco 2003 reported no significant difference between HF and HDF for systolic (Analysis 2.2.1 (1 study, 70 participants): MD -4.20 mm Hg, 95% CI -13.01 to 4.61) and diastolic blood pressure (Analysis 2.2.2 (1 study, 70 participants): MD -2.10 mm Hg, 95% CI -6.97 to 2.77). Altieri 2004 reported HDF lowered predialysis systolic blood pressure (Analysis 2.4.4) but had no significant effects on predialysis diastolic blood pressure (Analysis 2.4.5) and mean arterial pressure (Analysis 2.4.6). Similarly, Altieri 2004 also reported no significant differences between HF and HDF on postdialysis systolic (Analysis 2.4.7), diastolic (Analysis 2.4.8) and mean arterial pressure (Analysis 2.4.9).

Altieri 2004 reported no significant difference in the number of patients experiencing hypertension between HF and HDF (Analysis 2.4.10).

Quality of life

Data for quality of life comparing HF with HDF were not available from any of the included studies.

Urea clearance and B_2 microglobulin

Bolasco 2003 reported a significantly higher Kt/V with HDF compared with HF (Analysis 2.3 (1 study, 58 participants): MD -0.24, 95% CI -0.33 to -0.15). Similarly, Altieri 2004 reported HDF resulted in a higher Kt/V compared to HF (Analysis 2.4.11).

No data were available from the parallel RCTs for B_2 microglobulin. Altieri 2004 reported no significant difference between HDF and HF on predialysis B_2 microglobulin levels (Analysis 2.4.12). Meert 2009 reported HF resulted in higher B_2 microglobulin clearance compared to HDF (Analysis 2.4.13).

Symptoms (headaches, nausea, vomiting) related to dialysis

Altieri 2004 reported that patients tended to experience less headache on HF than HDF (P = 0.06) and that there was no significant differences for other intradialytic symptoms between convective therapies.

Convective therapy versus convective therapy: haemodiafiltration versus acetate-free biofiltration

Data for outcomes comparing HDF with AFB were not reported in any parallel RCTs.

Mortality

Data for mortality comparing HDF with AFB were not reported.

Hospitalisation

Movilli 1996 reported no significant difference between HDF and AFB on number of hospitalisations and length of hospital stay (Analysis 3.1.1; Analysis 3.1.2).

Change in dialysis modality

Data for change in dialysis modality comparing HDF with AFB were not reported.

Blood pressure

Coll 2009 and Movilli 1996 reported data for this outcome with inconsistent findings between studies. Movilli 1996 reported no significant difference in number of dialysis sessions complicated by hypotension (Analysis 3.1 .3), while Coll 2009 reported a significant reduction in hypotensive events in the AFB arm (Analysis 3.1.3).

Ding 2002 reported no significant difference between HDF and AFB on predialysis systolic blood pressure (Analysis 3.1.4) and mean

arterial pressure (Analysis 3.1.5) and postdialysis systolic blood pressure (Analysis 3.1.6).

Quality of life

Ding 2002 reported no significant difference between HDF and AFB on interdialysis symptom score (Analysis 3.1.7).

Urea clearance and B_2 microglobulin

Movilli 1996 reported no significant difference between HDF and AFB on Kt/V (Analysis 3.1.8). Ding 2002 reported no significant difference between HDF and AFB on URR (Analysis 3.1.9). Ding 2002 and Movilli 1996 both reported no significant difference between HDF and AFB on pre-dialysis B_2 microglobulin values (Analysis 3.1.10).

Symptoms (headaches, nausea, vomiting) related to dialysis

Movilli 1996 reported no significant difference between HDF and AFB on headache, nausea or vomiting (Analysis 3.1.11).

Bias from small-study effects and sensitivity analysis

For the 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 (Figure 4; Figure 5; Figure 6) suggestive of bias from small-study effects.

Figure 4. Funnel plot of comparison: 1 Convection (haemofiltration/HDF/acetate-free biofiltration) versus haemodialysis, outcome: 1.1 All-cause mortality.

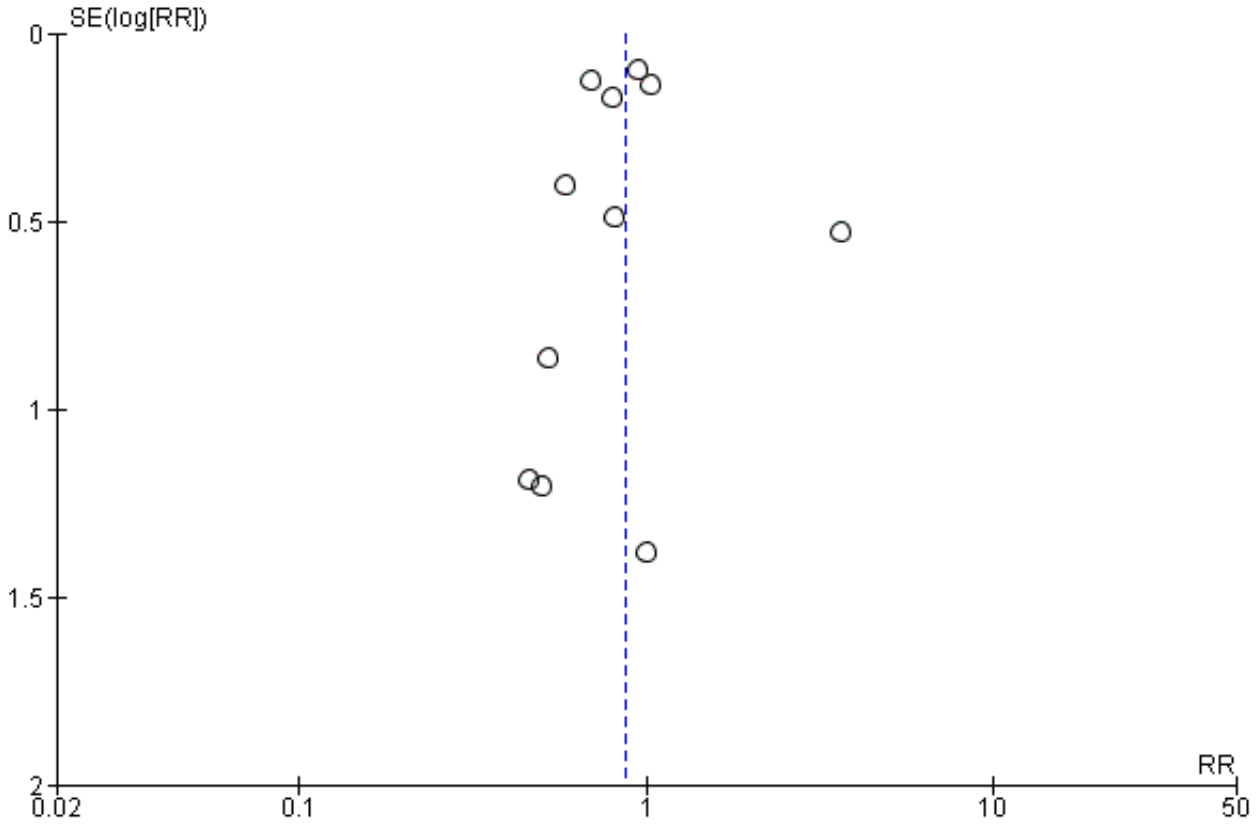


Figure 5. Funnel plot of comparison: 1 Convection (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis, outcome: 1.2 Cardiovascular mortality.

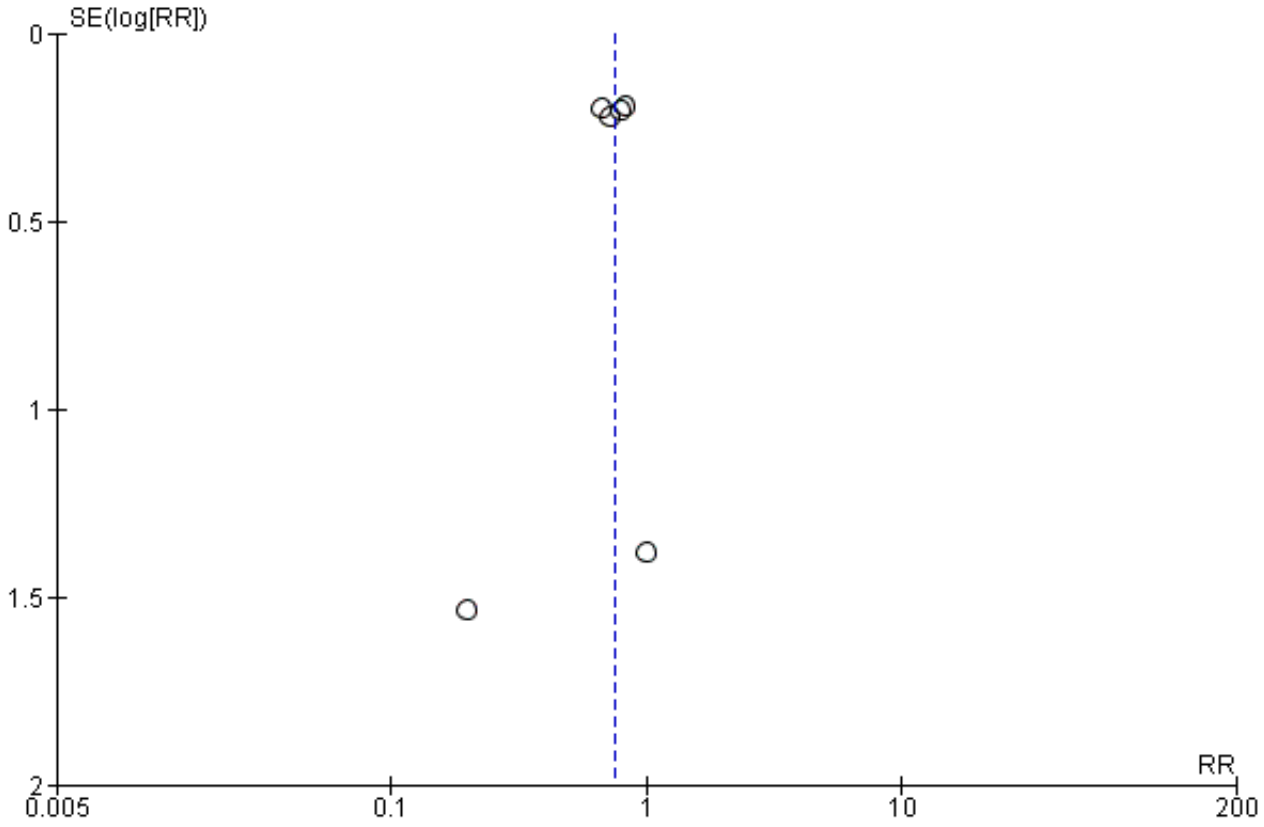
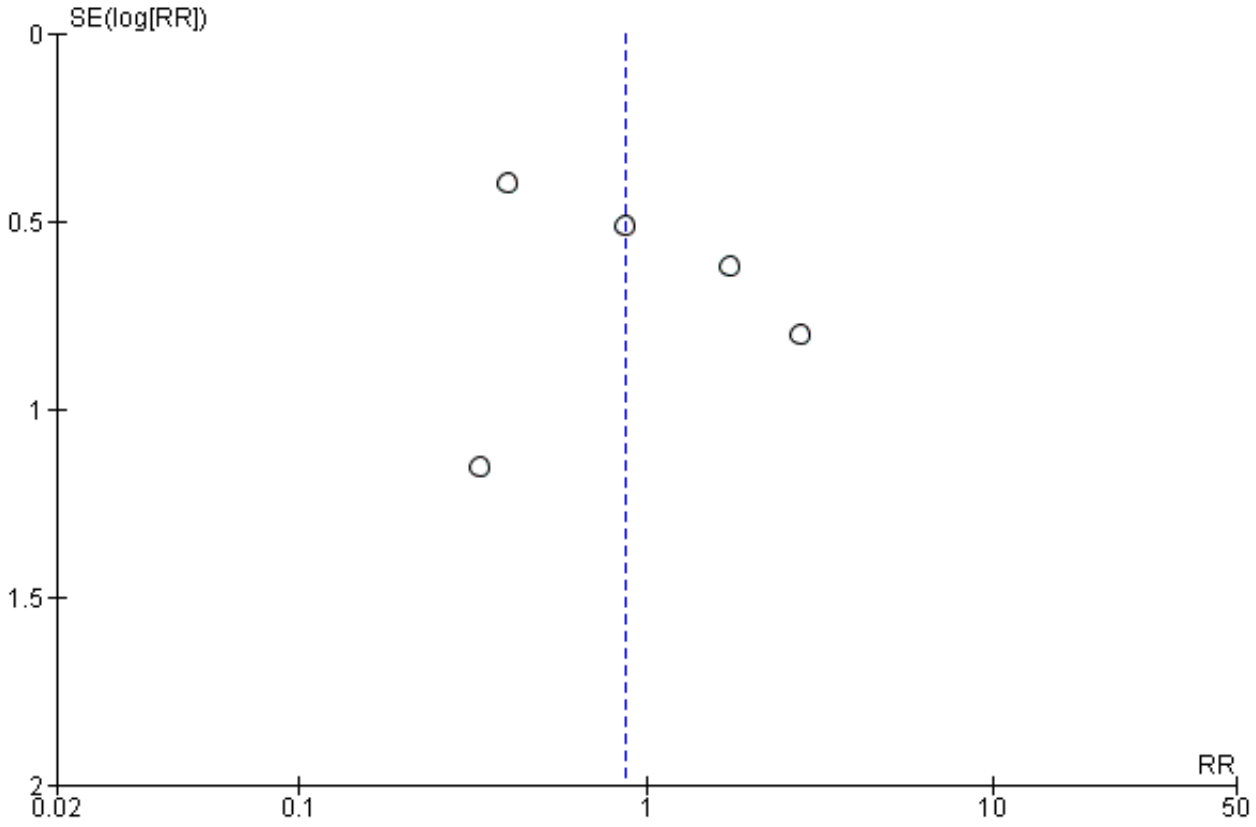


Figure 6. Funnel plot of comparison: 1 Convection (haemofiltration/HDF/acetate-free biofiltration) versus haemodialysis, outcome: 1.6 Change of dialysis modality.



When analyses of convection versus diffusion modalities were limited to studies comparing HDF with HD, we found very similar treatment effects. Compared to HD, HDF had no significant effect on all-cause mortality (7 studies, 2837 participants; RR 0.86, 95% CI 0.65 to 1.13) (Bolasco 2003; CONTRAST (Dutch) Study 2005; ESHOL Study 2011; Locatelli 1994; Schiffl 2007; TURKISH HDF 2013; Wizemann 2000) albeit with evidence of moderate heterogeneity (I^2= 53%, P = 0.046) HDF reduced cardiovascular mortality (4 studies, 2512 participants; RR 0.72, 95% CI 0.57 to 0.91)(CONTRAST (Dutch) Study 2005; ESHOL Study 2011; Schiffl 2007; TURKISH HDF 2013), but not change in dialysis modality (4 studies, 2512 participants; RR 0.99, 95% CI 0.49 to 2.00) (CONTRAST (Dutch) Study 2005; ESHOL Study 2011; Bolasco 2003; TURKISH HDF 2013). Data for rates of nonfatal cardiovascular events, hospitalisation and hypotension during dialysis were already limited to studies comparing HDF with HD.

DISCUSSION

Summary of main results

Thirty-five studies in 4039 dialysis patients compared convective dialysis treatment (HDF, HF or AFB) with HD and six studies (174 participants) compared convective therapy directly with another convective therapy. Convective dialysis modalities had little or no effect on all-cause mortality, may reduce cardiovascular death and hypotension during dialysis, but had uncertain effects on rates of nonfatal cardiovascular events and hospitalisation and serious limitations in study methodology markedly reduced our confidence in any treatment benefits of HDF. There was no difference in risks of changing dialysis modality between convective and diffusive modalities and treatment effects on clearances of urea and B_2 microglobulin were markedly inconsistent between studies.

Overall completeness and applicability of evidence

First, while there were statistical reductions in cardiovascular mortality and rates of hypotension with HDF treatment, serious limitations in study methodologies reduced confidence in the conclusions that might be drawn from the available evidence for convective and diffusive dialysis modalities. Allocation concealment, blinding of outcome assessment, complete reporting of patient-relevant outcomes and inclusion of patients in outcome analyses was inadequate in most studies, and therefore the evidence quality for clinical outcomes was downgraded to low or very 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.

Second, higher achieved convection volumes for HDF were associated with lower mortality in post-hoc non-randomised analyses within CONTRAST (Dutch) Study 2005, TURKISH HDF 2013, and ESHOL Study 2011. However, caution is needed before concluding this is evidence for the need to deliver high convection volumes to reduce all-cause mortality with HDF. Convection

volumes were not randomised treatment targets in any study (in other words, patients at randomisation were not equally likely to be assigned to specific convection volume targets) and as such the relationship observed between convection volume and mortality is also 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 poorer outcomes) 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 more viable and alternative explanations for the association between convection volume and risk of death.

Third, there was considerable heterogeneity in the dialysis interventions across studies 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 standardisation 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 no studies evaluated serious adverse events according to international definitions. Understanding hazards of treatment are 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 randomised study evidence.

Finally, the generalisability 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, as data were frequently limited to participants who had vascular access sufficient to sustain high convection volumes.

Potential biases in the review process

The strengths of this review include the searching of conference proceedings and inclusions of additional unpublished data to provide a comprehensive analysis of all available evidence and the rigorous assessment of quality which has been incorporated into review conclusions using the methods of the GRADE guidelines. The limitations in this review are largely due to the reporting adequacy of the primary included studies.

Agreements and disagreements with other studies or reviews

This is an update of a review reported in 2006, which found insufficient evidence to provide robust recommendations for convective therapy to improve clinical outcomes for men and women who have ESKD (Rabindranath 2006). Despite the addition of 20 new studies including 3483 participants between 2006 and 2015, evidence for the benefits and harms of convective dialysis therapy remains low or very low quality.

The European Best Practice Guidelines on Haemodialysis (EBPG 2007) suggest on-line HDF or HF should be considered to delay long-term complications of dialysis therapy and that exchange volumes should be as high as possible. Current utilisation of HDF varies widely. Prevalence of HDF ranges between 0.3 and 232 per million of population within countries and regions of Europe (ERA-EDTA Registry 2010) and the proportion of HDF as the treatment modality for patients in Australasia ranges between 0.8% and 23% (ANZDATA 2012). This review suggests the benefits of HDF or HF from contemporaneous RCTs are limited to reducing cardiovascular mortality and hypotension during dialysis and that evidence limitations lead to low confidence in these treatment benefits. None of the available studies randomised participants treated with HDF to different targeted convection volumes and accordingly robust evidence supportive of higher convection volumes to improve dialysis outcomes is not available.

This review draws similar conclusions to a recent systematic review and meta-analysis that compared convective dialysis therapies (including high-flux HD, HF, or HDF) with low-flux HD alone (Susantitaphong 2013). In that review which included 36 parallel arm studies showed that convective therapies had little or no effect on all-cause mortality (RR 0.88, 95% CI 0.76 to 1.02), and reduced risks of cardiovascular mortality (RR 0.84, 95% 0.71 to 0.98) and hypotension (RR 0.55, 95% CI 0.35 to 0.87). Unlike the present review, the quality of the available evidence was not incorporated into the review conclusions.

This review diverges from the conclusions of the largest HDF study to date (ESHOL Study 2011). This review finds no treatment effects of HDF in mortality, compared to a 30% relative reduction in risk of death from any causes during 36 months of follow-up in the ESHOL Study 2011. We suggest that the consistent findings across all studies in the meta-analysis for mortality in this review (variation in the estimates was not beyond that expected by chance) indicate the overall summary estimate is robust even accounting for the findings of the ESHOL Study 2011. Notably in that study, patients were withdrawn and not included in analyses if they did not receive the allocated treatment modality for two months or more, including those who did not achieve the minimum requested replacement volume (18L/session). As it is probable these participants might have had poorer outcomes (such as poorer vascular access due to other comorbidities including vascular disease or diabetes) and may have been preferentially excluded from follow-up, the ESHOL Study 2011 might unreliably estimate mortality risk. It would be informative to re-evaluate mortality data from ESHOL Study 2011 using intention-to-treat analyses that include mortality outcome data for all randomised patients according to their original treatment assignment.

AUTHORS' CONCLUSIONS

Implications for practice

While there is increasing but variable uptake of HDF in Europe, the current body of evidence provides low or very-low quality evidence suggesting confidence in estimated treatment effects of convective dialysis therapies is limited or very limited. Convective dialysis may reduce cardiovascular events or rates of hypotension during dialysis but effects on mortality, nonfatal cardiovascular events and hospitalisation in addition to quality of life and adverse events are inconclusive and the overall confidence in these results is low or very low. Until there are additional robust studies, widespread uptake of convective therapies including HDF is not warranted and targeting higher convection volumes to improve outcomes is not supported by high-quality evidence.

Implications for research

A significant number of studies have now been conducted to assess the effectiveness of convective dialysis therapies to improve clinical outcomes in people treated with HD. However, given the methodological limitations in the available studies, additional studies that are powered to evaluate treatment effects of HDF on mortality, major cardiovascular events, and adverse treatment effects are needed before widespread uptake of HDF is warranted. In addition, given the hypothesis that higher convection volumes might improve clinical outcomes from convective therapy, future studies targeting specific convection volumes and using intention-to-treat analysis that show benefit for clinical outcomes are required before higher convection volumes can be recommended.

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2006 review

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2015 review

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Altieri 2004

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 6 months
Participants	• Country: Italy • Setting: multi-centre (13 centres) • ESKD patients on dialysis for at least 6 months and were in stable clinical condition

Altieri 2004 *(Continued)*

- Number (randomised/analysed): 39/30
- Mean age ± SD: 58.4 ± 19.3
- Sex (M/F): 10/20
- Exclusion criteria: daily diuresis of more than 200 mL; presence of chronic infection, malignancy, systemic disease, liver insufficiency or active liver illness; overt malnutrition; clinically evident cardiac dysfunction; serious endocrine dysfunction; overt peripheral vascular disease; malfunction of vascular access; body weight exceeding 75 kg

Interventions	Treatment group
	• HF with high-flux polyflux 21S filter
	  ○ QB: 300 mL/min
	Control group
	• HDF with high-flux polyflux 14S filters
	  ○ QB: 300 mL/min
	  ○ QD: 500 mL/min
	Total substitution volume: 60 L/patient/session
	Treatment duration: 12 months

Outcomes	Intradialytic problems • Hypotension episode • Hypertension episode • Cardiac arrhythmias • Dyspnoea, fever cramps, headache, pruritus, nausea, vomiting Interdialytic problems • Hypotension episode • Hypertension episode • Cardiac arrhythmias • Dyspnoea, fever cramps, headache, pruritus, nausea, vomiting • Insomnia, fatigue, abnormal thirst, diarrhoea, constipation Other • Kt/V • B_2 microglobulin • Ambulatory BP monitoring
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding • Funding: commercial sponsor listed as author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated

Altieri 2004 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated; probably not done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated; probably not done
Incomplete outcome data (attrition bias) All outcomes	High risk	Not using intention-to-treat analysis; loss to follow-up 6/39 (23%)
Selective reporting (reporting bias)	Unclear risk	No protocol of the study available
Other bias	High risk	Carry over effect might be present because of the cross-over design; data at the end of first phase of treatment not available; commercial sponsor listed as author

Bammens 2004

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 2 weeks
Participants	• Country: Germany • Setting: single centre • Stable chronic HD patients ◦ Mean time on dialysis: 24.8 months • Number: 14 • Sex (M/F): 10/4 • Mean age ± SD: 66.6 ± 3.1 years • Exclusion criteria: not stated
Interventions	Treatment group 1 • HDF with replacement solution at 40, 60, 80 and 100 mL/min in a post-dilution mode Treatment group 2 • HDF with replacement solution at 80 mL/min in pre-dilution mode Both treatment groups • Duration of each session: 4 hours • Dialyser: Fresenius F80 • QD: 600 mL/min • QB: 300 mL/min • HDF with replacement solution at 120 mL/min in post-dilution mode, with a QB of 350 mL/min and an QD of 800 mL/min was also studied in 6 patients, 2 sessions each Control group • HD high-flux ◦ Duration of each session: 4 hours

Bammens 2004 *(Continued)*

	○ Dialyser: Fresenius F80 ○ QD: 600 mL/min ○ QB: 300 mL/min • HD with a QB of 350 mL/min and an QD of 800 mL/min was also studied in 6 patients, 2 sessions each Co-interventions: NS
Outcomes	• B_2 microglobulin reduction ratio • URR
Notes	• Additional data requested from authors: method of randomisation; details regarding blinding • Funding: "Supported in part by the Fonds voor Wetenschappelijk Onderzoek (FWO) grant no. 1127602N; FX80 dialyzers were provided by Fresenius Medical Care, Bad Homburg, Germany."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated; probably not done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated; probably not done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data about drop-outs provided after different cross-over phases; lost to follow-up: 0/14
Selective reporting (reporting bias)	High risk	Data at the end of first phase of treatment not available
Other bias	High risk	Carryover effect present because of the cross-over design; data not extractable for meta-analysis

Basile 2001

Methods	• Study design: cross-over RCT • Study time frame: NS • Duration of follow-up: 6 months/phase
Participants	• Country: Italy • Setting: single centre • HD patients aged 18 to 75 years; routine use of EPO with no change in the 3 months preceding enrolment; rHuEPO dosage: < 120 IU/Kg/wk and EPO resistance index, 10 IU/kg/wk of Hb in the 3 months preceding enrolment; assurance from patients not to use EPO during the study; maintenance bicarbonate dialysis thrice-weekly for at least 6 months previously with a cellulose dialyser; dialysis dosage

Basile 2001 *(Continued)*

> 1.2 of equilibrated single-pool Kt/V; negligible residual renal function; no change in iron, folic acid, vitamin B_{12} or ACEi in the 3 months preceding the study
  - Mean time on dialysis: 53.2 months
- Number (eligible/randomised/analysed): 23/15/10
- Mean age: 59.9 ± 7.2 years
- Gender (M/F): 6/4
- Exclusion criteria: unstable conditions in the 3 months prior to the study; treatment with drugs affecting erythropoiesis; blood transfusion in the 3 months preceding enrolment

Interventions	Treatment group
	• Thrice weekly AFB with AN69 dialyser
	  ○ Post-dilution infusion at a rate of 2L/h
	  ○ QB: approximately 300 mL/min
	  ○ QD: approximately 500 mL/min
	  ○ Infusion rate: 2 L/h
	  ○ Duration: 6 months (run-in period: 4 months)
	Control group
	• Thrice-weekly, low-flux HD with cellulose acetate membrane
	  ○ QB: approximately 300 mL/min
	  ○ QD: approximately 500 mL/min
	  ○ Duration: 6 months (run-in period: 4 months)
	Co-interventions: NS

Outcomes	• Kt/V • Mortality
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated; probably not done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated; probably not done
Incomplete outcome data (attrition bias) All outcomes	High risk	33% loss to follow-up (5/15 patients whose Hb dropped at monthly checks were withdrawn from the study)

Basile 2001 *(Continued)*

Selective reporting (reporting bias)	High risk	Data at the end of first phase of treatment not available
Other bias	High risk	Carry over effect present because of the cross-over design; data not available for meta-analysis

Beerenhout 2005

Methods	• Study design: parallel RCT • Study time frame: NS • Duration of follow-up: 12 months
Participants	• Country: Netherlands and Belgium • Setting: multi-centre (2) • Chronic HD patients on dialysis for at least 3 months and with adequate arteriovenous access ○ Mean time on dialysis (months): treatment group (33); control group (24) • Number: treatment group (20); control group (20) • Mean age ± SD (years): treatment group (59 ±13); control group (58 ± 12) • Sex (M/F): treatment group (12/11); control group (16/4) • Exclusion criteria: CV morbidity defined as ejection fraction < 25% and/or coronary heart disease (NYHA Class 3-4); severe intercurrent illness
Interventions	Treatment group • HF with high-flux polyamide (Polyflux 24S) dialysers Control group • HD with low-flux polyamide (Polyflux 8S) dialysers
Outcomes	• BP • URR • Kt/V • QoL
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding • Funding: "This study was supported by a research grant from Gambro Corporate Research, Lund, Sweden."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Centrally and envelopes were used
Blinding of participants and personnel (performance bias)	Unclear risk	Not stated

Beerenhout 2005 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing outcome data balanced across groups with similar reasons for missing data across groups but with 13/40 patients (32%) not included in the final analysis
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	High risk	Imbalanced ratio men/women between groups; interventions not matched; funded by industry

Bolasco 2003

Methods	• Study design: parallel RCT • Study time frame: 2003 to 2008 • Duration of follow-up: 1.5 years; median 0.8 to 2.2
Participants	• Country: Italy • Setting: multi-centre • Chronic HD patients on dialysis for at least 6 months; aged 18 to 80 years; thrice-weekly HD or HDF; body weight ≤ 90 kg ○ Mean time on dialysis: 3.0 (1.4 to 7.7) years • Number: 146 • Age: Mean 67.4 years • Sex (M/F): 84/62 • Exclusion criteria: malignancies, active systemic disease, active hepatitis or cirrhosis, instable diabetes, diuresis >200 mL/24 h, dysfunction of vascular access, with blood flow rate < 300 mL/min; clinically relevant infections, active systemic diseases

Interventions	Treatment group 1
	• HF with high-flux polyamide dialysers
	  ○ Infusate/blood flow ratio of 0.6
	  ○ Dialysate infusate rate of 700 mL/min
	Treatment group 2
	• HDF with high-flux polyamide dialysers
	  ○ Infusate/blood flow ratio of 0.6
	  ○ Dialysate infusate rate of 700 mL/min
	Control group
	• HD with low-flux dialysers
	  ○ Dialysate flow rate of 500 mL/min

Outcomes	• BP control • Intradialytic symptomatic hypotension • Mortality • Kt/V

Bolasco 2003 *(Continued)*

Notes	• Exclusions post randomisation but pre-intervention: 10 patients • Stop or end point/s: not stated • Additional data requested from authors: none • Funding source: "We thank Gambro-Hospal for the logistic support given to the investigator meetings."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computer generated: " randomisation list that was stratified by centre and prepared in advance by one author"
Allocation concealment (selection bias)	Unclear risk	Patients were centrally randomised using an email assignment from one of the authors
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	10/146 (14%) withdrew from study due to transfer to another technique, thrombosis or vascular access infection, withdrawal of consent, transfer to another centre, transfer to another study, infection)
Selective reporting (reporting bias)	High risk	Key patient relevant outcomes not reported
Other bias	High risk	Interventions and patient characteristics not matched; industry support provided

Coll 2009

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 15 months
Participants	• Country: Spain • Setting: multi-centre (6 centres) • Chronic HD patients on dialysis for at least 3 months; age > 18 years; thrice-weekly HD; stable regimen of anticoagulation and EPO; HCT > 28%; blood flow rate > 250 mL/min ○ Mean time on dialysis: 67 ± 57 (4 to 249) months • Number (enrolled/randomised/analysed): 35/30/21 • Mean age ± SD: 62 ± 14 years • Sex (M/F): 20/15 • Exclusion criteria: coagulation problems; survival rate < 18 months; diuresis > 400 mL/24h; CrCl > 2 mL/min
Interventions	Treatment group

Coll 2009 *(Continued)*

	• Predilution HDF acetate-free dialysate for 6 months, 3 to 4 hours, 3 times/week (611 free-acetate, Bellco, Mirandola, Italy) Control group • Predilution HDF with conventional bicarbonate dialysate for 6 months, 3 to 4 hours 3 times/week (Formula dialysis machine, Bellco, Mirandola, Italy)
Outcomes	• Number of hypotensive episodes (fall in SBP < 95 mm Hg, associated with symptoms requiring the intervention of healthcare professionals) • HD tolerance (number of headaches episodes, pruritus, vomiting or cramps per month) • Variation of biochemical parameters • B_2 microglobulin
Notes	• Exclusions post randomisation but pre-intervention: 5 patients • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding, supplementary data about hypotensive events, other non-reported outcomes • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Insufficient information, the method of concealment is not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	"no difference for dialysis tolerance between the groups"; no intention-to-treat analysis; lost to follow-up (9; no clear description of drop-outs, reasons or belonging)
Selective reporting (reporting bias)	High risk	Not all of the study's pre-specified primary outcomes have been reported; data at the end of first phase of treatment not available
Other bias	High risk	Important difference between selected and analysed patients (e.g. dialysis vintage 249 months in the selected initial group versus 164 months in the analysed group); carry over effect present because of the cross-over design

CONTRAST (Dutch) Study 2005

Methods	• Study design: parallel RCT • Study time frame: June 2004 to January 2011 • Duration of follow-up: 3 years

CONTRAST (Dutch) Study 2005 *(Continued)*

Participants	• Country: Canada, Netherlands, Norway
	• Setting: Multi-centre, 28 centres
	• Patients treated by HD 2 or 3 times/week, for at least 2 months; able to understand the study procedures; willing to provide written informed consent
	  ○ Mean time on dialysis: treatment group (2.8 ± 2.9); control group (3.0 ± 2.8)
	  ○ Diabetes: treatment group (26%); control group (22%)
	• Number: treatment group (358); control group (356)
	• Mean age ± SD (years): treatment group (64.1 ± 14.0); control group (64.0 ± 13.4)
	• Sex (M/F): treatment group (224/144); control group (231/125)
	• Exclusion criteria: current age < 18 years; treatment by HDF or high-flux HD in the 6 months preceding randomisation; severe noncompliance defined as non-adherence to the dialysis prescription, a life expectancy; 3 months due to causes other than kidney disease; and participation in another clinical intervention study evaluating CV outcome

Interventions	Treatment group • Post-dilution on-line HDF; 2 or 3 times/week, target convection volume 6 L/h Control group • Low-flux HD 2 or 3 times/week Both groups • Only biocompatible synthetic dialysers were used (Gambro or Fresenius products)
Outcomes	• All-cause mortality • Fatal and non-fatal CV events • LVMi, carotid intima media thickness, aortic pulse wave velocity • Laboratory markers of endothelial dysfunction, micro-inflammation, oxidative stress • Lipid profiles, uraemic toxins • QoL • Nutritional state • Anaemia management • Hospital admissions • BP and antihypertensive medication • Residual kidney function • Mineral bone disease • Parameters of treatment/treatment delivery (dialysis efficiency (Kt/V urea), blood flow, dialysate flow, ultrafiltration volume, (HDF) convection volume
Notes	• Exclusions post randomisation but pre-intervention: none • Stop or end point/s: 21 patients stopped for other reasons in the HDF group versus 32 patients in the HD group • Funding source: this study was partly supported by grants from Fresenius Medical Care, Gambro Healthcare, Baxter Healthcare Corporation and Roche Pharma AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally by blocks
Allocation concealment (selection bias)	Unclear risk	Centrally

CONTRAST (Dutch) Study 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not done: "Because of the nature of the intervention, it was not possible to blind the patients, the local study nurses, or the investigators to the treatment assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adjudication committee unaware of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the results are available
Selective reporting (reporting bias)	Low risk	All important outcomes are reported
Other bias	High risk	Interventions not matched between treatment groups; early termination due to futility; funded by industry

Cristofano 2004

Methods	• Study design: parallel RCT • Study time frame: not stated • Duration of follow-up: one dialysis session
Participants	• Country: Italy • Setting: single centre • Chronic stable HD patients ○ Mean time on dialysis: not stated • Number: treatment group (6); control group (6) • Age: not stated • Sex (M/F): 6/6 • Exclusion criteria: not stated
Interventions	Treatment group • HDF Control group • Low-flux HD
Outcomes	• B_2 microglobulin (mg/L) • B_2 microglobulin dialysate clearance • Other biochemical measurements
Notes	• Abstract-only publication • Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation, details regarding blinding, allocation concealment, supplementary results data • Funding: not stated

Risk of bias

Cristofano 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	The allocation was made by means of a computer generated sequence
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated. probably not done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated, probably not done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not sufficiently detailed
Selective reporting (reporting bias)	High risk	Insufficient information
Other bias	High risk	Abstract-only publication

Ding 2002

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 12 months
Participants	• Country: Italy • Setting: single centre • Stable maintenance HD patients ○ Mean duration on dialysis: 83.5 months • Number: 12 • Sex (M/F): 8/4 • Mean age ± SD: Mean 49.7 ± 11.3 years • Exclusion criteria: not stated

Interventions	Treatment group
	• HDF treatments carried out using F-60s high-flux polysulfone dialysers
	  ○ QB: 250 mL/min
	  ○ QD: Pre-dilution 620 mL/min, post-dilution 720 to 740 mL/min
	  ○ Infusion flow rate: pre-dilution 180 mL/min, post-dilution 60 to 80 mL/min
	Control group
	• AFB was buffer free and acidosis was corrected with a 166 mEq/L sodium bicarbonate solution as the substitution fluid
	  ○ QD: 500 mL/min
	  ○ Infusion fluid rate: 25 to 30 mL/min

Ding 2002 *(Continued)*

	Co-interventions: not stated
Outcomes	• URR • B_2 microglobulin reduction rate
Notes	• Exclusions post randomisation: 3 patients violated the study protocol • Stop or end point/s: not stated • Additional data requested from authors: none requested • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	High risk	"A second patient refused to finish post-HDF and insisted that AFB be tried because of his unbearable shoulder"
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis; 3 patients violated the study protocol (one patient's fistula failed during the second month of pre-HDF; one refused to finish post-HDF; one patient had severe headache accompanied by poorly controlled hypertension at the end of pre-HDF shift and dropped out of the study before starting post-HDF modality)
Selective reporting (reporting bias)	High risk	Data for end of first phase of treatment not available
Other bias	High risk	Carry over effect present because of the cross-over design

Eiselt 2000

Methods	• Study design: parallel RCT • Study time frame: not stated • Duration of follow-up: 12 months
Participants	• Country: Czech Republic • Setting: Single centre • Regular HD patients ○ Mean duration of dialysis (months): treatment group (50 ± 40); control group (41 ± 20) • Number: treatment group (10); control group (10) • Mean age ± SD (years): treatment group (38 ± 9); control group (47 ± 10) • Sex (M/F): not stated

Eiselt 2000 *(Continued)*

	• Exclusion criteria: presence of diabetes mellitus; infection or unstable clinical condition in the 3 months preceding commencement of study

Interventions	Treatment group
	• AFB, high-flux polyacrylonitrile dialysers, 3 times/week
	  ○ Mean dialysis session: 4 hours
	  ○ Mean buffer solution infusion rate: 1.73 L/h
	  ○ Duration: 12 months
	Control group
	• HD, low-flux dialysers, 3 times/week
	  ○ Mean dialysis session: 4.2 hours
	  ○ Duration: 12 months
	Co-interventions
	• rHuEPO (Hb 90 to 115 g/L)
	• IV iron

Outcomes	• Kt/V • Mortality
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details about blinding • Funding: 'supported by grant 4002-3 awarded by the Ministry of Health of the Czech Republic, and by research project n. 206032 (111400002) called Renal Replacement Therapy".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomised according to the cause of their underlying CKD
Allocation concealment (selection bias)	High risk	Inadequate: names were drawn from individual subgroups at the following ratios 1:1
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient data; no loss to follow-up
Selective reporting (reporting bias)	High risk	Not all patient important outcomes reported
Other bias	High risk	Interventions and baseline patient characteristics not matched

ESHOL Study 2011

Methods	• Study design: parallel RCT • Study time frame: May 2007 to October 2011 • Duration of follow-up: 3 years

Participants	• Country: Spain
	• Setting: multi-centre (27)
	• Patients aged ≥18 years; currently undergoing HD; clinical stability; stable vascular access
	  ○ Mean time on dialysis ± SD (months): treatment group (47.4 ± 55); control group (50.3 ± 71)
	  ○ Diabetes: treatment group (22.8%); control group (27.1)
	• Number: treatment group (456); control group (450)
	• Mean age ± SD (years): treatment group (64.56 ± 14.4); control group (66.36 ± 14.3)
	• Sex (M/F): treatment group (317/139); control group (289/161)
	• Exclusion criteria: chronic inflammatory diseases; liver cirrhosis; malignancies; chronic immunosuppressant or anti-inflammatory use; dialysis through temporary catheter or single puncture

Interventions	Treatment group • Post-dilution on-line HDF 3 times/week Control group • HD 3 times/week Both groups • The length of dialysis sessions in each treatment modality was not modified • For patients on post-dilution HDF, a minimum of 18 L/session replacement volume was requested
Outcomes	• Survival • Intradialysis tolerance (symptomatic hypotension episodes, cramps, headache, fatigue and thoracic pain) • Hospitalisations for any reason • Dialysis adequacy (time average concentration, Kt/V, URR, nutrition parameters) • BP control • Anaemia, lipid metabolism and phosphate control • B_2 microglobulin reduction ratio
Notes	• Exclusions post randomisation but pre-intervention: 33 • Stop or end point/s: not stated • Funding: this study was partly supported by grants from Fresenius Medical Care and Gambro Healthcare

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A central computerised random-generator
Allocation concealment (selection bias)	Unclear risk	Centrally
Blinding of participants and personnel (performance bias)	High risk	Open-label study

ESHOL Study 2011 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	High risk	355/906 discontinued the study, 39% from the total number of included patients, 41% in the HDF arm
Selective reporting (reporting bias)	Low risk	All the prespecified outcomes were reported
Other bias	High risk	Commercial sponsor on authorship or involved in data management; interventions and baseline patient characteristics not matched

Fox 1993

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: one dialysis session
Participants	• Country: USA • Setting: single centre • Stable patients on chronic HD; consent to participate in the study ○ Mean time on dialysis: 54 months • Number: 9 patients • Mean age ± SD: 63 ± 4 years • Sex (M/F): all male • Exclusion criteria: not stated

Interventions	Treatment group
	• HF
	  ○ QB: 400 mL/min
	  ○ Exchange volume: 1/3 of body weight
	  ○ Duration: one session
	Control group
	• HD
	  ○ QB: 250 to 300 mL/min
	  ○ QD: 600 mL/min
	  ○ Duration: one session
	Co-interventions: not stated

Outcomes	• BP • Hypotensive episodes (systolic BP < 100 mm Hg)
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation and details regarding blinding • Funding: not stated

Fox 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"by coin toss", an insecure method
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient data; no loss to follow-up
Selective reporting (reporting bias)	High risk	Data for end of first phase of treatment not available, no protocol of the study available
Other bias	High risk	Carry over effect present because of the cross-over design; data not extractable for meta-analysis

Kantartzi 2013

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 3 months on each dialysis technique
Participants	• Country: Greece • Setting: single centre • Age > 18 years, regular (for at least 3 months) HD 3 times/week ○ Mean time on dialysis: 31 ± 23.28 months • Number: 24 • Mean age ± SD: 62 ± 13.34 years • Sex (M/F): 19/5 • Exclusion criteria: not stated
Interventions	Treatment group 1 • On-line high-flux HDF Treatment group 2 • High-flux HDF with prepared bags of substitution (HDF) Control group • Low-flux conventional HD

Kantartzi 2013 *(Continued)*

Outcomes	• QoL • Kt/V • B_2 microglobulin
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Funding: not stated, "The authors report no conflicts of interest."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Lost to follow-up 2/24; no clear description of drop-outs or reasons
Selective reporting (reporting bias)	High risk	Data at the end of first phase of treatment not available
Other bias	High risk	Carry over effect due to cross-over design, interventions not matched

Karamperis 2005

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: one dialysis session on each dialysis technique
Participants	• Country: Denmark • Setting: single centre • aged > 18 years; stable without severe clinical symptoms of heart failure (NYHA 0 – II); regular (for at least 3 months) HD, HDF or HF 3 times/week; possibility to ultrafiltrate approximately 3% of the body weight during dialysis; HCT > 30% and stable arterio-venous fistula ○ Mean time on dialysis: 7 ± 7 years (range 0.5 to 20 years) • Number: 12 • Mean age ± SD: 54 ± 13 years • Sex (M/F): 8/4 • Exclusion criteria: body dry weight > 95 kg; intradialytic adverse events or hypotensive episodes requiring intervention in more than 1 dialysis session within 4 weeks; diabetes mellitus; acute MI within 3 months; angina pectoris; symptoms of severe heart failure (New York Heart Association Classes III

Karamperis 2005 *(Continued)*

	– IV); cerebrovascular incident within 3 months; arterial hypertension (DBP > 110 mm Hg at the beginning of dialysis, during the last 3 weeks); cardiac arrhythmia; haemodynamic significant cardiac valve defect; noncompliant fluid intake; predialysis plasma Ca-ion < 1.05 or > 1.40 mmol/L; infection; gastrointestinal haemorrhage; pregnancy; severe illness such as malignancy; alcohol or drug abuse and noncompliance or unwillingness to follow the protocol
Interventions	Treatment group • On-line predilution HDF for one dialysis session, 4.5 hours/session (Fresenius 4008H dialysis console with high-flux HDF100 S filters) Control group • Low-flux conventional HD for one dialysis session, 4.5 hours/session (Fresenius 4008H dialysis console with low-flux F8 HPS filters)
Outcomes	• Haemodynamic changes during dialysis session (hypotension, mean BP, cardiac output, stroke volume, cardiac work) • Kt/V • Total peripheral resistance
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation, allocation concealment, supplementary data about specific outcomes • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"The treatment modality was blinded to the patient by use of filter types unknown to the patients and not ordinarily used in the department. The tubing was mounted as to haemodiafiltration in all sessions, and the indicators showing the treatment modality on the console were covered." Investigators not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated, probably not done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clearly stated that all patients that performed one dialysis have done the second dialysis session as well
Selective reporting (reporting bias)	High risk	Data for end of first phase of treatment not available
Other bias	High risk	Study conducted in two consecutive dialysis sessions, "wash out effect" insufficient, carry over effect might be present because of the cross-over design; data not extractable for meta-analysis; interventions not matched

Lin 2001

Methods	• Study design: parallel RCT • Study time frame: not stated • Duration of follow-up: 15 months
Participants	• Country: Taiwan • Setting: single centre • Chronic stable and anuric ESKD patients on HD for more than 6 months • Number: treatment group (38); control group (29) • Mean age ± SD (years): treatment group (55.0 ± 11.0); control group (53.7 ± 11.4) • Sex (M/F): treatment group (24/14); control group (18/11) • Exclusion criteria: unstable clinical condition

Interventions	Treatment group
	• On line HDF, 3 times/week with high-flux F-80 polysulfone dialyser
	  ◦ QB: > 250 mL/min
	  ◦ QD: 500 mL/min
	Control group
	• High-flux HD 3 times/week with polysulfone F80 dialysers
	  ◦ QB: > 250 mL/min
	  ◦ QD: 500 mL/min
	Co-interventions: not stated

Outcomes	• Carpal tunnel syndrome • Intradialytic symptoms • Interdialytic symptoms • Intradialytic symptomatic hypotensive episodes • Drop in BP • Interdialytic patient well-being score • Kt/V • URR
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	High risk	Inadequate: "We used partially randomised patient preference (PRPP) design by incorporating patient preferences into this randomised trials"
Blinding of participants and personnel (performance bias)	Unclear risk	Not stated

Lin 2001 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated, insufficient information
Selective reporting (reporting bias)	High risk	Outcome/s of interest reported incompletely and cannot be used in meta-analysis; protocol of the study unavailable; failure to report a key/expected outcome (mortality, major CV events)
Other bias	Low risk	Not additional risks apparent

Locatelli 1994

Methods	• Study design: parallel RCT • Study time frame: May 1991 to November 1992 • Duration of follow-up: 1 year
Participants	• Country: Italy • Setting: multi-centre • Aged 18 to 70 years; RRT for at least 2 months; on dialysis for > 3 months; regular HD 3 times/week; stable clinical condition • Number: treatment group 1 (50); treatment group 2 (54); treatment group 3 (51); treatment group 4 (50) • Mean age ± SD (years): treatment group 1 (50.5 ± 13.5); treatment group 2 (53.7 ± 12.9); treatment group 3 (56.0 ± 12.2); treatment group 4 (52.7 ± 12.9) • Sex (M): treatment group 1 (66%); treatment group 2 (72.2%); treatment group 3 (70.6%); treatment group 4 (80.0%) • Exclusion criteria: presence of malignant disease; MI in the previous 12 months; stroke or TIA in the previous 6 months; severe heart failure (NYHA class 3 or 4)
Interventions	Treatment group 1 • Low-flux HD with cuprophane membranes Treatment group 2 • Low-flux HD with polysulfone membrane Treatment group 3 • High-flux HD with polysulfone membrane Treatment group 4 • High-flux HDF with polysulfone membrane Co-interventions: not stated
Outcomes	• Mortality • B_2 microglobulin levels • Number and length of hospitalisations

Locatelli 1994 *(Continued)*

	• Kt/V
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: none requested • Funding: the steering committee, the data coding and collection and the secretariat of this study included employees of Fresenius Medical Department, Italy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate: "Randomization was centralized at the Department of Nephrology at Lecco Hospital, using separate lists for each Center that were randomly divided into blocks of four for the assignment of two or four treatments (depending on the treatments available in the different Centers)."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	108/205 analysed (46%) (34% due to technical reasons, acute clinical reason, fistula-related reason, treatment inadequacy)
Selective reporting (reporting bias)	High risk	Key outcomes not reported
Other bias	High risk	Interventions not matched and patient characteristics not matched at baseline; interventions and patient characteristics not matched; commercial sponsor involved in the conduct of this study

Lornoy 1998

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 1 dialysis session
Participants	• Country: Belgium • Setting: single centre • Chronic anuric HD patients ○ Mean time on dialysis: 6.9 years • Number: 8 • Mean age (range): 68.33 years (60 to 75) • Sex (M/F): not stated • Exclusion criteria: not stated

Lornoy 1998 *(Continued)*

Interventions	Treatment group 1
	• HDF with replacement solution at 40, 60, 80 and 100 mL/min in a post-dilution mode
	Treatment group 2
	• HDF with replacement solution at 80 mL/min in pre-dilution mode
	Control group
	• HD
	  ○ Duration of each session: 4 hours
	  ○ Dialyser: Fresenius F80
	  ○ QD: 600 mL/min
	  ○ QB: 300 mL/min
	Co-interventions: not stated

Outcomes	• B_2 microglobulin clearance
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation and details regarding blinding • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/8 lost to follow-up
Selective reporting (reporting bias)	High risk	Insufficient information; protocol of the study not available; only data about B_2 microglobulin were available
Other bias	High risk	Carry over effect present because of the cross-over design; data not extractable for meta-analysis

Mandolfo 2008

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 6 weeks
Participants	• Country: Italy • Setting: multi-centre (2) • Chronic HD patients on dialysis for at least 12 months; clinically stable; vascular access with blood flow rate < 300 mL/min (inadequate vascular access) ○ Mean time on dialysis: 62 ± 24.0 months • Number: 8 • Mean age ± SD: 72.2 ± 4.8 years • Sex (M/F): 5/3 • Exclusion criteria: presence of vascular access recirculation higher than 5% with a Qb of 250 mL/nub
Interventions	Treatment group • Mid-dilution HDF a. Dialysis machine Formula 2000 (Bellco, Italy) b. High-flux filters Nephros OL-pure MD190 Control group • High-flux HD a. Dialysis machine Formula 2000 (Bellco, Italy) b. High-flux filters DIAPES BLS 819G
Outcomes	• B_2 microglobulin clearance • Dialysis adequacy (Kt/V) • Clinical tolerance
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding, allocation concealment • Funding: work supported by a grant from Bellco Mirandola (Italy)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Centrally randomised
Allocation concealment (selection bias)	Unclear risk	Centrally randomised
Blinding of participants and personnel (performance bias) All outcomes	High risk	Probably not done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Probably not done

Mandolfo 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	High risk	Key patient outcomes not provided
Other bias	High risk	Carry over effect present because of the cross-over design; commercial sponsor involved in authorship or data management

Meert 2009

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 9 weeks
Participants	• Country: Belgium • Setting: single centre • Chronic HD patients on dialysis for at least 6 months, age 18 to 85, clinically stable, at least one month on high-flux HD, vascular access with blood flow rate ≥ 300 mL/min ○ Mean time on dialysis: 30.2 ± 36.0 months • Number (randomised/analysed): 17/14 • Mean age ± SD: 63.5 ± 17.7 years • Sex (M/F): 7/7 • Exclusion criteria: expected survival < 1 year; expected transplant < 1 year; infectious disease; pregnancy; chronic inflammation; treated with single needle; treated with HDF or low-flux HD; expected intradialytic body weight gain ≥ 4 kg

Interventions	Treatment group
	• Predilution HDF
	  a. Dialysis machine AK 200 ULTRA S (Gambro, Sweden)
	  b. High-flux filters Polyflux 170 (Gambro, Lund, Sweden)
	Control group 1
	• Predilution HF
	  a. Dialysis machine AK 200 ULTRA S (Gambro, Sweden)
	  b. High-flux filters Polyflux 210 (Gambro, Lund, Sweden)
	Control group 2
	• Post dilution HDF
	  ○ Not included in our analysis as no random allocation was described

Outcomes	• B_2 microglobulin clearance • B_2 microglobulin reduction ratio (%) • Other biochemical measurements
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: 1 patient due to lack of compliance • Additional data requested from authors: method of randomisation; details regarding blinding, allocation concealment

Meert 2009 *(Continued)*

- Funding: this study was supported by Gambro Corporate and one of the authors is an employee of Gambro Corporate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Insufficient information. probably not done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information. probably not done
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing outcome data; loss to follow-up 3/17 (18%) (transplantation (2); lack of compliance (1))
Selective reporting (reporting bias)	High risk	Data for end of first phase of treatment not available
Other bias	High risk	Carry over effect present because of the cross-over design; in the reported results is included a comparison between random and non-randomly allocated groups; commercial sponsor involved in authorship or data management

Movilli 1996

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 6 months with each dialysis modality
Participants	• Country: Italy • Setting: single centre • Patients on HD for ESKD for at least 3 months; stable clinical condition for at least 3 months prior to start of the study • Number: 12 • Mean age ± SD: 76 ± 4 years • Sex (M/F): 7/5 • Exclusion criteria: acute illness
Interventions	Treatment group • HDF for 6 months using AN69 membrane ○ Post-dilution infusion rate: 66 mL/min Control group • AFB with AN69 (Polyacrylonitrile) membrane for 6 months

Movilli 1996 *(Continued)*

	◦ Buffer infusion rate: 2.8 L/h Co-interventions: not stated
Outcomes	• Intradialytic hypotension • Intradialytic symptoms • Kt/V • Hospitalisations
Notes	• Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	3/12 patients died
Selective reporting (reporting bias)	High risk	Data for end of first phase of treatment not available
Other bias	High risk	Carry over effect present because of the cross-over design

Noris 1998

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 1 week
Participants	• Country: Italy • Setting: single centre • Patients on regular bicarbonate HD for at least 12 months • Number: 5 • Mean age ± SD: 57.6 ± 9.6 years • Sex (M/F): 3/2 • Exclusion criteria: history or clinical evidence of unstable angina, MI, stroke or TIA; uncontrolled hypertension (diastolic BP > 100 mm Hg); severe systemic disease; on drugs known to affect haemosta-

Noris 1998 *(Continued)*

	sis; fever or signs of acute infection, inactive immunological processes; hypersensitivity to dialysis membrane material

Interventions	Treatment group
	• AFB with AN69 (polyacrylonitrile) membrane, 3 times/wk
	  ○ QB: 250 to 300 mL/min
	  ○ QD: 500 mL/min
	  ○ Buffer infusion rate: 2.2 L/h
	Control group
	• Acetate and bicarbonate HD with AN69 (Polyacrylonitrile) membrane
	  ○ QB: 250 to 300 mL/min
	  ○ QD: 500 mL/min
	Co-interventions: not stated

Outcomes	• Pre- and post-dialysis systolic BP • Difference between in pre- and post-dialysis systolic BP • Pre- and post-dialysis diastolic BP • Difference between pre- and post-dialysis BP • Pre- and post-dialysis body weight • Difference between pre- and post-dialysis body weight • Kt/V
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing outcome data balanced across groups; 0/5 lost to follow-up
Selective reporting (reporting bias)	High risk	Data for end of first phase of treatment not available; no protocol of the study available

Noris 1998 *(Continued)*

Other bias	High risk	Carry over effect present because of the cross-over design; data not extractable for meta-analysis and interventions not matched

Ohtake 2012

Methods	• Study time frame: May 2007 to 2008 • Study design: parallel RCT • Duration of follow-up: 1 year
Participants	• Country: Japan • Setting: single centre • CKD stage 5; aged 18 to 80 years; on dialysis < 6 months ◦ Mean time on dialysis (months): treatment group (64.5 ± 38.2); control group (58.8 ± 64.4) • Number: treatment group (13); control group (9) • Mean age ± SD (years): treatment group (58.6 ± 11.3); control group (62.4 ± 7.7) • Sex (M/F): 15/7 • Exclusion criteria: acute infection or hospitalizations within 4 weeks before study entry; functional failure of arteriovenous fistula with less than 5 mL/kg/min or more blood flow; malignancy, pregnancy, severely suppressed cardiac function (EF < 40%) and/or severe arrhythmia, and dialysis difficulty due to unstable intradialytic blood pressure status.
Interventions	Treatment group • On-line, predilution HDF ◦ High-flux/Polyflux H membrane, treatments performed with the APSEx, Asahi Kasei Kuraray Medical Co. Ltd, Tokyo, Japan Control group • High-flux HD • High-flux/Polyflux H membrane, treatments performed with the APSEx, Asahi Kasei Kuraray Medical Co. Ltd, Tokyo, Japan
Outcomes	• Left ventricular systolic and diastolic functional markers • Pulse wave velocity • Ankle-brachial pressure index and intima-media thickness of carotid artery • Adequacy of dialysis, mean urea Kt/V • End of treatment B_2 microglobulin levels (mg/L) pre-dialysis • End of treatment blood pressure • Other changes in CV measurements (e.g. LVMi) • Other biochemical measurements
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table

Ohtake 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear; insufficient information provided about losses to follow-up
Selective reporting (reporting bias)	High risk	Data about mortality events were missing
Other bias	Low risk	No additional risks identified

Pedrini 2011a

Methods	• Study time frame: not stated • Study design: cross-over RCT • Duration of follow-up: 1 year
Participants	• Country: Italy • Setting: multi-centre (8) • Patients aged 18 to 80 years; stable HD treatment 3 times/week for at least 3 months and native or prosthetic arteriovenous fistula with an effective blood flow > 300 mL/min ○ Mean time on dialysis: 7.4 ± 7.1 years • Number (enrolled/randomised/analysed): 69/62/62 • Mean age ± SD: 59.6 ± 12.9 years • Sex (M/F): 48/25 • Exclusion criteria: malignancy with poor prognosis; congestive heart failure; acute myocardial infarction or stroke in the last 3 months; diabetes or lipid disorders treated pharmacologically

Interventions	Treatment group
	• On-line HDF, 3 sessions/week
	  ○ Mean blood flow: 348 ± 38 mL/min
	  ○ Session length: 228 ± 22 min
	Control group
	• Low-flux HD, 3 sessions/week
	  ○ Mean blood flow: 348 ± 38 mL/min
	  ○ Session length: 228 ± 22 min

Outcomes	• Mean urea clearance • Kt/V • Vitamin B_{12} clearance • B_2 microglobulin levels

Pedrini 2011a *(Continued)*

	• Ca-P control
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: Method of randomisation, details regarding blinding, results after first phase of the cross ever study • Funding: "This trial was independently undertaken by the investigators. The expenses for the centralized analyses, performed at the Biochemistry Department of the Bolognini Hospital, Seriate, Italy, were covered by Fresenius Medical Care (FMC), Italy. Statistical analysis was conducted at the Institute of Health Sciences, University of Pavia, under the direction of Dr Mario Comelli in the context of a consultancy agreement between FMC and the University Institute"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised by central telephone into a 1:1 ratio"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not performed
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	High risk	10% lost for follow-up, 4% due to access failures (unclear whether imbalanced between groups)
Selective reporting (reporting bias)	High risk	Data for end of first phase of treatment not available
Other bias	High risk	Carry over effect present because of the cross-over design; commercial sponsorship on authorship or data management; interventions not matched

PROFIL Study 2011

Methods	• Study design: parallel RCT • Study time frame: May 2000 to September 2005 • Duration of follow-up: 2 years
Participants	• Country: Sweden and Denmark • Setting: multi-centre (10) • CKD stage 5; aged 18 to 80 years; on dialysis < 3 months ○ Mean time on dialysis: not stated • Number (randomised/analysed): 48/34; treatment group (?/18); control group (?/16) • Mean age ± SD (years): treatment group (62 ± 11); control group (64 ± 13) • Sex (M/F): 24/10

PROFIL Study 2011 *(Continued)*

	• Exclusion criteria: MI within 3 months; well-defined unstable angina; severe cardiac valvular disease; severe cardiac failure (NYHA III–IV); disseminated malignancy; expected HD treatment < 1 year; expected need of central venous catheter > 3 months; body weight > 100 kg; participation in other studies; patient not willing/not able to undergo examinations according to protocol

Interventions	Treatment group
	• · On-line, predilution HF, 3 sessions/week, High-flux/Polyflux H membrane, treatments performed with the AK 100/200 ULTRA (Gambro)
	  ○ Mean blood flow: 325 ± 15 mL/min
	  ○ Session length: 253 ± 4 min
	  ○ Ultrafiltration volume: 38.5 ± 6 L/session
	Control group
	• Low-flux HD, 3 sessions/week, low-flux membrane/Polyflux L (Gambro, Sweden), treatments performed with any HD machine
	  ○ Mean blood flow 273 ± 6 mL/min
	  ○ Session length 257 ± 6 min

Outcomes	• All-cause mortality • Intradialytic symptoms • Number of hospital admissions • Adequacy of dialysis, URR and urea Kt/V • End of treatment B_2 microglobulin levels (mg/L) pre-dialysis • End of treatment BP • Other changes in CV measurements (e.g. LVMi) • Other biochemical measurements
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: to be completed • Funding: commercial sponsorship

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"patients were randomised to treatment with either HF or HD using an online computer-based program stratified by age and diabetes "
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Probably not done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Echocardiograms read by an observer blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing outcome data balanced across groups but attrition is 29%; randomised (48), analysed (34), finished the 24 months follow-up (17, 35%)

PROFIL Study 2011 *(Continued)*

Selective reporting (reporting bias)	High risk	Study protocol available (ISRCTN83264534) and all pre-specified outcomes have been reported. All key patient outcomes not provided
Other bias	High risk	Commercial sponsor on authorship and/or involved in data management, interventions not matched

Righetti 2010

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 18 months
Participants	• Country: Italy • Setting: multi-centre (2) • Chronic HD patients, at least 2 months on dialysis, on a regular treatment with ESA (alpha epoetin), iron gluconate and vitamin B ○ Mean time on dialysis: 48.7 ± 9.9 months • Number: 24 • Mean age ± SD: 61.4 ± 2.9 years • Sex (M/F): 16/8 • Exclusion criteria: patients with residual renal function; severe CV disease (left ventricular ejection fraction less than 30% and/or a NYHA heart disease classification of III-IV); malignancy; basal albumin < 4 mg/dl.

Interventions	Treatment group
	• Internal HDF, high-flux membrane TS1.8UL (Toraysulfone), treatments performed with the AK 200/200-S ULTRA (Gambro), 3 sessions/week,
	  ○ Mean blood flow: 326 ± 3 mL/min
	  ○ Session length: 228 ± 22 min
	  ○ Ultrafiltration volume: about 14 L/session
	Control group
	• Low-flux HD, low-flux membrane BLS (Bellco, Italy) and Polyflux L (Gambro, Sweden); treatments performed with the AK 200/200-S ULTRA (Gambro), 3 sessions/week
	  ○ Mean blood flow: 335 ± 2 mL/min
	  ○ Session length: 228 ± 22 min

Outcomes	• Mean urea clearance (URR) • Urea Kt/V • End of treatment B_2 microglobulin levels (mg/L) pre-dialysis • Other biochemical measurements
Notes	• Exclusions post randomisation but pre-intervention: 4 • Stop or end point/s: not stated • Additional data requested from authors: Method of randomisation; details regarding blinding • Funding: "None of the authors has any financial arrangements with any of the companies whose products were used in the study"

Risk of bias

Bias	Authors' judgement	Support for judgement

Righetti 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Centrally: "An independent person performed randomisation for the sequence of treatment. "
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Probably not done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Probably not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across groups but no intention-to-treat analysis
Selective reporting (reporting bias)	High risk	Data for end of first phase of treatment not available; insufficient information, no study protocol available
Other bias	High risk	Carry over effect present because of the cross-over design; interventions not matched

Santoro 1999

Methods	• Study time frame: March 1998 to December 2006 • Study design: parallel RCT • Duration of follow-up: 4 years
Participants	• Country: European • Setting: multi-centre (92) • Incident critically ill HD patients, defined as one of the following: elderly (> 60 years); hypotension prone (≥ 5 hypotensive episodes/month); diabetic; CV instability (defined as a frequency of hypotensive episodes in more than 20% of dialysis sessions, or independently of frequency, if hypotension is accompanied by angina or major arrhythmia's) ◦ Mean time on dialysis: 6 to 8 months • Number: treatment group (177); control group (194) • Mean age ± SD (years): treatment group (66.9 ± 8.8); control group (67.1 ± 8.8) • Sex (M/F): treatment group (106/71); control group (112/82) • Exclusion criteria: older than 78 years; active neoplasia; severe cardiopathies (New York Heart Association [NYHA] Class III & Class IV); decompensating cirrhosis; poor vascular access function (pump flow < 200 mL/min or need for single needle system); previous continuous ambulatory peritoneal dialysis; treatment or kidney transplant; on waiting list for kidney transplant
Interventions	Treatment group • AFB conducted using the AN69 membrane, infusing a 145-167mM sodium bicarbonate solution usually warmed to a temperature similar to that of the dialysate, at a rate targeting for a post-dialysis plasma bicarbonate levels of 27 to 30 mEq/L Control group

Santoro 1999 *(Continued)*

	• BD, low- or high-flux synthetic membranes and dialysate with bicarbonate and acetate concentrations of 30 to 34 mM and 4 to 6 mM, respectively, were used according to each centre practice patterns
Outcomes	• Intradialytic CV instability (hypo or hypertensive episodes) • All-cause mortality • CV mortality • Changes in predialysis BP • Left ventricular mass • Major CV event
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: 39 dropouts in the AFB arm and 38 dropouts in the BD arm • Additional data requested from authors: method of randomisation; details regarding blinding, allocation concealment • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was done centrally (with a computerized random-number generator) using the balanced block randomisation technique with a 1:1 ratio, stratification according to the clinical centre concerned and a block size of eight"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated, probably not done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated, probably not done
Incomplete outcome data (attrition bias) All outcomes	High risk	21% loss to follow-up and dropouts censored at time of termination
Selective reporting (reporting bias)	High risk	Outcomes of interest are not reported
Other bias	High risk	Interventions not matched and patient baseline characteristics not matched

Santoro 2005a

Methods	• Study design: parallel RCT • Study time frame: June 2001 to July 2005 • Duration of follow-up: 3 years
Participants	• Country: Italian • Setting: multi-centre (20)

Santoro 2005a *(Continued)*

- Aged 16 to 80 years; dialysis treatment for at least 6 months with conventional HD; residual kidney function < 2 mL/min/1.73 m^2; Charlson Comorbidity Index of 3 or higher; presence of CV instability during dialysis in at least 15% of sessions
  - Mean time on dialysis (months): treatment group (70.3 ± 11.3); control group (59.9 ± 10.9)
- Number: treatment group (32); control group (32)
- Mean age ± SD (years): treatment group (69.0 ± 1.3); control group (66.4 ± 1.8)
- Sex (M/F): treatment group (14/18); control group (17/15)
- Exclusion criteria: neoplasia; acute clinical conditions (MI, congestive heart failure, stroke, recent surgery, or severe sepsis) within 3 months of enrolment in the study; any vascular access dysfunction (patients with central catheters were admitted if blood flow rate was > 300 mL/min; residual urinary output > 200 mL/24 h; body weight > 75 kg

Interventions	Treatment group • Predilution on-line HF, Poliflux 21S (Gambro), Gambro AK 100 Ultra; Gambro, Lund, Sweden Control group • Bicarbonate HD, Poliflux 8L (Gambro),Gambro AK 100 Ultra; Gambro, Lund, Sweden
Outcomes	• All-cause mortality • Hospitalisation rate • Dialysis sessions with hypotension • Biochemical parameters and indicators of nutritional status • Adequacy of dialysis and B_2 microglobulin removal
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding, allocation concealment • Note: Dr Strippoli was one of the authors • Funding: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were centrally randomised, 1:1 ratio
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	"There was no blinding of participants, investigators, or outcome assessors."
Blinding of outcome assessment (detection bias) All outcomes	High risk	"There was no blinding of participants, investigators, or outcome assessors."
Incomplete outcome data (attrition bias) All outcomes	High risk	20% withdrew from study due to personal reasons, transferred to another centre to centre not able to offer treatment (HF); imbalance between arms

Santoro 2005a *(Continued)*

Selective reporting (reporting bias)	High risk	Study protocol unavailable; outcomes of interest reported incompletely
Other bias	High risk	Baseline patient characteristics not matched

Schiffl 1992

Methods	• Study design: parallel RCT • Study time frame: not stated • Duration of follow-up: 48 months
Participants	• Country: Germany • Setting: single centre • Patients on HD for ESKD • Number: treatment group (8); control group (24) • Age range: 28 to 69 years • Sex (M/F): 12/18 • Exclusion criteria: not stated

Interventions	Treatment group
	• HF treatments carried out using F-60s high-flux polysulfone dialysers
	  ◦ QB: 250 mL/min
	  ◦ QF: pre-dilution 620 mL/min, post-dilution 720 to 740 mL/min
	  ◦ Infusion flow rate: pre-dilution 180 mL/min, post-dilution 60 to 80 mL/min
	Control group
	• Dialysate in AFB was buffer-free and acidosis was corrected with a 166 mEq/L sodium bicarbonate solution as the substitution fluid
	• QD: 500 mL/min
	• Infusion fluid rate: 25 to 30 mL/min
	Co-interventions: not stated

Outcomes	• Pre-dialysis B_2 microglobulin levels • Dialysate B_2 microglobulin levels • Mortality
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation and details regarding blinding • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated

Schiffl 1992 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	High risk	Limited amount of data reported for a 2 year study
Other bias	High risk	Data not extractable for data analysis, intervention not matched

Schiffl 2007

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 4 years (24 months plus 24 months)
Participants	• Country: Germany • Setting: single centre • Clinically stable ESKD patients for at least 6 months; treated thrice weekly with conventional HD, permanent and functional vascular access with a blood flow rate ≥ 250 mL/min ○ Mean time on dialysis: 26 months (9 to 280) • Number: treatment group (38); control group (38) • Mean age ± SD (years): treatment group (63 ± 9); control group (59 ± 10) • Sex (M/F): treatment group (22/16); control group (20/18) • Exclusion criteria: patients with a malignancy, severe comorbidity (heart failure NYHA class III-IV, liver cirrhosis, chronic inflammatory or infectious diseases, diabetic foot and dementia)

Interventions	Treatment group
	• On-line HDF, 3 times/week, 4 to 5 hours (mean 254 + 25 min); polysulfone F80 (Fresenius), MTS 4008 H (Fresenius)
	  ○ Blood flow rate range: 250 to 350 mL/min
	  ○ Volume of substitution fluid 4.5L/h
	Control group
	• Ultrapure high-flux HD, 3 times/week, 4 to 5 hours (mean 254 + 25 min), high-flux polysulfone F60 (Fresenius), MTS 4008, Fresenius
	  ○ Blood flow rate range: 250 to 350 mL/min
	  ○ Ultrapure dialysis fluid produced with an endotoxin absorbing membrane (Diasafe, Fresenius Medical Care)

Outcomes	• All-cause mortality • CV stability (hypotensive episodes) • QoL • Calcium phosphate homeostasis • Nutritional status

Schiffl 2007 *(Continued)*

	• Anaemia control • Biochemical tests (dialysis adequacy, B_2 microglobulin)
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding, allocation concealment • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"by coin flip", an insecure method
Allocation concealment (selection bias)	High risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Unblinded'
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Unblinded'
Incomplete outcome data (attrition bias) All outcomes	Low risk	3% loss to follow-up due to move away from dialysis centre; similar in both groups
Selective reporting (reporting bias)	High risk	Outcomes of interest not reported
Other bias	Low risk	Carry over effect present because of the cross-over design but we included in our analysis only the data available about the first phase of the study

Schrander vd Meer 1998

Methods	• Study design: parallel RCT • Time-frame: not stated • Duration of follow-up: 12 months
Participants	• Country: Netherlands • Setting: single centre • Patients on stable bicarbonate HD for at least 1 year • Number: treatment group (11); control group (9) • Mean age (years): treatment group (64.2); control group (66.3) • Sex (M/F): treatment group (8/3); control group (6/3) • Exclusion criteria: diabetes mellitus
Interventions	Treatment group

Schrander vd Meer 1998 *(Continued)*

	• AFB with a biocompatible high-flux membrane (polyacrylonitrile crystal 2800 or 3400) ○ Buffer solution infusion rate: 1.8 L/h Control group • Bicarbonate HD with a biocompatible high-flux membrane (polyacrylonitrile crystal 2800 or 3400) Co-interventions: not stated
Outcomes	• Pre-dialysis MAP • Percentage of dialysis sessions with hypotension • Kt/V/week • Mortality
Notes	• Exclusions post randomisation: 4 patients (1 received kidney transplantation, 1 developed allergy to the AN69 membrane, 1 patient refused to take medication and 1 patient complained of arthritis whilst on AFB) • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding • Funding: "This study was supported by a grant from the Dutch Kidney Foundation (grant number C 94–1417)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Each pair of patients was randomised to either AFB or HD
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	13% lost to follow-up due to allergy, refusal or side-effects. Unclear whether imbalance between groups
Selective reporting (reporting bias)	High risk	Not all the expected outcomes were reported
Other bias	Low risk	No additional risks identified

Selby 2006a

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 4 weeks

Selby 2006a *(Continued)*

Participants	• Country: UK • Setting: single centre • Chronic HD patients hypotension-prone (6 patients) or stable on HD ○ Mean time on dialysis: 39.5 ± 18.7 months • Number: 12 • Mean age ± SD: 68 ± 11.2 years • Sex (M/F): 10/2 • Exclusion criteria: Hb < 10 g/dL, or if they had significant comorbidity that, in the opinion of the investigator, would make completion of the study unlikely

Interventions	Treatment group
	• Acetate-free HDF
	  ○ Dialysis machine Formula 2000 (Bellco, Italy)
	  ○ "Diapes polyether sulphone double chamber dialyzers consisting of a combined 1.9 m^2 dialyzer and 0.7 m^2 ultrafilter (Bellco, Mirandola, Italy)
	Control group
	• Low-flux standard HD
	  ○ Dialysis machine Formula 2000 (Bellco, Italy)
	  ○ Low-flux filters LOPS 18/20 (Braun Medical Ltd., UK)

Outcomes	• Changes in BP • Cardiac function measurements (stroke volume, cardiac output), and total peripheral resistance in response to HD) • Clinical tolerance/ Intradialytic hypotension • Changes in cardiac troponin T
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding, allocation concealment • Funding: "The authors gratefully acknowledge Bellco, who provided the consumables and dialysis monitors for this study"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Probably not done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Probably not done
Incomplete outcome data (attrition bias)	High risk	Insufficient reporting

Selby 2006a *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Study protocol unavailable and data for end of first phase of treatment not available
Other bias	High risk	Patients included were selected using two different inclusion criteria (prone to hypotension or stable patients) with no clear description of the initial number of analysed number. Carry over effect present because of the cross-over design; data not extractable for meta-analysis and interventions not matched

Stefansson 2012

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 4 months (2 months for phase 1 and 2 months for phase 2)
Participants	• Country: Sweden • Setting: single centre • Chronic HD patients on dialysis for at least 3 months, >18 years, either on HD or HDF • Number: 20 • Mean age ± SD: 60 ± 13.6 years • Sex (M/F): 14/6 • Exclusion criteria: not in stable condition, with any signs of acute inflammation, infection or CV disease
Interventions	Treatment group • HDF in on-line post-dilution mode with AK 200 Ultra dialysis machines (Gambro, Lund, Sweden) Control group • Low-flux HD with Polyflux 17 L filters and AK 200 Ultra dialysis machines (Gambro, Lund, Sweden)
Outcomes	• Number of hypotensive episodes • HD tolerance • End of treatment BP control • B_2 microglobulin • QoL and health questionnaire • Dialysis efficacy
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: 1 patient in the HDF arm • Additional data requested from authors: supplementary results, method of randomisation; details regarding blinding, allocation concealment • Funding: "This study was supported by the Swedish Medical Research Council 9898, the Inga-Britt and Arne Lundberg Research Foundation, the John and Brit Wennerström Research Foundation, the Medical Association of Gothenburg, and the Sahlgrenska University Hospital Grant LUA/ALF"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated

Stefansson 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study was patient-blinded and partially investigator-blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The interviewers did not know which treatment was performed
Incomplete outcome data (attrition bias) All outcomes	High risk	20% loss to follow-up (pain, intracerebral bleeding, patient request, and dialysis access problems)
Selective reporting (reporting bias)	High risk	Study protocol unavailable; outcomes of interest not all reported
Other bias	High risk	Carry over effect present because of the cross-over design; interventions not matched

Teo 1987

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 8 months
Participants	• Country: Canada • Setting: single centre • Maintenance HD for at least 6 months • Number: 13 • Sex (M/F): 9/4 • Mean age ± SEM: 36.5 ± 2.9 years • Exclusion criteria: presence of systemic diseases other than that which caused the CKD; coronary artery disease, heart failure, pericardial effusion

Interventions	Treatment group
	• HDF carried out using F-60s high-flux polysulfone dialysers
	  ◦ QB: 250 mL/min
	  ◦ QF: pre-dilution 620 mL/min; post-dilution 720 to 740 mL/min
	  ◦ Infusion flow rate: pre-dilution 180 mL/min; post-dilution 60 to 80 mL/min
	Control group
	• Dialysate in AFB was buffer-free and acidosis was corrected with a 166 mEq/L sodium bicarbonate solution as the substitution fluid
	  ◦ QD: 500 mL/min
	  ◦ Infusion fluid rate: 25 to 30 mL/min
	Co-interventions: not stated

Outcomes	• BP

Teo 1987 *(Continued)*

Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: none requested • Funding: "This study was supported by the Grant 7219 from the Special Services and Research Committee of University of Alberta Hospitals and from a grant from Hospal Canada Ltd"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	15% loss to follow-up (declined by patient and personal reasons)
Selective reporting (reporting bias)	High risk	Study protocol unavailable but no data available to be included
Other bias	High risk	Carry over effect present because of the cross-over design; data not extractable for meta-analysis, interventions not matched

Todeschini 2002

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 3 dialysis sessions
Participants	• Country: Italy • Setting: single centre • Stable patients on HD 3 times/week; HCT > 30%; informed consent • Number: 9 • Age: Mean 63.6 ± 7.2 years • Sex (M/F): 3/6 • Exclusion criteria: uncontrolled hypertension (diastolic BP > 100 mm Hg); clinical evidence of unstable angina pectoris; on drugs known to affect haemostasis; evidence of acute illness or neoplasia
Interventions	Treatment group • AFB with a biocompatible high-flux polyacrylonitrile (AN69) membrane for 3 sessions ○ QB: 300 mL/min

Todeschini 2002 *(Continued)*

	○ QD: 500 mL/min ○ Duration of each dialysis session: 240 min Control group • Bicarbonate HD with a biocompatible high-flux polyacrylonitrile membrane (AN69) membrane • QB: 300 mL/min • QD: 500 mL/min • Duration of each dialysis session: 240 min Co-interventions: not stated
Outcomes	• Kt/V • Pre- and post-dialysis systolic BP • Difference between pre- and post-dialysis systolic BP • Pre- and post-dialysis diastolic BP • Difference between pre- and post-dialysis diastolic BP
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding • Funding: none stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear; no loss to follow-up
Selective reporting (reporting bias)	High risk	Data for end of first phase of treatment not available
Other bias	High risk	Carry over effect present because of the cross-over design; data not extractable for meta-analysis

Tuccillo 2002

Methods	• Study design: cross-over RCT

Tuccillo 2002 *(Continued)*

- Study time frame: not stated
- Duration of follow-up: 3 months

Participants	• Country: Italy • Setting: single centre • Diuresis < 200 mL during interdialysis period; clinically stable; permanent vascular access; no diabetes, liver cirrhosis or oedema • Number: 12 • Sex (M/F): 7/5 • Mean age ± SD: 53 ± 4 years • Exclusion criteria: not stated

Interventions	Treatment group
	• HDF with polysulfone Fresenius F8 1.8 m^2 dialysis membrane, PMMA Filter B3-2, 2 m^2
	  ○ Duration: 1 session in the acute phase, 3 months in the chronic phase
	  ○ QB: 315 to 345 mL/min
	  ○ QD: 500 mL/min
	Control group
	• HD with polysulfone Fresenius F8 1.8 m^2 dialysis membrane, PMMA Filters B3-2, m^2
	  ○ Duration: 1 session in the acute phase, 3 months in the chronic phase
	  ○ QB: 315 to 345 mL/min
	  ○ QD: 500 mL/min
	Co-interventions: not stated

Outcomes	• Kt/V
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: none requested • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but review authors judge that outcome measurement not likely influenced
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Short duration of study, < 10% attrition

Tuccillo 2002 *(Continued)*

Selective reporting (reporting bias)	High risk	Data for end of first phase of treatment not available
Other bias	High risk	Carry over effect present because of the cross-over design; data not extractable for meta-analysis; abstract only publication

TURKISH HDF 2013

Methods	• Study design: parallel RCT • Study time frame: January 2007 to March 2010 • Duration of follow-up: 2 years

Participants	• Country: Turkey
	• Setting: multi-centre (10)
	• Aged > 18 years on maintenance bicarbonate HD scheduled thrice weekly 12 h/week, achieved mean single pool Kt/V above 1.2; willingness to participate in the study with a written informed consent
	  ○ Mean time on dialysis: 57.9 ± 13.9 months
	  ○ Diabetes: 34.7%
	• Number: treatment group (391); control group (391)
	• Mean age ± SD (years): treatment group (56.4 ± 13.0); control group (56.5 ± 14.9)
	• Sex (F): treatment group (40.4%); control group (41.9%)
	• Exclusion criteria: scheduled for living donor renal transplantation; serious life-limiting co-morbid situations, namely active malignancy, active infection, end-stage cardiac, pulmonary, or hepatic disease; pregnancy or lactating; Current requirement for HD more than 3 times/week due to medical co-morbidity; GFR > 10 mL/min/1.73 m^2 as measured by the average of urea and CrCl obtained from a urine collection of at least 24 hours; use of temporary catheter; insufficient vascular access (blood flow rate < 250 mL/min); urine output > 250mL/d; mental incompetence

Interventions	Treatment group
	• Post-dilution on-line HDF, 3 times/week, 4 hours; FX series high-flux helixone membranes used; ONLINEplus integrated Fresenius 4008S machines
	• Duration of each session: 240 minutes
	• Blood flow rates: 250 to 400 mL/min
	• Substitution volume > 15 L
	Control group
	• High-flux HD, 3 times/week, 4 hours; FX series high-flux helixone membranes used
	  ○ Duration of each session: 240 minutes
	  ○ Blood flow rates: 250 to 400 mL/min

Outcomes	• Composite of overall mortality and new CV events to include MI, stroke, revascularization, and unstable angina pectoris requiring hospitalisation • CV mortality • Hospitalisation rate • Intradialytic complications including hypotension and cramp • Health-related QoL, depression burden, cognitive function • Required medications • Changes in BP, left ventricular geometry, arterial stiffness, post-dialysis body weight, upper mid-arm circumference, HCT and related rHuEPO doses, the levels of phosphorus, albumin, lipid parameters, C-reactive protein, and B_2 microglobulin • Postdialysis total body water determined by bioimpedance analysis

TURKISH HDF 2013 *(Continued)*

Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding, allocation concealment, supplementary data/results • Funding: "Sponsors and Collaborator-Fresenius Medical Care North America"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	High risk	20% loss to follow-up plus imbalance in loss to follow-up due to vascular access problems
Selective reporting (reporting bias)	Low risk	Study protocol available and all patient important outcomes were reported
Other bias	High risk	Commercial sponsorship of study

Vaslaki 2006

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 48 weeks (24 weeks for phase 1 and 24 weeks for phase 2)
Participants	• Country: Hungary • Setting: multi-centre (7) • Chronic adult HD patients on dialysis for at least 3 months • Number: 129 • Mean age ± SD: 62.3 ± 12.4 years • Sex (M/F): 24/46 • Exclusion criteria: pregnancy; lactation; infectious disease; simultaneous participation in another clinical study
Interventions	Treatment group • On-line HDF; high-flux polysulfone dialysers, 4008 HD machines form Fresenius Medical Care ○ Mean volume of substitution fluid: 20.3 ± 3.0 L Control group

Vaslaki 2006 *(Continued)*

	• Low-flux HD; polysulfone dialysers, HPS series and 4008 HD machines, Fresenius Medical Care
Outcomes	• Number of intradialytic morbid events (e.g. symptomatic hypotension, muscle cramps, dizziness, nausea, headache) requiring the intervention of healthcare professionals • Intradialytic hypotension • Variation of biochemical parameters (e.g. anaemia status, inflammation status) • Dialysis adequacy • B_2 microglobulin
Notes	• Exclusions post randomisation but pre-intervention: unclear • Stop or end point/s: 39 withdraws (Kt/V < 1.2 in the first 3 weeks of the study) • Additional data requested from authors: no • Funding: commercial sponsor involved in authorship and data management

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	A random code was used, with a separate list for each study centre
Allocation concealment (selection bias)	Unclear risk	Centrally performed by an independent institute
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open"
Incomplete outcome data (attrition bias) All outcomes	High risk	46% lost and dropped out patients "not replaced"; lost to follow-up: 20 drop-outs (4 died, 11 were transplanted and other reasons for 5) and 49 withdrawn patients
Selective reporting (reporting bias)	High risk	Insufficient information about patient important outcomes
Other bias	High risk	Commercial sponsor involved in authorship and data management; interventions not matched

Verzetti 1998

Methods	• Study design: cross-over RCT • Study time frame: not stated • Duration of follow-up: 1 year, 6 months for each phase
Participants	• Country: Italy • Setting: multi-centre • Stable patients with diabetic kidney disease who had received HD for at least 3 months • Number: 41 • Mean age ± SD: 60 ± 10 years

Verzetti 1998 *(Continued)*

- Sex (M/F): 17/24
- Mean duration on dialysis: 25 months
- Exclusion criteria: neoplasia; severe cardiopathy; liver disease; marked nutritional disorders

Interventions	Treatment group
	• AFB using polyacrylonitrile (AN69) membrane for 6 months
	  ◦ QB: 250 to 300 mL/min
	  ◦ QD: 500 mL/min
	  ◦ Dialysis duration: 180 to 240 min
	  ◦ Mean amount of fluid exchange: 13.5 L/session
	Control group
	• Bicarbonate HD with cuprophane membrane for 6 months
	  ◦ QB: 250 to 300 mL/min
	  ◦ QD: 500 mL/min
	  ◦ Dialysis duration: 180 to 240 min
	Co-interventions: not stated

Outcomes	• Intradialytic symptoms • Intradialytic hypotensive episodes • Kt/V • Mortality
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	20% loss to follow-up
Selective reporting (reporting bias)	High risk	Outcome/s of interest reported incompletely, cannot be used in meta-analysis; "Intradialysis status P = 0.003"; study protocol unavailable

Verzetti 1998 *(Continued)*

Other bias	High risk	Carry over effect present because of the cross-over design; data not extractable for meta-analysis and interventions not matched

Ward 2000

Methods	• Study design: parallel RCT • Time-frame: 6 months • Duration of follow-up: 12 months
Participants	• Country: Germany • Setting: single centre • Stable chronic HD patients on dialysis for at least 2 months; permanent dialysis access capable of delivering a blood flow rate of at least 250 mL/min • Number: treatment group (24); control group (21) • Mean age ± SD (years): treatment group (61 ± 3); control group (52 ± 3) • Sex (M/F): treatment group (15/9); control group (14/7) • Exclusion criteria: not stated

Interventions	Treatment group
	• HDF with high-flux polyamide membrane for 12 months
	  ◦ Substitution solution infusion rates: 65 to 85 mL/min
	Control group
	• HD with high-flux polyamide membrane for 12 months
	  ◦ QD: 500 mL/min
	Co-interventions: not stated

Outcomes	• B_2 microglobulin clearance • Kt/V • QoL Index
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: none stated • Additional data requested from authors: method of randomisation; details regarding blinding; groups to which patients who died belonged • Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Each pair of patients was randomised to either AFB or HD
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated

Ward 2000 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	22% patients lost-to-follow-up
Selective reporting (reporting bias)	High risk	All outcomes of interest not reported
Other bias	High risk	Patient baseline characteristics not matched

Wizemann 2000

Methods	• Study design: parallel RCT • Study time frame: not stated • Duration of follow-up: 48 months
Participants	• Country: Germany • Setting: single centre • Chronic HD patients on dialysis with low-flux HD for at least 3 months • Number: treatment group (23); control group (21) • Mean age ± SD (years): treatment group (61 ± 12); control group (60 ± 11) • Sex (M/F): treatment group (12/11); control group (13/8) • Exclusion criteria: not stated

Interventions	Treatment group
	• HDF with high-flux polysulfone (Fresenius F-80S) membranes for 24 months
	  ○ QD: 100 to 200 mL/min
	  ○ Duration of each dialysis session: 4.5 hours
	  ○ Total substitution fluid volume was targeted to 60 L/session
	Control group
	• HD with low-flux polysulfone (Fresenius F8) membranes for 24 months
	  ○ QB: 400 to 500 mL/min
	  ○ QD: 500 mL/min
	  ○ Dialysis duration: 4.5 hours
	Co-interventions: not stated

Outcomes	• B_2 microglobulin reduction ratio • URR
Notes	• Exclusions post randomisation but pre-intervention: not stated • Stop or end point/s: not stated • Additional data requested from authors: method of randomisation; details regarding blinding; raw data for B_2 microglobulin values • Funding: sponsor involved in authorship and/or data management
Risk of bias	

Wizemann 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	18% loss to follow-up
Selective reporting (reporting bias)	High risk	Study protocol unavailable and outcomes of interest reported incompletely, cannot be used in meta-analysis (e.g. BP)
Other bias	High risk	Sponsor involved in authorship and/or data management; interventions not matched

ACEi - angiotensin-converting enzyme inhibitor; AFB - acetate-free biofiltration; BD - conventional bicarbonate dialysis; BP - blood pressure; CKD - chronic kidney disease; CrCl - creatinine clearance; CV - cardiovascular; EPO - erythropoietin; ESKD - end-stage kidney disease; Hb - haemoglobin; HCT - haematocrit; HD - haemodialysis; HF - haemofiltration; HDF - haemodiafiltration; HTN - hypertension; LVMi - left ventricular mass index; MAP - mean arterial pressure; MI - myocardial infarction; QB - blood flow rate; QD - dialysate flow rate; QoL - quality of life; rHuEPO: recombinant human EPO; RRT - renal replacement therapy; TIA - transient Ischaemic attack; URR - urea reduction ratio

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adam 1996	Population included not relevant to this review (patients with acute kidney injury
Ahrenholz 1997	Not RCT
Ahrenholz 1998	Not RCT
Ahrenholz 2004	Not RCT; interventions not relevant to this review
Altieri 1997	Not RCT
Altieri 1999	Not RCT
Altieri 2000	Not RCT
Altieri 2001	Not RCT
Baldamus 1980	Not RCT

Study	Reason for exclusion
Baldamus 1982	Not RCT
Baldamus 1985	Not RCT
Baragett 2003	Not RCT
Basile 1985	Not RCT
Basile 1985a	Not RCT
Basile 1987	Interventions not relevant to this review
Basile 1988	Outcomes not relevant to this review
Bazzatto 1988	Outcomes not relevant to this review
Beerenhout 2002	Not RCT
Bolasco 2000	Not RCT
Bonaudo 1998	Interventions not relevant to this review
Bonomini 2004	Outcomes not relevant to this review
Bordin 2002	Not RCT
Bosc 1997	Interventions not relevant to this review
Bosc 1998	Interventions not relevant to this review
Boscticardo 1981	Not RCT
Brink 1995	Not RCT
Calo 2007	Outcomes not relevant to this review
Canaud 1994	Not RCT
Canaud 2000	Not RCT
Canaud 2001	Not RCT
Cappelli 1985	Not RCT
Carozzi 1992	Not RCT
Cavalcanti 2004	Not an RCT
Cerulli 2000	Outcomes not relevant to this review
Champagne 2008	Outcomes not relevant to this review
Chanard 1988	Not RCT
Chang 1979	Not RCT

Study	Reason for exclusion
Chauveau 1993	Outcomes not relevant to this review
Chen 2005c	Not RCT
Chiappini 2004	Interventions not relevant to this review
Cirillo 2011	Interventions not relevant to this review
Collins 1985	Not RCT
David 2000	Not RCT
Duranti 2004	Not RCT
Feliciani 2007	Interventions not relevant to this review
Fu 2006	Not RCT
Gerdemann 2002	Interventions not relevant to this review
Giannattasio 2006	Interventions not relevant to this review
Harzallah 2008	Interventions not relevant to this review
Hdez-Jaras 1994	Outcomes not relevant to review
Henderson 1980	Not RCT
Higuchi 2004	Outcomes not relevant to review
Hillion 1997	Interventions not relevant to this review
Hmida 2002	Not RCT
Ikebe 2006	Interventions not relevant to this review
Jahn 1981	Not RCT
Jose 2008	Outcomes not relevant to this review
Joyeux 2009	Outcomes not relevant to this review
Kanter 2008	Interventions not relevant to this review
Katschnig 1980	Not RCT
Kim 2009	Interventions not relevant to this review
Kishimoto 1980	Not RCT
Klemm 1997	Not RCT
Klingel 2004	Outcomes not relevant to review
Krieter 2005	Interventions not relevant to this review

Study	Reason for exclusion
Krieter 2008a	Interventions not relevant to this review
Krieter 2010	Interventions not relevant to this review
Kuno 1994	Not RCT
Leber 1980	Not RCT
Li 1997	Interventions not relevant to this review
Lin 2003a	Outcomes not relevant to this review (serum AGE level reduction rates)
Liomin 1984	Not RCT
Locatelli 1998	Not RCT
Locatelli 1999	Not RCT
Locatelli 2001	Not RCT
Locatelli 2002	Not RCT (review article)
Lornoy 1998a	Not RCT
Lornoy 2001	Interventions not relevant to this review
Maeda 1990	Not RCT
Maggiore 2000	Not RCT (review article)
Maheshwari 2012	Interventions not relevant to this review
Malberti 1991	Not RCT
Mastrangelo 1986	Not RCT
Mesic 2011	Interventions not relevant to this review
Minutolo 2002	Interventions not relevant to this review
Mioli 1986	Not RCT
Mishkin 2002	Not RCT
Mohini 1989	Interventions not relevant to this review
Morena 2006	Interventions not relevant to this review
Movilli 2011	Not RCT
Mrowka 1993	Interventions not relevant to this review
Nakazawa 1997	Not RCT
Ohyama 1981	Not RCT

Study	Reason for exclusion
Pacitti 1993	Not RCT
Panichi 1994	Not RCT
Panichi 1998	Not RCT
Panichi 2006	Interventions not relevant to this review
Pedrini 1999	Interventions not relevant to this review
Pedrini 2006	Interventions not relevant to this review
Pedrini 2009	Interventions not relevant to this review
Pedrini 2011	Interventions not relevant to this review
Petras 2005	Interventions not relevant to this review
Pizzarelli 2004	Outcomes not relevant to this review
Quellhorst 1983	Not RCT
Quellhorst 1983a	Not RCT
Ragazzoni 2004	Interventions not relevant to this review
Ramunni 2006	Interventions not relevant to this review
Rius 2007	Interventions not relevant to this review
Ronco 2000	Interventions not relevant to this review
Sakurai 1990	Interventions not relevant to this review
Santoro 2005	Interventions not relevant to this review
Santoro 2008	Interventions and outcomes not relevant to this review
Savoldi 2004	Outcomes not relevant to this review
Shaldon 1998	Not RCT
Sidoti 2004	Interventions not relevant to this review
Sirolli 2004	Outcomes not relevant to review
Spongano 1992	Not RCT
Strujic 2006	Not RCT
Susantitaphong 2008	Interventions not relevant to this review
Timio 1986	Outcomes not relevant to this review
Tomo 2004	Outcomes not relevant to review

Study	Reason for exclusion
Umimoto 2000	Not RCT
Vantelon 1977	Not RCT
Vaslaki 1998	Outcomes not relevant to review
Vaslaki 2000	Not RCT
Vaslaki 2002	Outcomes not relevant to review
Vaslaki 2003	Outcomes not relevant to review
Vaslaki 2005	Outcomes not relevant to review
Wang 2004d	Outcomes not relevant to review
Wizemann 2001	Not RCT (review article)
Zehnder 1999	Not RCT
Zimmerman 2003	Not RCT
Zucchelli 1988	Not RCT

Characteristics of studies awaiting assessment *[ordered by study ID]*

Beerenhout 2004

Methods
Participants
Interventions
Outcomes
Notes

Bellien 2014

Methods
Participants
Interventions
Outcomes
Notes

Cornelis 2014

Methods	Country: Netherlands Setting: unclear, Netherlands centres Study time frame: October 2011 to October 2012 Study design: cross-over RCT Enrolment: not reported Duration of follow-up: at 15, 30, 60,1 20, 240 minutes (4-hour and 8-hour sessions) and at 360 and 480 minutes (8-hour sessions)
Participants	Ages eligible for study: 18 to 80 years Inclusion criteria prevalent conventional HD patients; AV-fistula enabling double-needle vascular access with blood flow rate of at least 350 mL/min; informed consent; age more than 18 years Exclusion criteria withdrawal of consent; acute intercurrent illness (infection, malignancy, cardiovascular event, uncontrolled diabetes)
Interventions	Assigned interventions 4-hour HD, 4-hour HDF, 8-hour HD and 8-hour HDF Prevalent conventional HD (CHD) patients (dialysing 3 days a week during 4 hours per dialysis session) will undergo, in random order, a mid-week 4-hour HD session, a mid-week 4-hour HDF session, a mid-week 8-hour HD session, and a mid-week 8-hour HDF session with a 2-week interval between every session to assess the influence of treatment duration and of convection on the removal of uraemic toxins and on the haemodynamic responses and autonomic nervous regulation In between the study dialysis sessions these patients will receive routine CHD treatments
Outcomes	Primary outcome measures Removal of uraemic toxins Secondary outcome measures Haemodynamic response: BP, heart rate, heart rate variability, cardiac output and systemic vascular resistance will be measured. Skin microcirculation will be measured with laser Doppler flowmetry.
Notes	source: http://clinicaltrials.gov/ct2/show/study/NCT01328119?term=NCT01328119&rank=1

de Sequera 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Francisco 2013

Methods
Participants
Interventions
Outcomes
Notes

Gonzales-Diez 2012

Methods
Participants
Interventions
Outcomes
Notes

Krieter 2010a

Methods
Participants
Interventions
Outcomes
Notes

Characteristics of ongoing studies *[ordered by study ID]*

NCT01098149

Trial name or title	Tolerance to hemodialysis in insulin-requiring diabetic patients: BD vs AFB with blood volume biofeedback (THIRD)
Methods	Country: Italy Setting: multi-centre, 5 Italian centres Study time frame: 2006 to March 2010 Study design: cross-over RCT Enrolment: 55 patients Duration of follow-up: 3 months
Participants	Ages eligible for study: 18 to 85 years Inclusion criteria

NCT01098149 *(Continued)*

	End stage renal disease patients; patients affected by diabetic nephropathy with insulin therapy, for, at least, 6 months; patients with renal replacement therapy with haemodialysis three time a week, for, at least, 6 months; age between 18 and 85 years Exclusion criteria Patients affected by neoplasm and/or mental illness; patients with residual diuresis > 500 mL/d; patients in single needle bicarbonate dialysis
Interventions	The study, 9 months long, is aimed to verify the treatment tolerance of insulin requiring diabetic patients, by using standard bicarbonate dialysis (BD), or acetate free biofiltration (AFB) and/or a blood volume control (BVC). The study is divided in three phases: the first one, three months long, is the baseline in standard bicarbonate dialysis, then all the patients are shifted to AFB with BVC, for other three months, while the last three months long phase, after a randomisation, has the aim to identify the relative contribution of each factor (absence of acetate in the bath or BVC) in the treatment tolerance improvement (if any). The treatment tolerance will be evaluated considering the frequency of intradialytic hypotensive events.
Outcomes	Primary outcome measures tolerance to dialysis. (time frame: 3 months) The treatment tolerance is measured by the number of intra dialytic hypotensive events Secondary outcome measures The secondary outcome measure is to evaluate the relative efficiency of each factor (AFB in the bath and blood volume control) to reach this result. (time frame: 3 months) The evaluation will be done on: frequency of hypotensive events; number of nurse interventions (defined as ultrafiltration rate stop, or saline infusion); antihypertensive drugs.
Starting date	March 2006
Contact information	Dott. Ezio Movilli, Dept of Nephrology -Brescia, Italy
Notes	Study details as provided by Università deg li Studi di Brescia. source: http://clinicaltrials.gov/ct2/show/NCT01098149

NCT01327391

Trial name or title	Tolerance of "on Line" hemodiafiltration in chronic renal failure patients (on-line-HDF)
Methods	Country: France Setting: multi-centre, 36 French centres Study time frame: 2005 to December 2012 Study design: parallel RCT Enrolment: 600 patients Duration of follow-up: 2 years
Participants	Ages eligible for study: 65 to 90 years Inclusion criteria: patient who has signed the written consent form; aged > 65 and < 90 years; creatinine clearance < 10 mL/min; on dialysis for a minimum of 3 months; with 3 times/week haemodialysis sessions; erythropoietin dosage needed to maintain haemoglobin at a constant level (range of haemoglobin: 9 to 13 g/dL without any variation of more than 2g/dL for less than 3 months); without any problem of vascular access

NCT01327391 *(Continued)*

	Exclusion criteria: patient aged < 65 and > 90 years; presence of severe malnutrition (albumin < 20 g/L);, unstable clinical condition; unipuncture or failed vascular access flow; known problems of coagulation
Interventions	Active arm: on-line haemodiafiltration Haemodialysis patients treated with on line HDF technic Procedure: on line haemodiafiltration 3 sessions/week; 3-4 hours per session Comparator: haemodialysis Haemodialysis patients treated with conventional haemodialysis technic using high-flux dialyzers Procedure: haemodialysis 3 sessions/week; 3-4 hours per session; high-flux dialyzers
Outcomes	Primary outcome measures Tolerance of "on line" HDF treatment versus conventional high-flux haemodialysis in terms of adverse events occurring during dialysis sessions (time frame: between day 30 and day 120 of treatment) Secondary outcome measures Quality of life evaluated with the KDQOL questionnaire (time frame: day 0, 180, 365, 730) Incidence of cardiovascular events (time frame: day 180, 365, 730) Influence of the technic on mineral metabolism disturbances (time frame: day 180, 365, 730); measure of mineral metabolism parameters (Ca, PO4, PTH) All-cause and cardiovascular mortality (time frame: day 180, 365, 730) Influence of the technic on inflammatory parameters (time frame: day 180, 365, 730) measure of pro-inflammatory cytokines and acute phase reactant proteins Influence of the technic on microbiological safety (time frame: day 180, 365, 730); measure of microbiological purity of dialysate Influence of the technic on oxidative stress parameters (time frame: day 180, 365, 730) measure of oxidative stress markers (AOPP, AGE) and antioxidant systems (vitamin E)
Starting date	May 2005
Contact information	Prof Bernard CANAUD, Centre Hospitalier Universitaire Montpellier France Sponsors and Collaborators: University Hospital, Montpellier Ministry of Health, France
Notes	Estimated study completion date: December 2012 source: http://clinicaltrials.gov/ct2/results?term=NCT01327391&Search=Search

NCT01396863

Trial name or title	Acute brain volume changes in haemodialysis: comparison of low flux haemodialysis with pre-dilution haemodiafiltration
Methods	Country: Denmark Setting: single centre Study time frame: July 2011 to February 2012 Study design: cross-over RCT Enrolment: 12 patients

NCT01396863 *(Continued)*

	Duration of follow-up: 4.5 hours after one haemodialysis session and 4.5 hours after one session of HDF
Participants	Ages eligible for study: 18 years and older Inclusion criteria Age ≥ 18 years Informed consent; patient with end-stage renal disease (ESRD); stabile haemodialysis treatment (Kt/V ≥ 1.3); no contraindications against MRI (pacemaker or other metal implants, claustrophobia, severe adiposity); weight < 140 kg Exclusion criteria Clinical signs of new structural, thromboembolic or vascular brain disease the last 3 month before entering the study; changes in corticosteroid treatment during the last two weeks; change in diuretics during the last two weeks; non-compliant with regard to salt and fluid intake; acute disease
Interventions	Assigned intervention Procedure: HDF during the first examination The patient will receive treatment with pre-dilution HDF during the first examination. During the second examination the patient will receive treatment with low-flux hemodialysis. MRI of the brain will be performed before and after the treatment. The MRI-data will later be processed to determine the degree of brain volume change due to the treatment. Assigned comparison Procedure: HD during the first examination. The patient will receive treatment with low-flux haemodialysis during the first examination. During the second examination the patient will receive treatment with pre-dilution hemodiafiltration. MRI of the brain will be performed before and after the treatment. The MRI-data will later be processed to determine the degree of brain volume change due to the treatment.
Outcomes	Primary outcome measures Percent brain volume change (PBVC), brain volume before and after one haemodialysis session (4,5 hours) and one session of HDF (4,5 hours)
Starting date	July 2011
Contact information	Study director: Jens D. Jensen, MD, PhD, Department of Renal Medicine C, Aarhus University Hospital, Skejby, Denmark Principal Investigator: Niels Johansen, Department of Renal Medicine C, Aarhus University Hospital, Skejby, Denmark
Notes	Study completion date: February 2012 source: http://clinicaltrials.gov/ct2/show/NCT01396863?term=NCT01396863&rank=1

NCT01445366

Trial name or title	Solute removal with high volume hemodiafiltration versus long high flux hemodialysis
Methods	Country: Belgium Setting: single centre Study time frame: April 2012 to July 2012 Study design: cross-over RCT Enrolment: 10 patients

NCT01445366 *(Continued)*

	Duration of follow-up: 2 weeks
Participants	Ages eligible for study: 18 years and older Inclusion criteria Chronic kidney disease (CKD) stage 5 with haemodialysis or HDF treatment for more than three months; no vascular access related problems (Arteriovenous (A/V) fistula, graft or bi-flow catheter); double needle/lumen vascular access; no ongoing infection; signed informed consent form Exclusion criteria Inclusion criteria not met; known HIV or active hepatitis B or C infection (Positive Polymerisation Chain Reaction (PCR)); pregnancy; unstable clinical condition (e.g. cardiac or vascular instability); known coagulation problems; patients participating in another study interfering with the planned study
Interventions	Intervention: high volume post dilution HDF Comparator: high-flux haemodialysis This is a prospective cross-over study including 10 stable haemodialysis patients with chronic kidney disease stage 5. The cross-over study lasts 2 weeks with the study dialysis sessions at midweek. During one session, the patient will be dialyzed during 4 hours with high volume post dilution haemodiafiltration (HDF) with an FX800 haemodialyser (Fresenius Medical Care) and a blood flow of 300mL/min, dialysate flow of 500mL/min, and substitution flow of 75 mL/min. During the other midweek session, the patient will be dialyzed during 8 hours with high-flux haemodialysis (HD) with an FX80 haemodialyser (Fresenius Medical Care) and a blood flow of 200mL/min and a dialysate flow of 500mL/min.
Outcomes	Primary outcome measures Uraemic retention solute concentrations from pre and post dialysis blood samples, dialyzer inlet and outlet blood samples, and spent dialysate samples. (time frame: during 4 hours) Uraemic retention solute concentrations from pre and post dialysis blood samples, dialyzer inlet and outlet blood samples, and spent dialysate samples. (time frame: during 8 hours)
Starting date	April 2012
Contact information	Raymond Vanholder, PhD, MD University Hospital Ghent, Ghent, Belgium, 9000
Notes	Estimated study completion date: December 2012

NCT02374372

Trial name or title	Prospective randomized study comparing the hemodiafiltration on-line and conventional hemodialysis in terms of cost-benefit
Methods	Country: Canada Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open label

NCT02374372 *(Continued)*	
	Primary purpose: treatment
Participants	Chronic renal failure; haemodialysis
Interventions	Active comparator: conventional haemodialysis Active comparator: haemodiafiltration on-line haemodiafiltration
Outcomes	Compare the medication cost between the 2 groups (HD and HDF) (time frame: 3 years) Demonstrate lower cost of erythropoietin in HDF, with same control of anaemia to HD group (time frame: 3 years) Demonstrate lower cost of phosphate binder in HDF, with same control of phospho-calcium balance to HD group (time frame: 3 years) Demonstrate lower need of erythropoietin and best control of anaemia in HDF (time frame: 3 years) Demonstrate lower need of phosphate binder and best control of phospho-calcium balance in HDF (time frame: 3 years) Demonstrate less hospitalisation stay and cost related in HDF group (time frame: 3 years) Stabilisation or regression of left ventricular hypertrophy (time frame: 3 years)
Starting date	January 2011
Contact information	Renée Lévesque, MD, renee.levesque@sympatico.ca Marie-Line Caron, B.Sc, marie-line.caron.chum@ssss.gouv.qc.ca
Notes	Estimated completion date: June 2016 Source: clinicaltrials.gov/ct2/show/study/NCT02374372

DATA AND ANALYSES

Comparison 1. Convection (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	11	3396	Risk Ratio (IV, Random, 95% CI)	0.87 [0.72, 1.05]
2 Cardiovascular mortality	6	2889	Risk Ratio (IV, Random, 95% CI)	0.75 [0.61, 0.92]
3 Nonfatal cardiovascular event (rate/person-years follow-up)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Hospitalisation	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Hospital admissions/year	1	45	Mean Difference (IV, Random, 95% CI)	0.20 [-0.07, 0.47]

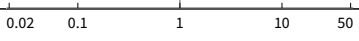
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Days spent in hospital	2	67	Mean Difference (IV, Random, 95% CI)	-1.22 [-7.47, 5.03]
5 Hospitalisation (rate/person-years follow-up)	2	400	Risk Ratio (IV, Random, 95% CI)	1.23 [0.93, 1.63]
6 Change of dialysis modality	5	2919	Risk Ratio (IV, Random, 95% CI)	0.87 [0.41, 1.84]
7 Hypotension during dialysis (rate/person-years follow-up)			Other data	No numeric data
8 Dialysis sessions with hypotension	2	42	Mean Difference (IV, Random, 95% CI)	-4.05 [-15.39, 7.30]
9 Predialysis blood pressure	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Systolic blood pressure	7	1859	Mean Difference (IV, Random, 95% CI)	1.19 [-1.46, 3.84]
9.2 Diastolic blood pressure	6	1154	Mean Difference (IV, Random, 95% CI)	-0.25 [-1.06, 0.56]
10 Maximal drop in blood pressure during dialysis	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.1 Systolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11 Kidney diseases questionnaire and well-being scores	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 Inter-dialysis patient well-being score	1	67	Mean Difference (IV, Random, 95% CI)	0.60 [0.30, 0.90]
11.2 Physical symptoms	2	121	Mean Difference (IV, Random, 95% CI)	-0.54 [-1.52, 0.44]
11.3 Fatigue	1	45	Mean Difference (IV, Random, 95% CI)	0.0 [-0.98, 0.98]
11.4 Depression	1	45	Mean Difference (IV, Random, 95% CI)	0.20 [-0.50, 0.90]
11.5 Relationships	1	45	Mean Difference (IV, Random, 95% CI)	0.10 [-0.73, 0.93]
11.6 Frustration	1	45	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.61, 1.21]
12 Kt/V	14	2022	Mean Difference (IV, Random, 95% CI)	0.07 [-0.00, 0.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Urea reduction ratio	3	879	Std. Mean Difference (IV, Random, 95% CI)	0.39 [0.06, 0.72]
14 Predialysis serum B_2 microglobulin	12	1813	Mean Difference (IV, Random, 95% CI)	-5.55 [-9.11, -1.98]
15 B_2 microglobulin clearance	3	65	Mean Difference (IV, Random, 95% CI)	13.05 [-5.94, 32.04]
16 Dialysate B_2 microglobulin level	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
17 Data from cross-over studies			Other data	No numeric data
17.1 Hospitalisation			Other data	No numeric data
17.2 Patients experiencing hypotension			Other data	No numeric data
17.3 Intradialytic hypotensive events			Other data	No numeric data
17.4 Symptomatic intradialytic hypotensive events			Other data	No numeric data
17.5 Predialysis systolic blood pressure (mm Hg)			Other data	No numeric data
17.6 Predialysis diastolic blood pressure (mm Hg)			Other data	No numeric data
17.7 Predialysis mean arterial pressure (mm Hg)			Other data	No numeric data
17.8 Postdialysis systolic blood pressure (mm Hg)			Other data	No numeric data
17.9 Postdialysis diastolic blood pressure (mm Hg)			Other data	No numeric data
17.10 Postdialysis fall in systolic blood pressure (mm Hg)			Other data	No numeric data
17.11 Postdialysis mean arterial pressure (mm Hg)			Other data	No numeric data
17.12 Difference between pre- and postdialysis systolic blood pressure (mm Hg)			Other data	No numeric data
17.13 Difference between pre- and postdialysis diastolic blood pressure (mm Hg)			Other data	No numeric data
17.14 Intradialysis mean systolic blood pressure (mm Hg)			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.15 Intradialysis mean diastolic blood pressure (mm Hg)			Other data	No numeric data
17.16 Intradialysis mean arterial pressure (mm Hg)			Other data	No numeric data
17.17 Kt/V			Other data	No numeric data
17.18 Urea reduction ratio			Other data	No numeric data
17.19 Predialysis serum B_2 microglobulin level (mg/L)			Other data	No numeric data

Analysis 1.1. Comparison 1 Convection (haemofiltration/haemodiafiltration/ acetate-free biofiltration) versus haemodialysis, Outcome 1 All-cause mortality.

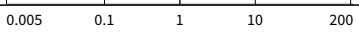
Study or subgroup	Favours convection n/N	Diffusion n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Beerenhout 2005	1/20	1/20		0.47%	1[0.07,14.9]
Schiffl 2007	1/38	2/38		0.62%	0.5[0.05,5.28]
Wizemann 2000	1/23	2/21		0.63%	0.46[0.04,4.68]
PROFIL Study 2011	2/27	3/21		1.17%	0.52[0.1,2.83]
Locatelli 1994	7/50	6/155		2.94%	3.62[1.27,10.26]
Bolasco 2003	7/76	8/70		3.41%	0.81[0.31,2.11]
Santoro 2005a	7/32	12/32		4.8%	0.58[0.26,1.29]
TURKISH HDF 2013	52/391	65/391		16.62%	0.8[0.57,1.12]
Santoro 1999	65/177	69/194		20.56%	1.03[0.79,1.35]
ESHOL Study 2011	85/456	122/450		22.34%	0.69[0.54,0.88]
CONTRAST (Dutch) Study 2005	131/358	138/356		26.43%	0.94[0.78,1.14]
Total (95% CI)	**1648**	**1748**		**100%**	**0.87[0.72,1.05]**
Total events: 359 (Favours convection), 428 (Diffusion)					
Heterogeneity: Tau^2=0.03; Chi^2=15.1, df=10(P=0.13); I^2=33.79%					
Test for overall effect: Z=1.49(P=0.14)					



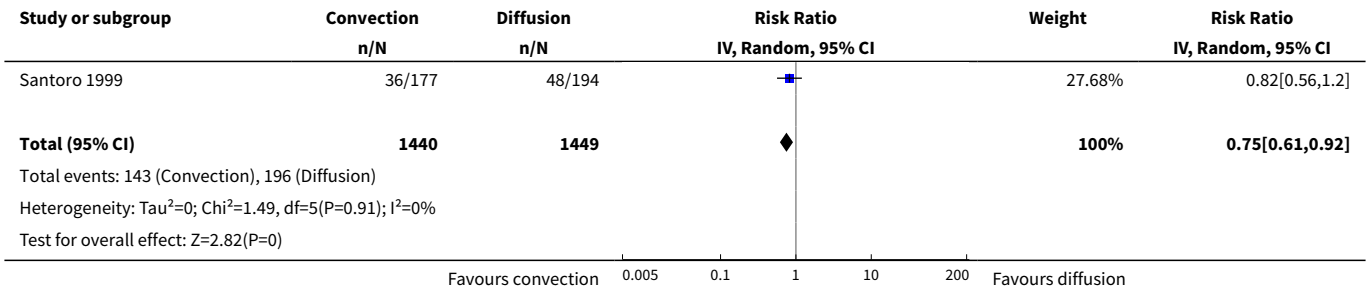
Favours convection — Favours diffusion

Analysis 1.2. Comparison 1 Convection (haemofiltration/haemodiafiltration/ acetate-free biofiltration) versus haemodialysis, Outcome 2 Cardiovascular mortality.

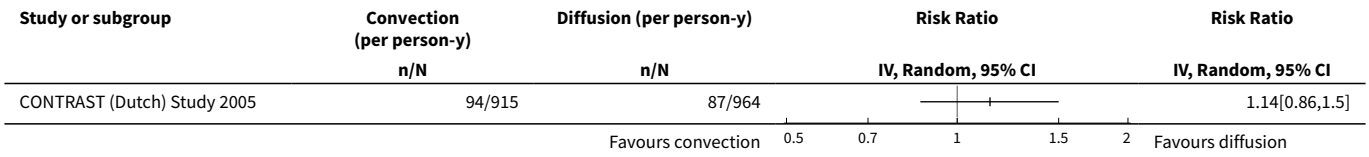
Study or subgroup	Convection n/N	Diffusion n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Schiffl 2007	0/38	2/38		0.45%	0.2[0.01,4.03]
Beerenhout 2005	1/20	1/20		0.55%	1[0.07,14.9]
TURKISH HDF 2013	32/391	44/391		21.42%	0.73[0.47,1.12]
CONTRAST (Dutch) Study 2005	37/358	46/356		24.25%	0.8[0.53,1.2]
ESHOL Study 2011	37/456	55/450		25.66%	0.66[0.45,0.99]



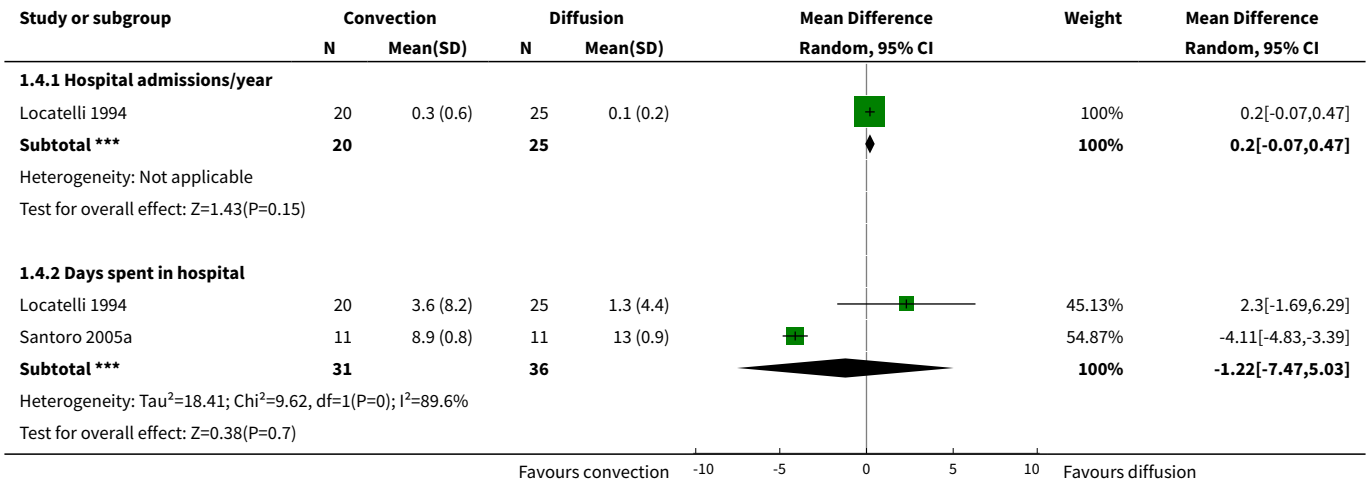
Favours convection — Favours diffusion



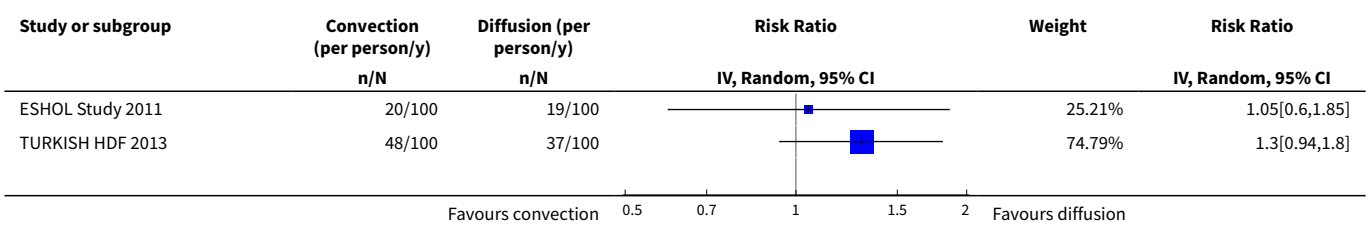
Analysis 1.3. Comparison 1 Convection (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis, Outcome 3 Nonfatal cardiovascular event (rate/person-years follow-up).

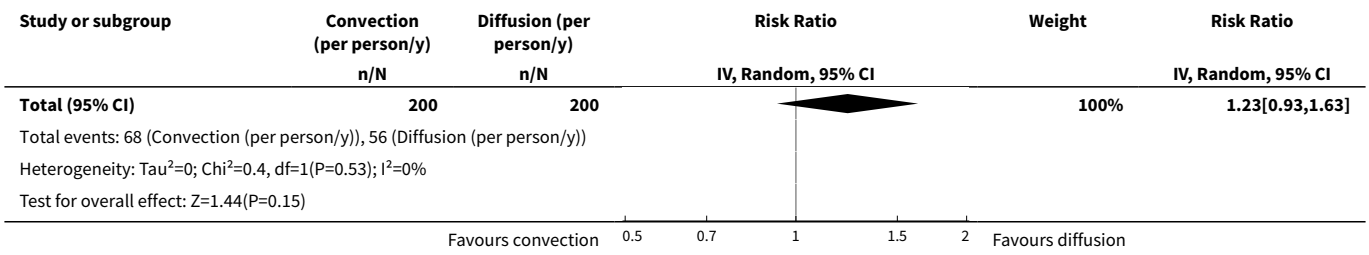


Analysis 1.4. Comparison 1 Convection (haemofiltration/haemodiafiltration/ acetate-free biofiltration) versus haemodialysis, Outcome 4 Hospitalisation.

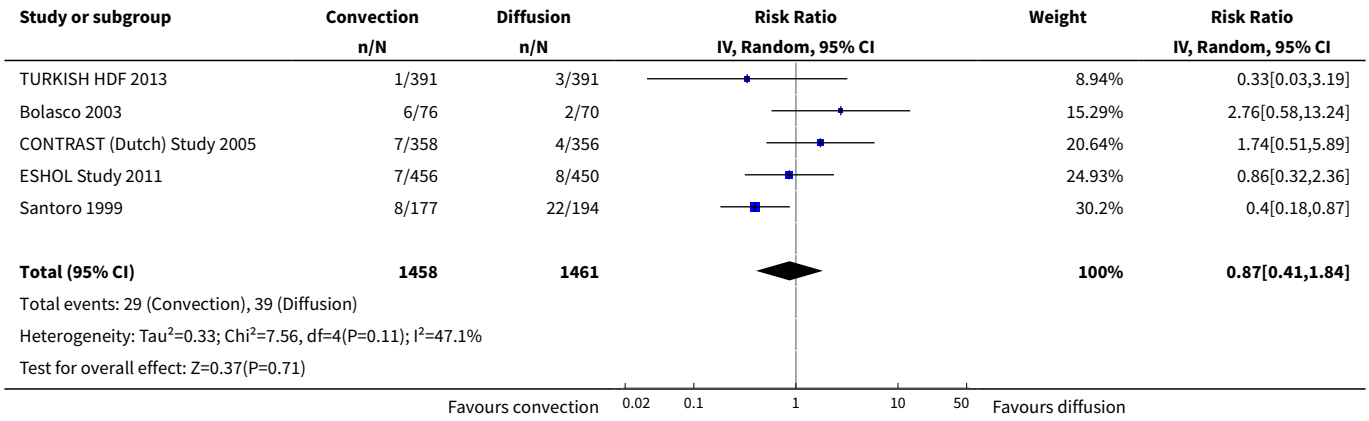


Analysis 1.5. Comparison 1 Convection (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis, Outcome 5 Hospitalisation (rate/person-years follow-up).





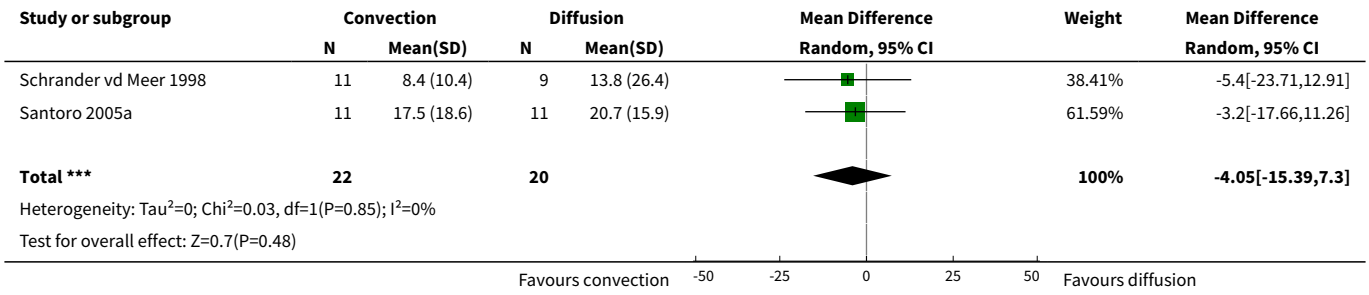
Analysis 1.6. Comparison 1 Convection (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis, Outcome 6 Change of dialysis modality.



Analysis 1.7. Comparison 1 Convection (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis, Outcome 7 Hypotension during dialysis (rate/person-years follow-up).

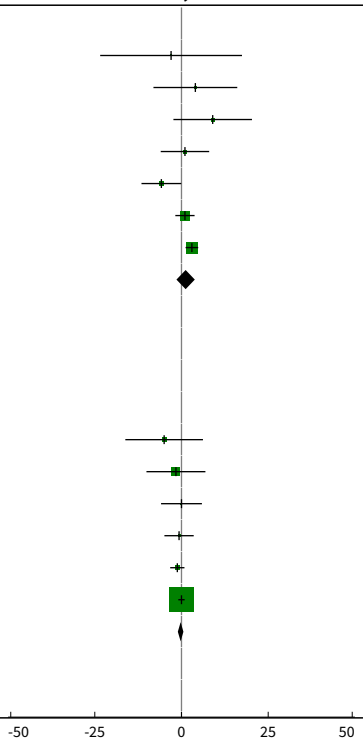
	Hypotension during dialysis (rate/person-years follow-up)	
Study	**Treatment effect**	**No. of participants**
ESHOL Study 2011	In this study which reporting the number of hypotensive events/person-years follow-up, convective dialysis reduced the rate of hypotension during dialysis (906 participants: RR 0.72, 95% CI 0.66 to 0.80)	906

Analysis 1.8. Comparison 1 Convection (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis, Outcome 8 Dialysis sessions with hypotension.



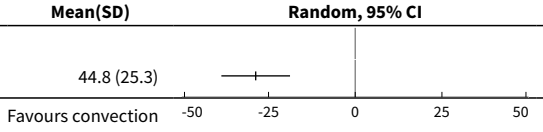
Analysis 1.9. Comparison 1 Convection (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis, Outcome 9 Predialysis blood pressure.

Study or subgroup	Convection N	Convection Mean(SD)	Diffusion N	Diffusion Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.9.1 Systolic blood pressure							
PROFIL Study 2011	10	148 (25)	7	151 (18)		1.62%	-3[-23.44,17.44]
Ohtake 2012	13	155 (13)	9	151 (15)		4.32%	4[-8.08,16.08]
Beerenhout 2005	13	144 (15)	14	135 (15)		4.85%	9[-2.32,20.32]
Bolasco 2003	39	141.5 (18.8)	66	140.5 (15.5)		10.74%	1[-5.99,7.99]
Santoro 1999	84	138 (18.4)	108	143.8 (22.1)		14.2%	-5.8[-11.53,-0.07]
CONTRAST (Dutch) Study 2005	358	146 (18.9)	356	145 (18.9)		28.96%	1[-1.77,3.77]
TURKISH HDF 2013	391	129 (13)	391	126 (13)		35.32%	3[1.18,4.82]
Subtotal ***	**908**		**951**			**100%**	**1.19[-1.46,3.84]**
Heterogeneity: Tau^2=4.31; Chi^2=10.64, df=6(P=0.1); I^2=43.63%							
Test for overall effect: Z=0.88(P=0.38)							
1.9.2 Diastolic blood pressure							
PROFIL Study 2011	10	74 (16)	7	79 (7)		0.52%	-5[-16.19,6.19]
Ohtake 2012	13	81.2 (13.1)	9	82.8 (7.1)		0.9%	-1.6[-10.1,6.9]
Beerenhout 2005	19	76 (9)	17	76 (9)		1.87%	0[-5.89,5.89]
Bolasco 2003	39	74.7 (11.4)	66	75.4 (9.3)		3.64%	-0.7[-4.92,3.52]
Santoro 1999	84	74.7 (9.6)	108	75.9 (0.6)		15.35%	-1.2[-3.26,0.86]
TURKISH HDF 2013	391	77 (6)	391	77 (7)		77.72%	0[-0.91,0.91]
Subtotal ***	**556**		**598**			**100%**	**-0.25[-1.06,0.56]**
Heterogeneity: Tau^2=0; Chi^2=1.95, df=5(P=0.86); I^2=0%							
Test for overall effect: Z=0.61(P=0.54)							



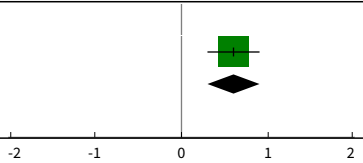
Analysis 1.10. Comparison 1 Convection (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis, Outcome 10 Maximal drop in blood pressure during dialysis.

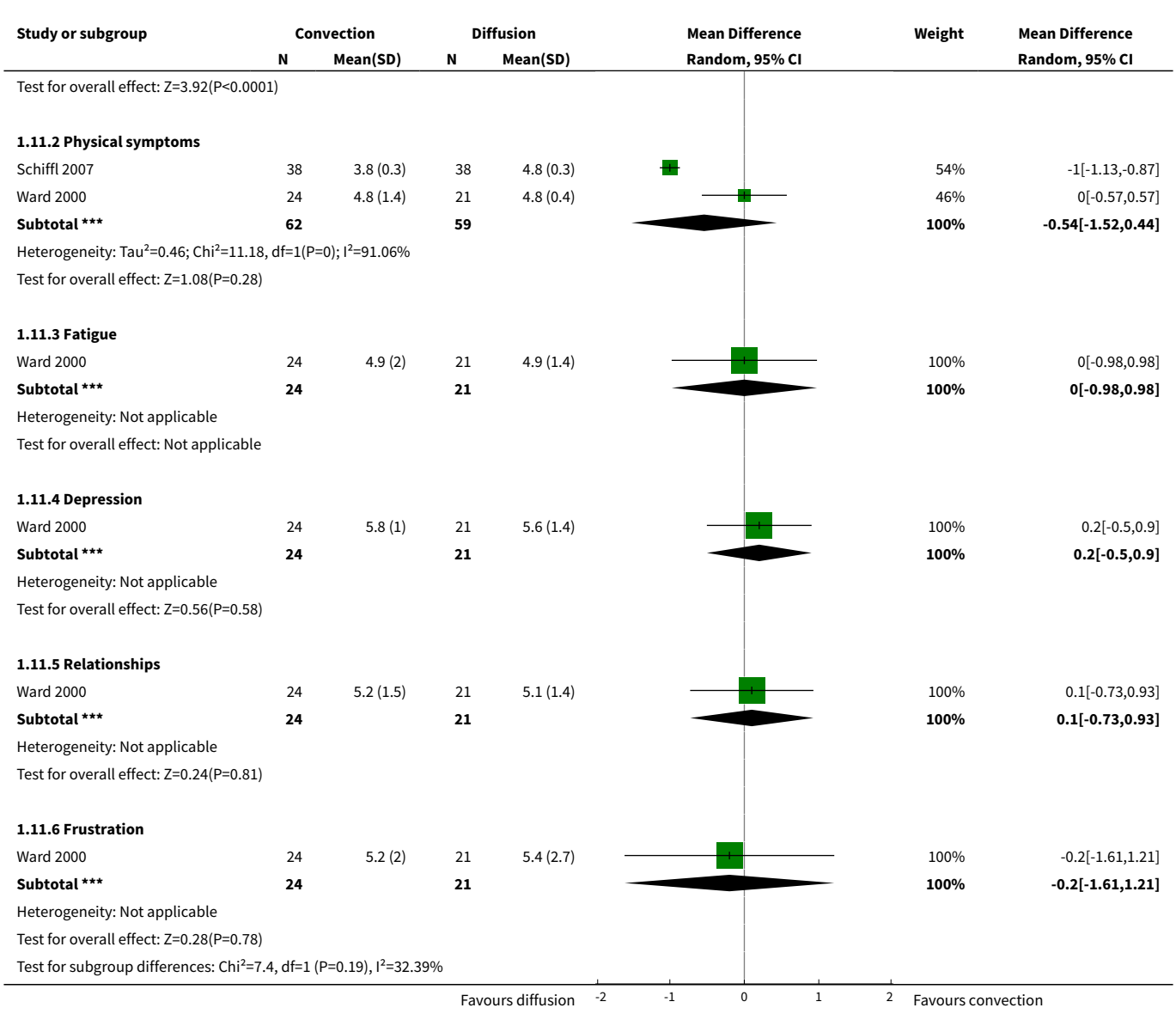
Study or subgroup	Convection N	Convection Mean(SD)	Diffusion N	Diffusion Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.10.1 Systolic blood pressure						
Lin 2001	38	16.1 (11.4)	29	44.8 (25.3)		-28.7[-38.6,-18.8]



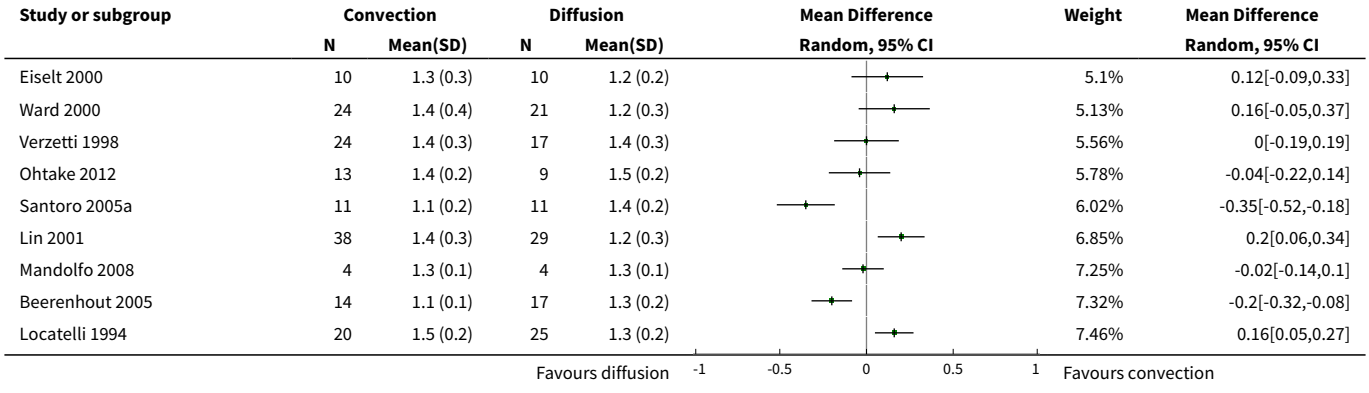
Analysis 1.11. Comparison 1 Convection (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis, Outcome 11 Kidney diseases questionnaire and well-being scores.

Study or subgroup	Convection N	Convection Mean(SD)	Diffusion N	Diffusion Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.11.1 Inter-dialysis patient well-being score							
Lin 2001	38	2.5 (0.5)	29	1.9 (0.7)		100%	0.6[0.3,0.9]
Subtotal ***	**38**		**29**			**100%**	**0.6[0.3,0.9]**
Heterogeneity: Not applicable							

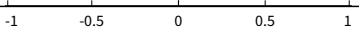




Analysis 1.12. Comparison 1 Convection (haemofiltration/haemodiafiltration/ acetate-free biofiltration) versus haemodialysis, Outcome 12 Kt/V.

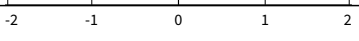


Study or subgroup	Convection N	Convection Mean(SD)	Diffusion N	Diffusion Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bolasco 2003	29	1.4 (0.2)	57	1.3 (0.2)		8.2%	0.05[-0.03,0.13]
Vaslaki 2006	34	1.4 (0.1)	36	1.3 (0.1)		8.7%	0.09[0.03,0.15]
CONTRAST (Dutch) Study 2005	358	1.6 (0.4)	356	1.5 (0.4)		8.72%	0.18[0.13,0.23]
Schiffl 2007	35	1.6 (0.1)	34	1.3 (0.1)		8.84%	0.3[0.25,0.35]
TURKISH HDF 2013	391	1.4 (0.2)	391	1.3 (0.2)		9.08%	0.14[0.11,0.17]
Total * **	**1005**		**1017**			**100%**	**0.07[-0,0.14]**
Heterogeneity: Tau²=0.01; Chi²=133.6, df=13(P<0.0001); I²=90.27%							
Test for overall effect: Z=1.89(P=0.06)							



Analysis 1.13. Comparison 1 Convection (haemofiltration/haemodiafiltration/ acetate-free biofiltration) versus haemodialysis, Outcome 13 Urea reduction ratio.

Study or subgroup	Convection N	Convection Mean(SD)	Diffusion N	Diffusion Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Beerenhout 2005	13	0.7 (0.1)	17	0.7 (0.1)		15.74%	-0.16[-0.88,0.57]
Lin 2001	38	73.7 (7.2)	29	67 (11.4)		26.12%	0.72[0.22,1.22]
TURKISH HDF 2013	391	75.2 (4.7)	391	73.2 (5.3)		58.14%	0.4[0.26,0.54]
Total * **	**442**		**437**			**100%**	**0.39[0.06,0.72]**
Heterogeneity: Tau²=0.04; Chi²=3.81, df=2(P=0.15); I²=47.55%							
Test for overall effect: Z=2.34(P=0.02)							



Analysis 1.14. Comparison 1 Convection (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis, Outcome 14 Predialysis serum B_2 microglobulin.

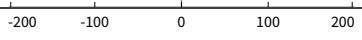
Study or subgroup	Convection N	Convection Mean(SD)	Diffusion N	Diffusion Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cristofano 2004	6	21.3 (12)	6	22.6 (20.6)		2.69%	-1.34[-20.42,17.74]
Mandolfo 2008	4	53.5 (6)	4	51 (9)		5.76%	2.5[-8.1,13.1]
Santoro 2005a	11	23.9 (5.9)	11	36.9 (16.8)		5.8%	-13[-23.52,-2.48]
Beerenhout 2005	14	20.4 (10.1)	17	42.8 (17.1)		6.28%	-22.4[-32.1,-12.7]
Locatelli 1994	20	32.2 (14.2)	25	28.8 (14.2)		7.14%	3.4[-4.95,11.75]
Vaslaki 2006	22	23.7 (11.2)	21	29 (12.3)		8.05%	-5.3[-12.34,1.74]
Ohtake 2012	13	27.3 (6.8)	9	23.9 (4.7)		9.67%	3.4[-1.41,8.21]
Wizemann 2000	15	19.1 (2.6)	16	36.4 (8.9)		9.84%	-17.37[-21.94,-12.8]
PROFIL Study 2011	18	21.1 (5.4)	16	26.4 (7)		10.07%	-5.3[-9.54,-1.06]
Schiffl 2007	35	22 (4)	34	25 (2)		11.51%	-3[-4.49,-1.51]
CONTRAST (Dutch) Study 2005	358	26.4 (7)	356	35.4 (10.2)		11.56%	-9[-10.28,-7.72]
TURKISH HDF 2013	391	27.1 (6.4)	391	27.2 (6.8)		11.65%	-0.1[-1.03,0.83]
Total * **	**907**		**906**			**100%**	**-5.55[-9.11,-1.98]**
Heterogeneity: Tau²=28.14; Chi²=188.54, df=11(P<0.0001); I²=94.17%							
Test for overall effect: Z=3.05(P=0)							

Analysis 1.15. Comparison 1 Convection (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis, Outcome 15 B_2 microglobulin clearance.

Study or subgroup	Convection N	Convection Mean(SD)	Diffusion N	Diffusion Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cristofano 2004	6	60.9 (69.9)	6	60.1 (106.1)		3.27%	0.8[-100.86,102.46]
Mandolfo 2008	4	53.5 (6)	4	51 (9)		44.99%	2.5[-8.1,13.1]
Ward 2000	24	61 (4.9)	21	38 (4.6)		51.74%	23[20.23,25.77]
Total ***	**34**		**31**			**100%**	**13.05[-5.94,32.04]**

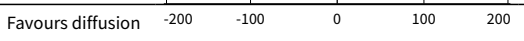
Heterogeneity: Tau^2=179.45; Chi^2=13.61, df=2(P=0); I^2=85.31%

Test for overall effect: Z=1.35(P=0.18)



Analysis 1.16. Comparison 1 Convection (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis, Outcome 16 Dialysate B_2 microglobulin level.

Study or subgroup	Convection N	Convection Mean(SD)	Diffusion N	Diffusion Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Schiffl 1992	8	257 (78)	12	124 (52)		133[71.46,194.54]



Analysis 1.17. Comparison 1 Convection (haemofiltration/haemodiafiltration/acetate-free biofiltration) versus haemodialysis, Outcome 17 Data from cross-over studies.

Data from cross-over studies			
Study	**Convective therapy**	**Diffusive therapy**	**P value from paper**
Hospitalisation			
Verzetti 1998	8	17	Not reported
Patients experiencing hypotension			
Fox 1993	1/9	0/9	Not reported
Karamperis 2005	0/12	0/12	Not significant
Pedrini 2011a	2/62	5/62	Not reported
Teo 1987	0/10	0/10	Not reported
Intradialytic hypotensive events			
Selby 2006a	23	37	Not significant
Stefansson 2012	32 dialysis sessions with hypotension from a total of 520 sessions	28 dialysis sessions with hypotension from a total of 520 sessions	Not significant
Symptomatic intradialytic hypotensive events			
Selby 2006a	2	2	Not significant
Predialysis systolic blood pressure (mm Hg)			
Karamperis 2005	12 patients Mean (± SE): 145.0 (7)	12 patients Mean (± SE): 144.0 (6)	Not significant
Noris 1998	5 patients Mean (± SE): 136.3 (2.7)	5 patients Mean (± SE): 128.3 (3.6)	P > 0.05
Pedrini 2011a	62 patients Mean (± SE): 140 (22)	62 patients Mean (± SE): 147 (22)	P = 0.014
Stefansson 2012	20 patients Mean (± SE): 161.2 (29.9)	20 patients Mean (± SE): 157.5 (26.1)	Not reported
Todeschini 2002	9 patients Mean (± SE): 153 (8)	9 patients Mean (± SE): 153 (6)	P > 0.05

Study	Convective therapy	Diffusive therapy	P value from paper
Data from cross-over studies			
Predialysis diastolic blood pressure (mm Hg)			
Karamperis 2005	12 patients Mean (± SE): 81.0 (3)	12 patients Mean (± SE): 83.0 (3)	Not significant
Noris 1998	5 patients Mean (± SE): 78.0 (2.7)	5 patients Mean (± SE): 75.3 (3.4)	P > 0.05
Pedrini 2011a	62 patients Mean (± SE): 75.0 (13)	62 patients Mean (± SE): 80.0 (13)	P = 0.05
Stefansson 2012	20 patients Mean (± SE): 88.9 (12.6)	20 patients Mean (± SE): 86.4 (10.8)	Not reported
Todeschini 2002	9 patients Mean (± SE): 83 (2)	9 Mean (± SE): 88 (2)	P > 0.05
Predialysis mean arterial pressure (mm Hg)			
Karamperis 2005	12 patients Mean (± SE): 103.0 (4)	12 patients Mean (± SE): 104.0 (4)	Not significant
Teo 1987	10 patients Mean (± SEM): 94.4 (6.7)	10 patients Mean (± SEM): 94.7 (6.1)	"Statistically insignificant"
Postdialysis systolic blood pressure (mm Hg)			
Karamperis 2005	12 patients Mean (± SE): 128.0 (8)	12 patients Mean (± SE): 129.0 (5)	Not significant
Noris 1998	5 patients Mean (± SE): 136.3 (4.2)	5 patients Mean (± SE): 127.1 (3.6)	P > 0.05
Pedrini 2011a	62 patients Mean (± SE): 138 (25)	62 patients Mean (± SE): 138 (21)	"not differ significantly"
Stefansson 2012	20 patients Mean (± SE): 161.6 (25.1)	20 patients Mean (± SE): 157.1 (22.8)	Not reported
Todeschini 2002	9 patients Mean (± SE): 114 (4)	9 patients Mean (± SE): 121 (3)	P > 0.05
Postdialysis diastolic blood pressure (mm Hg)			
Karamperis 2005	12 patients Mean (± SE): 73.0 (4)	12 patients Mean (± SE): 77.0 (4)	Not significant
Pedrini 2011a	62 patients Mean (± SE): 77.0 (14)	62 patients Mean (± SE): 76.0 (13)	"not differ significantly"
Stefansson 2012	20 patients Mean (± SE): 86.8 (12.8)	20 patients Mean (± SE): 85.3 (10.3)	Not reported
Postdialysis fall in systolic blood pressure (mm Hg)			
Todeschini 2002	9 patients Mean (± SE): -39 (8)	9 patients Mean (± SE): -32 (6)	P > 0.05
Postdialysis mean arterial pressure (mm Hg)			
Karamperis 2005	12 patients Mean (± SE): 91.0 (5)	12 patients Mean (± SE): 94.0 (3)	Not significant
Teo 1987	10 patients Mean (± SEM): 90.7 (3.8)	10 patients Mean (± SEM): 96.3 (5.9)	"Statistically insignificant"
Difference between pre- and postdialysis systolic blood pressure (mm Hg)			
Noris 1998	5 patients Mean (± SE): 0 (4.8)	5 patients Mean (± SE): -0.3 (4.6)	P > 0.05
Difference between pre- and postdialysis diastolic blood pressure (mm Hg)			
Noris 1998	5 patients Mean (± SE): -1.4 (2.7)	5 patients Mean (± SE): -3.1 (2.8)	P > 0.05
Todeschini 2002	9 patients Mean (± SE): -8 (6)	9 patients Mean (± SE): -13 (3)	P > 0.05
Intradialysis mean systolic blood pressure (mm Hg)			
Selby 2006a	12 patients Mean (± SEM): 137.8 (5.3)	12 patients Mean (± SEM): 145.5 (8.0)	P < 0.0001
Intradialysis mean diastolic blood pressure (mm Hg)			
Selby 2006a	12 patients Mean (± SEM): 79.2 (1.9)	12 patients Mean (± SEM): 80.8 (3.5)	P = 0.005
Intradialysis mean arterial pressure (mm Hg)			
Selby 2006a	12 patients Mean (± SEM): 104.1(5.2)	12 patients Mean (± SEM): 100.5 (2.9)	P < 0.0001
Teo 1987	10 patients Mean (± SEM): 89.5 (5.6)	10 patients Mean (± SEM): 95.3 (5.5)	"statistically insignificant decrease"
Kt/V			

Study	Convective therapy	Diffusive therapy	P value from paper
Data from cross-over studies			
Basile 2001	10 patients Mean (± SD): .28 (0.05)	10 patients Mean (± SD): 1.30 (0.05)	No significant difference
Kantartzi 2013	48 patients Mean (± SD): 1.45 (0.16)	48 patients Mean (± SD): 1.42 (0.02)	P = 0.33
Karamperis 2005	12 patients Mean (± SD): 1.8 (0.20)	12 patients Mean (± SD): 1.70 (0.00)	No significant difference
Noris 1998	5 patients Mean (± SE) = 1.28 (0.08)	5 patients Mean (± SE): 1.16 (0.11)	P > 0.05
Pedrini 2011a	62 patients Mean (± SE): 1.60 (0.31)	62 patients Mean (± SE): 1.44 (0.26)	P < 0.0001
Righetti 2010	24 patients Mean (± SE): 1.6 (0.02)	24 patients Mean (± SE): 1.51 (0.02)	P < 0.01
Selby 2006a	12 patients Mean (± SE): 1.37 (0.28)	12 patients Mean (± SE): 1.38 (0.32)	P = 0.91
Stefansson 2012	20 patients Mean (± SE): 1.51 (0.2)	20 patients Mean (± SE): 1.47 (0.24)	Not reported
Todeschini 2002	9 patients Mean (± SE): 1.54 (0.09)	9 patients Mean (± SE): 1.46 (0.05)	P > 0.05
Tuccillo 2002	12 patients Mean (± SD): 1.49 (0.20)	12 patients Mean (± SD): 1.41 (0.24)	P > 0.05
Urea reduction ratio			
Righetti 2010	24 patients Mean (± SE): 73.1 (0.5)	24 patients Mean (± SE): 70.9 (0.5)	P < 0.01
Predialysis serum B_2 microglobulin level (mg/L)			
Kantartzi 2013	48 patients Mean (± SE): 31.9 (7.64)	48 patients Mean (± SE): 47.36 (12.21)	P < 0.01
Pedrini 2011a	62 patients Mean (± SE): 22.2 (7.8)	62 patients Mean (± SE): 33.5 (11.8)	P < 0.0001
Righetti 2010	24 patients Mean (± SE): 26.0 (0.5)	24 patients Mean (± SE): 30.9 (0.6)	P < 0.01
Stefansson 2012	20 patients Mean (± SE): 23.7 (8.1)	20 patients Mean (± SE): 34.6 (17)	Not reported

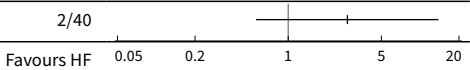
Comparison 2. Convection versus convection (haemofiltration versus haemodiafiltration)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Predialysis blood pressure	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Systolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Diastolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Kt/V	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Data from cross-over studies			Other data	No numeric data
4.1 Days spent in hospital			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Average number of episodes of hypotension/patient/month			Other data	No numeric data
4.3 Number of patients experiencing hypotension			Other data	No numeric data
4.4 Predialysis systolic blood pressure (mm Hg)			Other data	No numeric data
4.5 Predialysis diastolic blood pressure (mm Hg)			Other data	No numeric data
4.6 Predialysis mean arterial pressure (mm Hg)			Other data	No numeric data
4.7 Postdialysis systolic blood pressure (mm Hg)			Other data	No numeric data
4.8 Postdialysis diastolic blood pressure (mm Hg)			Other data	No numeric data
4.9 Postdialysis mean arterial blood pressure (mm Hg)			Other data	No numeric data
4.10 Number of patients experiencing hypertension			Other data	No numeric data
4.11 Kt/V			Other data	No numeric data
4.12 Predialysis serum B_2 microglobulin (mg/L)			Other data	No numeric data
4.13 B_2 microglobulin clearance (mL/min)			Other data	No numeric data

Analysis 2.1. Comparison 2 Convection versus convection (haemofiltration versus haemodiafiltration), Outcome 1 All-cause mortality.

Study or subgroup	HF n/N	HDF n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bolasco 2003	5/36	2/40		2.78[0.57,13.44]

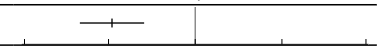


Analysis 2.2. Comparison 2 Convection versus convection (haemofiltration versus haemodiafiltration), Outcome 2 Predialysis blood pressure.

Study or subgroup	HF N	HF Mean(SD)	HDF N	HDF Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.2.1 Systolic blood pressure						
Bolasco 2003	31	137.3 (18.6)	39	141.5 (18.8)		-4.2[-13.01,4.61]
2.2.2 Diastolic blood pressure						
Bolasco 2003	31	72.6 (9.4)	39	74.7 (11.4)		-2.1[-6.97,2.77]

Analysis 2.3. Comparison 2 Convection versus convection (haemofiltration versus haemodiafiltration), Outcome 3 Kt/V.

Study or subgroup	HF N	HF Mean(SD)	HDF N	HDF Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Bolasco 2003	29	1.1 (0.2)	29	1.4 (0.2)		-0.24[-0.33,-0.15]



Analysis 2.4. Comparison 2 Convection versus convection (haemofiltration versus haemodiafiltration), Outcome 4 Data from cross-over studies.

Study	Data from cross-over studies: Haemodiafiltraton	Haemofiltration	P value from paper
Days spent in hospital			
Altieri 2004	30 patients Mean (± SD): 1.3 (4.7)	30 patients Mean (± SD)L 1.9 (4.9)	Not significant
Average number of episodes of hypotension/patient/month			
Altieri 2004	30 patients Mean (± SD): 1.1 (1.5)	30 patients Mean (± SD): 0.5 (0.7)	P = 0.0169
Number of patients experiencing hypotension			
Altieri 2004	2/30	0/30	P > 0.05
Predialysis systolic blood pressure (mm Hg)			
Altieri 2004	30 patients Mean (± SD): 130.9 (18.5)	30 patients Mean (± SD): 140.2 (16.2)	P = 0.044
Predialysis diastolic blood pressure (mm Hg)			
Altieri 2004	30 patients Mean (± SD): 75.3 (9.7)	30 patients Mean (± SD): 77.5 (10.4)	P > 0.05
Predialysis mean arterial pressure (mm Hg)			
Altieri 2004	30 patients Mean (± SD): 93.8 (11.5)	30 patients Mean (± SD): 98.4 (10.8)	P > 0.05
Postdialysis systolic blood pressure (mm Hg)			
Altieri 2004	30 patients Mean (± SD): 129 (19.8)	30 patients Mean (± SD): 1135.3 (15.7)	P > 0.05
Postdialysis diastolic blood pressure (mm Hg)			
Altieri 2004	30 patients Mean (± SD): 75.3 (9.3)	30 patients Mean (± SD): 74.5 (7.9)	P > 0.05
Postdialysis mean arterial blood pressure (mm Hg)			
Altieri 2004	30 patients Mean (± SD): 93.2 (11.6)	30 patients Mean (± SD): 94.8 (9.3)	P > 0.05
Number of patients experiencing hypertension			
Altieri 2004	6/30	7/30	P > 0.05
Kt/V			

Data from cross-over studies			
Study	**Haemodiafiltraton**	**Haemofiltration**	**P value from paper**
Altieri 2004	30 patients Mean (± SD): 1.3 (0.1)	30 patients Mean (± SD): 1.2 (0.1)	P < 0.001
Predialysis serum B_2 microglobulin (mg/L)			
Altieri 2004	30 patients Mean (± SD): 17.8 (5.0)	30 patients Mean (± SD): 19.3 (6.1)	Not significant
B_2 microglobulin clearance (mL/min)			
Meert 2009	14 patients Mean (± SD): 67.2 (18.5)	14 patients Mean (± SD): 87.5 (9.6)	P < 0.017

Comparison 3. Convection versus convection (haemodiafiltration versus acetate-free biofiltration)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Data from cross-over studies			Other data	No numeric data
1.1 Number of hospitalisations/patient during observation period			Other data	No numeric data
1.2 Length of hospitalisation stay/patient (days/patient)			Other data	No numeric data
1.3 Number of dialysis sessions with hypotension			Other data	No numeric data
1.4 Predialysis systolic blood pressure (mm Hg)			Other data	No numeric data
1.5 Predialysis mean arterial pressure (mm Hg)			Other data	No numeric data
1.6 Postdialysis systolic blood pressure (mm Hg)			Other data	No numeric data
1.7 Interdialysis symptom score			Other data	No numeric data
1.8 Kt/V			Other data	No numeric data
1.9 Urea reduction ratio			Other data	No numeric data
1.10 Predialysis B_2 microglobulin (mg/L)			Other data	No numeric data
1.11 Number of dialysis sessions with side effects (nausea, vomiting, headaches)			Other data	No numeric data

Analysis 3.1. Comparison 3 Convection versus convection (haemodiafiltration versus acetate-free biofiltration), Outcome 1 Data from cross-over studies.

Data from cross-over studies			
Study	**Haemodiafiltration**	**Acid-free biofiltration**	**P value from paper**
Number of hospitalisations/patient during observation period			
Movilli 1996	12 patients Mean (± SD): 0.33 (0.71)	12 patients Mean (± SD): 0.78 (0.93)	Not significant
Length of hospitalisation stay/patient (days/patient)			
Movilli 1996	12 patients	12 patients	Not significant

Study	Haemodiafiltration	Acid-free biofiltration	P value from paper
	Mean (± SD): 2.70 (5.7)	Mean (± SD): 3.60 (5.2)	
Data from cross-over studies			
Number of dialysis sessions with hypotension			
Coll 2009	21 patients 7/545 sessions	21 patients 46/545 sessions	"On-line HDF was associated with fewer hypotensive episodes than treatment with on-line HDF without acetate (P=0.019)"
Movilli 1996	12 patients 10/72 sessions	12 patients 9/72 sessions	Not significant
Predialysis systolic blood pressure (mm Hg)			
Ding 2002	9 patients Mean (± SD): 142.0 (10.0)	9 patients Mean (± SD): 142.0 (11.0)	Not significant
Predialysis mean arterial pressure (mm Hg)			
Ding 2002	9 patients Mean (± SD): 94.0 (16.5)	9 patients Mean (± SD): 89.2 (17.7)	Not reported
Postdialysis systolic blood pressure (mm Hg)			
Ding 2002	9 patients Mean (± SD): 141.0 (8.0)	9 patients Mean (± SD): 141.00 (12.1)	Not significant
Interdialysis symptom score			
Ding 2002	9 patients Mean (± SD): 1.99 (2.49)	9 patients Mean (± SD): 2.57 (2.93)	Not significant
Kt/V			
Movilli 1996	12 patients Mean (± SD): 1.32 (0.12)	12 patients Mean (± SD): 1.32 (0.13)	Not significant
Urea reduction ratio			
Ding 2002	9 patients Mean (± SD): 71.0 (7.9)	9 patients Mean (± SD): 67.0 (6.5)	Not significant
Predialysis B_2 microglobulin (mg/L)			
Coll 2009	21 patients Mean (± SD): 27.7 (7.2)	21 patients Mean (± SD): 27.4 (6.7)	Not significant
Ding 2002	9 patients Mean (± SD): 26.3 (7.9)	9 patients Mean (± SD): 25.9 (6.3)	Not significant
Number of dialysis sessions with side effects (nausea, vomiting, headaches)			
Movilli 1996	12 patients 1/72 sessions	12 patients 1/72 sessions	Not significant

ADDITIONAL TABLES

Table 1. Categories of interventions used in individual studies and duration of follow-up

Study ID	Intervention	Duration	Number of patients
Altieri 2004	HDF versus HF	12 months	39
Bammens 2004	HDF versus HD	2 weeks	14
Basile 2001	AFB versus HD	12 months	11
Beerenhout 2005	HF versus HD	12 months	40
Bolasco 2003	HF versus HDF versus HD	18 months	146
Coll 2009	AFB versus HDF	15 months	30
CONTRAST (Dutch) Study 2005	HDF versus HD	36 months	714

Table 1. Categories of interventions used in individual studies and duration of follow-up *(Continued)*

Cristofano 2004	HDF versus HD	1 session	12
Ding 2002	HDF versus AFB	36 weeks	12
Eiselt 2000	AFB versus HD	12 months	20
ESHOL Study 2011	HDF versus HD	36 months	906
Fox 1993	HF versus HD	1 session	9
Kantartzi 2013	HDF versus HD	3 months	24
Karamperis 2005	HDF versus HD	2 sessions	12
Lin 2001	HDF versus HD	15 months	67
Locatelli 1994	HDF versus HD	24 months	205
Lornoy 1998	HDF versus HD	1 session	8
Mandolfo 2008	HDF versus HD	6 weeks	8
Meert 2009	HDF versus HF	9 weeks	14
Movilli 1996	HDF versus AFB	6 months	12
Noris 1998	AFB versus HD	1 week	5
Ohtake 2012	HDF versus HD	12 months	22
Pedrini 2011a	HDF versus HD	12 months	69
PROFIL Study 2011	HF versus HD	24 months	48
Righetti 2010	HDF versus HD	18 months	24
Santoro 1999	AFB versus HD	48 months	371
Santoro 2005a	HF versus HD	36 months	64
Schiffl 1992	HF versus HD	48 months	32
Schiffl 2007	HDF versus HD	48 months	76
Schrander vd Meer 1998	AFB versus HD	12 months	24
Selby 2006a	AFB versus HD	4 weeks	12
Stefansson 2012	HDF versus HD	4 months	20
Teo 1987	HDF versus HD	8 months	13
Todeschini 2002	AFB versus HD	3 sessions	9
Tuccillo 2002	HDF versus HD	3 months	12

Table 1. Categories of interventions used in individual studies and duration of follow-up *(Continued)*

TURKISH HDF 2013	HDF versus HD	24 months	782
Vaslaki 2006	HDF versus HD	48 weeks	129
Verzetti 1998	AFB versus HD	12 months	41
Ward 2000	HDF versus HD	12 months	50
Wizemann 2000	HDF versus HD	24 months	44

AFB - acetate-free biofiltration; HDF - haemodiafiltration; HD - haemodialysis; HF - haemofiltration

Table 2. Description of included studies according with the interventions used

Categories of intervention	Study	Total number of studies	Total number of patients
HDF versus HD	Bammens 2004; Lin 2001; Locatelli 1994; Lornoy 1998; Teo 1987; Tuccillo 2002; Ward 2000; Wizemann 2000; Bolasco 2003; CONTRAST (Dutch) Study 2005; Cristofano 2004; Karamperis 2005; Mandolfo 2008; Pedrini 2011a; Righetti 2010; Schiffl 2007; Stefansson 2012; TURKISH HDF 2013; Vaslaki 2006 ESHOL Study 2011; Kantartzi 2013; Ohtake 2012	22	3299
HF versus HD	Beerenhout 2005; Fox 1993; Schiffl 1992; Bolasco 2003; Santoro 2005a; PROFIL Study 2011	6	325
AFB versus HD	Basile 2001; Santoro 1999; Eiselt 2000; Noris 1998; Schrander vd Meer 1998; Selby 2006a; Todeschini 2002; Verzetti 1998	8	487
HDF versus AFB	Coll 2009; Ding 2002; Movilli 1996	3	59
HDF versus HF	Altieri 2004; Bolasco 2003; Meert 2009	3	199
More than two treatment arms	Bolasco 2003; Locatelli 1994; Schiffl 1992	3	383

AFB - acetate-free biofiltration; HDF - haemodiafiltration; HD - haemodialysis; HF - haemofiltration

Table 3. Summary of quality of life findings

Study ID	Comparison	Quality of Life scale used	Time of assessment	End of study result	Selective reporting of quality of life dimensions
Beerenhout 2005	HF versus HD	Kidney Disease Questionnaire	Before randomisation, at 6 months and at 1 year	No significant difference in scores in all five components of the scoring system between interventions	Yes
CONTRAST (Dutch) Study 2005	HDF versus HD	Kidney Disease Quality of Life-Short Form	Median follow-up of 2 years	There were no significant differences in changes in health-related quality of life over time between groups (generic or kidney-disease specific domains)	No

Table 3. Summary of quality of life findings *(Continued)*

Kantartzi 2013	HDF versus HD	SF-36	At 3 months	There were statistical significant differences in QoL for the total SF-36 (36.1 (26.7 to 45.7) and 40.7 (30.2 to 62.8)), for classic low-flux HD and high-flux HDF, for bodily pain (45 (26.9 to 66.9) and 55 (35.6 to 87.5)), and for role limitations due to emotional functioning (0 (0 to 33.3) and 33.3 (0 to 100)), respectively *No data were available for the end of the first phase of treatment*	No
Lin 2001	HDF versus HD	Patient well-being score	Once weekly for 15 months	Patients on HDF had significantly better scores ((physical well-being score) MD 0.60, 95% CI 0.30 to 0.90).	No
Schiffl 2007	HDF versus HD	Kidney Disease Questionnaire	after 52 weeks	None of the other dimensions of the KDQ showed a change during the course of the study *No data were available for the end of the first phase of treatment*	Yes
Stefansson 2012	HDF versus HD	Physical functioning domain of IQOLA SF-36 questionnaire	At day 60	With the exception of a lower score for social functioning with HDF ($P < 0.05$), there was no significant difference in quality of life between HD and HDF *No data were available for the end of the first phase of treatment*	No
Verzetti 1998	AFB	Subjective well-being	Monthly	Reported well-being significantly higher in patients receiving AFB in multivariate analysis although unclear whether between-groups comparison was reported *No data were available for the end of the first phase of treatment*	No
Ward 2000	HDF versus HD	Kidney Disease Questionnaire	At 6 months and 1 year	No significant difference in scores in all five components of the scoring system between interventions	No

AFB - acetate-free biofiltration; HDF - haemodiafiltration; HD - haemodialysis; HF - haemofiltration; SF-36 - Short-Form Health Survey with 36 questions

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms used
CENTRAL	1. MeSH descriptor Renal Replacement Therapy, this term only 2. MeSH descriptor Hemofiltration explode all trees 3. hemofiltrat* or haemofiltrat*:ti,ab,kw in Clinical Trials

(Continued)

	4. hemodiafiltrat* or haemodiafiltrat*:ti,ab,kw in Clinical Trials 5. ultrafiltrat*:ti,ab,kw in Clinical Trials 6. biofiltrat*:ti,ab,kw in Clinical Trials 7. (acetate-free near/3 biofiltration):ti,ab,kw in Clinical Trials 8. (HDF or HF or AFB or RRT):ti,ab,kw in Clinical Trials 9. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) 10. MeSH descriptor Renal Replacement Therapy, this term only 11. MeSH descriptor Renal Dialysis, this term only 12. MeSH descriptor Hemodialysis, Home, this term only 13. MeSH descriptor Kidney Failure, Chronic, this term only 14. (hemodialysis or haemodialysis):ti,ab,kw in Clinical Trials 15. (end-stage NEXT kidney):ti,ab,kw or (end-stage NEXT renal):ti,ab,kw or (endstage NEXT kidney):ti,ab,kw or (endstage NEXT renal):ti,ab,kw in Clinical Trials 16. (#10 OR #11 OR #12 OR #13 OR #14 OR #15) 17. (#9 AND #16)
MEDLINE	1. Renal Replacement Therapy/ 2. Renal Dialysis/ 3. Hemodialysis, Home/ 4. Kidney Failure, Chronic/ 5. (hemodialysis or haemodialysis).tw. 6. (end-stage kidney or end-stage renal or endstage kidney or endstage renal).tw. 7. (ESKD or ESKF or ESRD or ESRF).tw. 8. or/1-7 9. Renal Replacement Therapy/ 10. exp Hemofiltration/ 11. (hemofiltrat$ or haemofiltrat$).tw. 12. (hemodiafiltrat$ or haemodiafiltrat$).tw. 13. (acetate-free adj2 biofiltration).tw. 14. (HDF or HF or AFB or RRT).tw. 15. or/9-14
EMBASE	1. renal replacement therapy/ 2. hemodialysis/ 3. home dialysis/ 4. (hemodialysis or haemodialysis).tw. 5. Chronic Kidney Disease/ 6. Kidney Failure/ 7. Chronic Kidney Failure/ 8. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 9. (ESRF or ESKF or ESRD or ESKD).tw. 10. or/1-9 11. renal replacement therapy/ 12. hemodiafiltration/ 13. hemofiltration/ 14. (acetate-free adj2 biofiltration).tw. 15. (HDF or AFB or HF).tw. 16. (extracorporeal adj RRT).tw. 17. (haemodiafiltrat$ or hemodiafiltrat$).tw. 18. (haemofiltrat$ or hemofiltrat$).tw. 19. or/11-18

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.

(Continued)

	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
18 February 2015	New search has been performed	Updated incorporating data
18 February 2015	New citation required and conclusions have changed	Review update - 20 new studies added
22 November 2011	Amended	Search strategies & search methods revised

CONTRIBUTIONS OF AUTHORS

Original review (2006)

- Giovanni FM Strippoli: Design, conduct, data-analysis, writing review
- Alison M MacLeod: Design and writing the review
- Conal Daly: Designing, screening search results, selecting relevant studies and writing the review

- Paul Roderick: Design and writing the review.
- Sheila Wallace: Develop search strategy
- Kannaiyan S Rabindranath: Develop search strategy, screen search titles, select studies, data extraction and analysis, writing review

Updated review (2015)

- Ionut Nistor: Screening and identification of additional studies for inclusion, development of database, data extraction, completion of tables and figures, drafting of first version of updated manuscript
- Suetonia Palmer: Data checking and analysis, revision of first and subsequent drafts, generation of additional tables
- Valeria Saglimbene: Screening and identification of additional studies for inclusion, data extraction and checking
- Jonathan C. Craig: Data analysis and revision of first and subsequent drafts
- Giovanni FM Strippoli: Screening and identification of additional studies for inclusion, data analysis and revision of first and subsequent drafts

DECLARATIONS OF INTEREST

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External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk of bias assessment tool has replaced the quality assessment checklist (Rabindranath 2005).

INDEX TERMS

Medical Subject Headings (MeSH)

Cardiovascular Diseases [mortality]; Cause of Death; Hemodiafiltration [adverse effects] [methods]; Hemofiltration [adverse effects] [*methods]; Hospitalization; Hypotension [etiology]; Kidney Failure, Chronic [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Male