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[Intervention Review]

High-flux versus low-flux membranes for end-stage kidney disease

Suetonia C Palmer¹, Kannaiyan S Rabindranath², Jonathan C Craig^{3,4}, Paul J Roderick⁵, Francesco Locatelli⁶, Giovanni FM Strippoli^{4,7,8,9}

¹Department of Medicine, University of Otago Christchurch, Christchurch, New Zealand. ²Renal Unit, Waikato District Hospital, Hamilton, New Zealand. ³Sydney School of Public Health, The University of Sydney, Sydney, Australia. ⁴Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. ⁵School of Medicine, Community Clinical Sciences, University of Southampton, Southampton, UK. ⁶Nephrology and Dialysis Department, Ospedale A Manzoni, Lecco, Italy. ⁷Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy. ⁸Medical Scientific Office, Diaverum, Lund, Sweden. ⁹Diaverum Academy, Bari, Italy

Contact address: Giovanni FM Strippoli, Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, NSW, 2145, Australia. giovanni.strippoli@uniba.it, gfmstrippoli@gmail.com.

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ABSTRACT

Background

Clinical practice guidelines regarding the use of high-flux haemodialysis membranes vary widely.

Objectives

We aimed to analyse the current evidence reported for the benefits and harms of high-flux and low-flux haemodialysis.

Search methods

We searched the Cochrane Renal Group's Specialised Register (July 2012) 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: Quarterly searches of the Cochrane Central Register of Controlled Trials CENTRAL, weekly searches of MEDLINE OVID SP, handsearching of renal-related journals and the proceedings of major renal conferences, searching of the current year of EMBASE OVID SP, weekly current awareness alerts for selected renal journals and searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

We included randomised controlled trials (RCTs) that compared high-flux haemodialysis with low-flux haemodialysis in people with end-stage kidney disease (ESKD) who required long-term haemodialysis.

Data collection and analysis

Data were extracted independently by two authors for study characteristics (participants and interventions), risks of bias, and outcomes (all-cause mortality and cause-specific mortality, hospitalisation, health-related quality of life, carpal tunnel syndrome, dialysis-related arthropathy, kidney function, and symptoms) among people on haemodialysis. Treatment effects were expressed as a risk ratio (RR) or mean difference (MD), with 95% confidence intervals (CI) using the random-effects model.

Main results

We included 33 studies that involved 3820 participants with ESKD. High-flux membranes reduced cardiovascular mortality (5 studies, 2612 participants: RR 0.83, 95% CI 0.70 to 0.99) but not all-cause mortality (10 studies, 2915 participants: RR 0.95, 95% CI 0.87 to 1.04) or infection-related mortality (3 studies, 2547 participants: RR 0.91, 95% CI 0.71 to 1.14). In absolute terms, high-flux membranes may prevent three cardiovascular deaths in 100 people treated with haemodialysis for two years. While high-flux membranes reduced predialysis beta-2 microglobulin levels (MD -12.17 mg/L, 95% CI -15.83 to -8.51 mg/L), insufficient data were available to reliably estimate the effects of membrane flux on hospitalisation, carpal tunnel syndrome, or amyloid-related arthropathy. Evidence for effects of high-flux membranes was limited by selective reporting in a few studies. Insufficient numbers of studies limited our ability to conduct subgroup analyses for membrane type, biocompatibility, or reuse. In general, the risk of bias was either high or unclear in the majority of studies.

Authors' conclusions

High-flux haemodialysis may reduce cardiovascular mortality in people requiring haemodialysis by about 15%. A large well-designed RCT is now required to confirm this finding.

PLAIN LANGUAGE SUMMARY

Does haemodialysis membrane type influence outcomes in people with kidney disease?

Haemodialysis removes excess fluid and metabolic products from the blood in people who have limited kidney function. Haemodialysis membranes are classified as high-flux or low-flux based on their ability to remove fluid and molecules. It has been suggested that removal of larger solutes across high-flux haemodialysis membranes may better reflect normal kidney function and improve clinical outcomes. To investigate this issue, we analysed 33 studies that involved 3820 people which directly compared haemodialysis using high-flux or low-flux membranes.

We found that high-flux dialysis membranes reduced deaths from heart and circulatory (cardiovascular) causes by 17%, but did not reduce overall risk of death. This means that if 100 people were treated with high-flux dialysis for approximately two years, three deaths from cardiovascular causes may be prevented in people who need long-term haemodialysis.

Based on the available evidence, we could not be certain that the type of membrane flux involved had any effect on deaths from infection, hospital admissions, joint problems due to long term dialysis, quality of life, or kidney function in people on long-term haemodialysis.

BACKGROUND

Dialysis is the mainstay of treatment for people with end-stage kidney disease (ESKD). Mortality rates relating to both cardiovascular and non-cardiovascular causes for people commencing haemodialysis is nearly 30 to 50 times that of the general population (de Jager 2009). However, recent evidence suggests that the high rates of mortality and hospital admission in people who need dialysis may be improving (USRDS Annual Report 2010). Numerous interventions, including statin therapy (4D 2005; AURORA 2009), epoetins targeting higher haemoglobin levels (Besarab 1998), and dialysis dose (HEMO 2002) have not been shown to improve all-cause mortality in people who need dialysis. Frequent haemodialysis (six times weekly) may offer improved survival rates compared with the current standard of three times weekly (Chertow 2010); however, interventions that clearly reduce mortality in people on haemodialysis are urgently required.

In the absence of sufficient kidney function, haemodialysis removes accumulated water and metabolites from the blood across a semi-permeable dialysis membrane. The earliest haemodialysis membranes consisted of cellulose that was associated with an inflammatory response and had a small pore size, only allowing clearance of molecules smaller than 5000 Daltons into the dialysate. As dialysis membrane technology has improved, high-flux membranes with larger pore sizes have been developed to allow greater clearances of larger retention molecules with reduced induction of inflammatory mediators (improved biocompatibility) (Clark 1999; Woffindin 1988). The larger “middle” molecules cleared by high-flux membranes include the amyloidogenic beta-2 microglobulin and advanced glycation end products. While observational studies suggest high-flux haemodialysis is associated with lower mortality (Koda 1997; Port 2001; Woods 2000) and dialysis-related amyloidosis (Chanard 1989; Koda 1997; van Ypersele de Strihou 1991) individual randomised controlled trials (RCTs) have not confirmed that high-flux haemodialysis improves clinical outcomes (HEMO 2002; MPO 2009). High-flux dialysis membranes have larger pore sizes that may increase transportation of dialysate impurities or contaminants from the dialysate to the bloodstream even when the dialysate quality complies with acceptable standards (Schiffl 2011), although some evidence suggests that high-flux membranes may actively absorb endotoxins and impede their back-transfer from dialysate into the bloodstream (Jaber 1998; Lonnemann 1992).

Clinical practice guidelines on dialysis membrane flux are variable (Table 1). The EBPG 2002 strongly recommend that high-flux haemodialysis should be used in all high risk patients, and given the small incremental cost, should be considered for people with ESKD starting haemodialysis (Tattersall 2010). The Renal Association 2009 guidelines suggest that high-flux dialysers be used instead of low-flux dialysers, and the Kidney Disease Outcomes Quality Initiative (KDOQI 2006) recommends that using poorly biocompatible, unmodified cellulose dialyser membranes for haemodialysis be discouraged. The Australasian guidelines make no recommendations about membrane flux, citing insufficient evidence (CARI 2005).

While individual studies suggest benefits for high-flux membranes on clinical outcomes in subgroups of patients on haemodialysis, particularly those with longer times on haemodialysis (HEMO 2002) or higher comorbidity (MPO 2009), the overall efficacy and safety

of high-flux compared with low-flux membranes for dialysis in all available RCTs remains uncertain.

OBJECTIVES

Our objective was to determine if high-flux membranes improved clinical outcomes compared with low-flux membranes in people with ESKD who require long-term haemodialysis.

METHODS

Criteria for considering studies for this review

Types of studies

We sought 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) that compared high-flux with low-flux dialysis membranes for inclusion in this systematic review.

Types of participants

We included studies that enrolled adults who required long-term haemodialysis.

Types of interventions

Our study inclusion criteria specified any (or several) high-flux haemodialysis membranes versus any (or several) low-flux haemodialysis membranes for one month or longer.

Where unspecified, membrane flux was classified as high- or low-flux based on ultrafiltration coefficient (kUF) (the rate at which water crosses the membrane at a given trans-membrane pressure) or beta-2 microglobulin clearance (FDA 1998; HEMO 2002). High-flux was defined as an ultrafiltration coefficient greater than 12 mL/h/mm Hg or beta-2 microglobulin clearance greater than 20 mL/min; and low-flux haemodialysis membranes were defined as having an ultrafiltration coefficient less than 12 mL/h/mm Hg or beta-2 microglobulin clearance less than 10 mL/min.

Types of outcome measures

Primary outcomes

1. All-cause mortality
2. Cause-specific mortality (cardiovascular mortality, infection-related mortality)
3. Hospitalisation (number of patients who were admitted to hospital, number of hospital admissions/patient/year, length of hospital stay (days)).

Secondary outcomes

1. Infection requiring hospitalisation, parenteral antibiotic treatment or described as 'significant' in the included studies
2. Health-related quality of life
3. Predialysis (that is, from blood obtained before a dialysis session) beta-2 microglobulin concentration
4. Adequacy of dialysis measured either by Kt/V_{urea} or urea reduction ratio (URR)
5. Dialysis-associated amyloid-related complications (carpal tunnel syndrome, dialysis-related arthropathy)
6. Withdrawal due to treatment inadequacy

7. Kidney function (e.g. residual renal function (RRF))
8. Lipid profile.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's Specialised Register (July 2012) 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 and 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 and 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.

Searching other resources

1. Authors of studies identified as potentially eligible for inclusion were contacted both to clarify missing data or methodological details and to ask for additional published or unpublished studies.
2. Studies presented in conference proceedings were included.
3. Reference lists of previous reviews (including systematic reviews) and previous studies were included
4. Papers in languages other than English were included and translation facilities available from the Cochrane Collaboration were used as required.

Data collection and analysis

Selection of studies

All titles and abstracts were independently assessed by two or more authors (KSR, AMM, SCP). Full papers were then obtained for those studies that might fulfil the inclusion criteria. At least two authors (KSR, AMM, SCP) independently assessed these studies to determine if they were eligible for inclusion. Disagreements were resolved by discussion with another author (GFMS).

Data extraction and management

At least two authors (KSR, CB, SCP) extracted data independently. Discrepancies were resolved by discussion with another author (GFMS). When data were not reported or incomplete, study authors were contacted for clarification. When more than one report of a study was identified, reports were grouped and the publication providing the most data was designated as the primary reference.

We took care not to duplicate data from multiple published sources of the same study.

Assessment of risk of bias in included studies

Two authors assessed the risk of bias in the included studies using a standard checklist developed by the Cochrane Collaboration (including the domains of sequence generation, allocation concealment, blinding of patients, investigators and outcome assessors, analysis by intention-to-treat, whether incomplete data were addressed, freedom from selective reporting, and other biases). We did not use a summary scoring system to assess study risks of bias.

Measures of treatment effect

Treatment effects were summarised as risk ratios (RR) for dichotomous outcomes or mean differences (MD) for continuous outcomes, together with 95% confidence intervals (CI), using a random-effects model to pool data ([DerSimonian 1986](#)). For dichotomous data (all-mortality, cardiovascular mortality, infection-related mortality, hospital admission, symptoms during dialysis, carpal tunnel syndrome, dialysis-related arthropathy, withdrawal due to treatment inadequacy) the RR was used together with 95% CI. For continuous data (Kt/V_{urea}, URR, beta-2 microglobulin levels, serum cholesterol and triglycerides, health-related quality of life, and RRF), the MD was used.

Dealing with missing data

Any further information required from the original author was requested by written correspondence and any relevant information obtained in this manner was included in the review. Additional unpublished data for outcomes or risks of bias were provided by the investigators of five studies and included in the analyses ([Blankestijn 1995](#); [Churchill 1993](#); [HEMO 2002](#); [Jeloka 2001](#); [Klemm 2004](#)).

Evaluation of important numerical data, such as numbers of participants screened and randomised; intention-to-treat; as-treated and per-protocol population analyses were performed. Rates of attrition due to drop-out, loss to follow-up and withdrawal, were investigated. Issues of missing data and imputation methods (such as last-observation-carried-forward) were critically appraised ([Higgins 2011](#)).

Assessment of heterogeneity

Heterogeneity was analysed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test ([Higgins 2002](#)). I² values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

Insufficient numbers of randomised studies were available to assess for publication bias.

Data synthesis

Data were pooled using a random-effects model, but the fixed-effect model was also analysed to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

We could not perform additional planned subgroup analysis and random effects meta-regression to explore how study characteristics (membrane biocompatibility or reuse; comorbid conditions; and time on dialysis) might have influenced treatment effects due to the insufficient number of identified trials reporting each outcome (generally fewer than four).

Sensitivity analysis

We performed sensitivity analyses to explore the influence of the following factors on effect size:

- repeating the analysis excluding unpublished studies;
- repeating the analysis taking account of risk of bias, as specified;
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results; and

- repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

RESULTS

Description of studies

Results of the search

Our search identified 1034 unique citations, of which 682 were excluded because they evaluated interventions that were not relevant to the review, were not clinical studies, or were not RCTs (Figure 1). Full-text assessment of 352 potentially eligible citations identified 33 eligible studies (3820 participants) reported in 81 publications that were included in this systematic review. We identified one ongoing study which we will include in a future update (NCT00004285).

Figure 1. Study flow diagram

Included studies

We could include 16 studies in the meta-analyses that involved 3221 participants (Aylly 2005; Blankestijn 1995; Fishbane 1997; Gardinali 1994; Hartmann 1997; HEMO 2002; House 1999; Klemm 2004;

Kuchle 1996; Lang 2001; Li 2010; Locatelli 1996; Locatelli 2000; MPO 2009; Ottosson 2001; Simon 1993). The 17 remaining, generally smaller studies (total of 599 participants) were included, but not meta-analysed, because of a number of factors: relevant outcomes were not reported; studies were cross-over designs and did not

provide data for the end of the first phase of treatment; or did not report data in an extractable format (Acchiardo 1989; Brown 1989; Chu 2006; Churchill 1993; Collins 1993; De Vriese 2003; Goldberg 1996; INFLUX 2008; Jeloka 2001; Krieter 2002; Li 2007a; Mohini 1989; Opatrny 2002; Rizvi 1995; Sawaya 1989; Skroeder 1993; Takasawa 2005).

All 33 included studies compared high-flux with low-flux dialysis membranes in people who required chronic haemodialysis and were published between 1989 and 2010 (Table 2). Study size varied from 12 to 1846 participants; and follow-up ranged from one month to six years. Median follow-up was three months (interquartile range 2 to 12 months). Nearly two-thirds of studies (20/33) conducted follow-up over fewer than six months (Acchiardo 1989; Blankestijn 1995; Chu 2006; Collins 1993; De Vriese 2003; Fishbane 1997; Gardinali 1994; Goldberg 1996; House 1999; INFLUX 2008; Jeloka 2001; Klemm 2004; Krieter 2002; Li 2007a; Locatelli 2000; Mohini 1989; Opatrny 2002; Ottosson 2001; Rizvi 1995; Skroeder 1993). A third of included studies (12/33) applied cross-over study designs (Churchill 1993; Collins 1993; De Vriese 2003; Gardinali 1994; Goldberg 1996; Klemm 2004; Krieter 2002; Li 2010; Opatrny 2002; Rizvi 1995; Skroeder 1993; Takasawa 2005). Overall, 28 studies focused on the effects of dialysis membrane flux on dialysis tolerance (4) (Churchill 1993; Collins 1993; Locatelli 1996; Rizvi 1995); beta-2 microglobulin, advanced glycation end product, or urea clearance (4) (Fishbane 1997; Jeloka 2001; Li 2007a; Skroeder 1993); biocompatibility (3) (Gardinali 1994; Krieter 2002; Li 2010); oxidative stress (2) (Chu 2006; Klemm 2004); lipids (3) (Blankestijn 1995; Goldberg 1996; Ottosson 2001); haemoglobin (6) (Acchiardo 1989; Ayli 2005; Locatelli 2000; Mohini 1989; Opatrny 2002; Takasawa 2005); homocysteine levels (2) (De Vriese 2003; House 1999); RRF (2) (Hartmann 1997; Lang 2001); visual-evoked potentials (1) (Sawaya 1989); or C-reactive protein (1) (INFLUX 2008).

Five studies (13%) evaluated patient-level clinical outcomes. Of these, Brown 1989 and Kuchle 1996 assessed dialysis-related arthropathy for six months and six years of follow-up respectively. Three studies primarily evaluated treatment effects on mortality: Simon 1993 followed up 54 participants for 12 months; HEMO 2002 (1846 participants) was conducted over a mean of 4.48 years; and MPO 2009 (Membrane Permeability Outcome) (738 participants) followed up participants for a minimum of three years.

High-flux membranes used in the studies generally consisted of polysulfone, polyacrylonitrile, polyamide, or polymethylmethacrylate (PMMA), although three studies evaluated high-flux cellulose or cuprammonium membranes (Table 3; Churchill 1993; De Vriese 2003; MPO 2009). Low-flux membranes were cuprophane or cellulose, although 12 generally more recent studies used low-flux polysulfone (Ayli 2005; Chu 2006; Fishbane 1997; House 1999; INFLUX 2008; Klemm 2004; Li 2007a; Locatelli 1996; Opatrny 2002; Rizvi 1995; Takasawa 2005); or polyamide (Li 2010). Participants in the HEMO 2002 study were assigned to a variety of membrane types for both high-flux and low-flux treatment. The ultrafiltration coefficient or beta-2 microglobulin clearances of the high-flux and low-flux membranes were specified in 12 studies (Chu 2006; Churchill 1993; Collins 1993; De Vriese 2003; Hartmann 1997; HEMO 2002; Lang 2001; Li 2007a; Li 2010; Opatrny 2002; Ottosson 2001; Rizvi 1995). HEMO 2002 specifically

defined high-flux membrane as an ultrafiltration coefficient > 14 mL/h/mm Hg and a mean beta-2 microglobulin clearance of > 20 mL/min; and low-flux membrane as a mean beta-2 microglobulin clearance of < 10 mL/min; whereas MPO 2009 defined high-flux as a sieving coefficient for beta-2 microglobulin > 0.6 and ultrafiltration coefficient $\geq$ 20 mL/h/mm Hg and low-flux as a sieving coefficient of beta-2 microglobulin of 0 and an ultrafiltration coefficient $\leq$ 10 mL/h/mm Hg. We identified seven studies that reported reuse of dialysis membranes (Acchiardo 1989; Chu 2006; Churchill 1993; HEMO 2002; Li 2010; Mohini 1989; Skroeder 1993); and 10 studies that permitted single use of dialysis membranes only (Blankestijn 1995; De Vriese 2003; Hartmann 1997; House 1999; INFLUX 2008; Kuchle 1996; Lang 2001; Locatelli 2000; MPO 2009; Ottosson 2001). The other included studies did not clearly report if membrane reuse was practised (Table 2).

Studies generally enrolled patients with a mean age of between 50 and 65 years. In the two larger studies (HEMO 2002; MPO 2009), participants were on average aged 57.6 and 59.8 years, respectively, which is similar to the average ages of US and European dialysis populations (Miskulin 2009). MPO 2009 enrolled incident patients (on dialysis $\leq$ 2 months).

The remaining studies included patients if they had been on dialysis for at least two months (Locatelli 1996); three months (Acchiardo 1989; Churchill 1993; De Vriese 2003; HEMO 2002; House 1999; Li 2010; Ottosson 2001; Skroeder 1993); six months (Blankestijn 1995; Chu 2006; Fishbane 1997; INFLUX 2008; Locatelli 2000) and 12 months (Simon 1993). Time on dialysis was not an eligibility criterion in the remaining 18 studies. The actual time on dialysis before enrolment varied widely: from 151 months reported by Brown 1989 in a study evaluating dialysis arthropathy; 44.4 months in HEMO 2002; and one month in MPO 2009. Patients with diabetes mellitus contributed to nearly half the population in two studies (1886 participants) (Collins 1993; HEMO 2002); from 25% to 50% of participants in two studies (69 participants) (Chu 2006; Klemm 2004) between 0% and 25% in two studies (784 participants) (Li 2010; MPO 2009) and were specifically excluded in six small studies (177 participants) (Blankestijn 1995; Gardinali 1994; Hartmann 1997; House 1999; Opatrny 2002; Skroeder 1993). Fishbane 1997 (30 participants) included only participants with diabetes mellitus.

Excluded studies

After detailed full-text review we excluded 225 studies (270 reports) (Characteristics of excluded studies) because:

- was a description of a proposed study (1);
- they were not an appropriate intervention (56);
- did not include people who had chronic kidney disease (3);
- did not measure a prespecified outcome (75);
- were not randomised (72);
- were of short duration (6), or
- were reviews or commentaries (12).

Risk of bias in included studies

Assessments of the risk of bias in the included studies are reported in Characteristics of included studies; Figure 2; and Figure 3. In general, the risk of bias was either high or unclear in most studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Acchiardo 1989	?	?	-	?	+	-	?
Ayli 2005	?	?	-	?	+	+	?
Blankestijn 1995	?	+	-	-	+	-	?
Brown 1989	?	?	-	?	?	-	?
Chu 2006	?	?	-	?	+	-	?
Churchill 1993	?	?	+	+	-	-	?
Collins 1993	?	?	-	?	-	-	-
De Vriese 2003	?	?	-	?	?	-	?
Fishbane 1997	?	?	-	?	-	-	-
Gardinali 1994	?	?	-	?	+	-	?

Figure 3. (Continued)

Gardinali 1994	?	?	-	?	+	-	?
Goldberg 1996	?	?	-	?	+	-	?
Hartmann 1997	?	?	-	-	+	+	+
HEMO 2002	+	+	-	+	+	+	+
House 1999	-	?	-	?	+	-	-
INFLUX 2008	?	?	-	?	?	-	?
Jeloka 2001	+	?	-	-	?	-	?
Klemm 2004	?	?	-	?	+	-	-
Krieter 2002	?	-	-	?	-	?	?
Kuchle 1996	?	?	-	?	+	+	?
Lang 2001	-	-	-	?	?	-	?
Li 2007a	?	?	-	?	?	-	?
Li 2010	+	+	-	?	+	+	-
Locatelli 1996	?	+	-	?	+	+	+
Locatelli 2000	?	?	-	-	+	?	+
Mohini 1989	?	?	-	?	-	-	?
MPO 2009	+	+	-	-	+	+	+
Opatrny 2002	?	-	-	?	+	-	?
Ottosson 2001	+	?	-	?	+	-	?
Rizvi 1995	?	?	-	?	+	?	?
Sawava 1989	?	?	+	?	?	-	?

Figure 3. (Continued)

Sawaya 1989	?	?	+	?	?	-	?
Simon 1993	?	?	-	?	+	+	?
Skroeder 1993	?	?	-	?	-	-	-
Takasawa 2005	?	?	-	?	?	-	?

Allocation

- Allocation concealment was adequate in only five studies (Blankestijn 1995; HEMO 2002; Li 2010; Locatelli 1996; MPO 2009); inadequate in two (Krieter 2002; Lang 2001) and unclear in the remainder.
- Sequence generation methods were adequate in five studies (HEMO 2002; Jeloka 2001; Li 2010; Ottosson 2001); inadequate in two (Lang 2001; House 1999) and unclear in the remainder.

Blinding

Participants were blinded to treatment allocation in one study (Churchill 1993), investigators were blinded to treatment allocation in two studies (Churchill 1993; Sawaya 1989), and outcome assessors were blinded to treatment allocation in two studies (Churchill 1993; HEMO 2002).

Incomplete outcome data

Data were complete in four studies (Hartmann 1997; HEMO 2002; Lang 2001; Rizvi 1995); inadequate in 13 (Chu 2006; Collins 1993; De Vriese 2003; Fishbane 1997; Klemm 2004; Krieter 2002; Kuchle 1996; Li 2010; Locatelli 2000; MPO 2009; Ottosson 2001; Simon 1993; Skroeder 1993); and unclear in the remainder.

Selective reporting

We found that 25 studies were at high risk of bias due to selective reporting. Reasons included: data not extractable for meta-analysis (Acchiardo 1989); insufficient prespecified data or insufficient mortality or adverse event data (Ayli 2005; Brown 1989; Chu 2006; De Vriese 2003; Fishbane 1997; Gardinali 1994; Goldberg 1996; House 1999; INFLUX 2008; Jeloka 2001; Klemm 2004; Krieter 2002; Li 2007a; Li 2010; Locatelli 2000; Mohini 1989; Opatrny 2002; Ottosson 2001; Rizvi 1995; Sawaya 1989; Skroeder 1993; Takasawa 2005); and selective reporting of quality of life data (Churchill 1993); or adequacy assessment (Locatelli 1996).

Other potential sources of bias

Analysis was based on intention-to-treat in two studies (HEMO 2002; MPO 2009). Our analysis indicated that four studies were at risk of other sources of bias. These included: unclear methods for selecting participants included in the analyses (Simon 1993); participants repeating assessments to make up for loss to follow-up (Skroeder 1993); not all treatments available at participating sites (Locatelli 1996); and inconsistency in the number of included subjects in multiple study reports (Churchill 1993).

Effects of interventions

Mortality

High-flux membranes did not reduce all-cause mortality when compared with low-flux membranes (Analysis 1.1 (10 studies, 2915 participants): RR 0.95, 95% CI 0.87 to 1.04) or death due to infection (Analysis 1.2 (3 studies, 2547 participants): RR 0.90, 95% CI 0.71 to 1.14). However, cardiovascular mortality was significantly reduced by 17% in people who received high-flux membrane haemodialysis (Analysis 1.3 (5 studies, 2612 participants): RR 0.83; 95% CI 0.70 to 0.99) across a median follow-up of 24 months. In absolute terms, treating 100 people with ESKD using high-flux membrane haemodialysis for approximately two years will not reduce deaths from any cause (one death prevented, 95% CI -3 to 4), but may prevent three deaths attributable to cardiovascular causes (95% CI 0 to 6).

Hospital admissions

In analyses that included two studies or fewer, high-flux membranes were not associated with reduced hospitalisation due to any cause (Analysis 1.4.1 (2 studies, 36 events, 74 participants): RR 0.79, 95% CI 0.52 to 1.20); cardiovascular disease (Analysis 1.4.2 (1 study, 54 participants): RR 0.92, 95% CI 0.23 to 3.70); or infection (Analysis 1.4.3 (1 study, 20 participants): RR 0.33, 95% CI 0.02 to 7.32). The number of hospital admissions was significantly reduced by 0.2/year (Analysis 1.5 (155 participants): 95% CI -0.37 to -0.03) with high-flux membrane dialysis in one study (Locatelli 1996). MPO 2009 reported no significant difference between the number of all-cause hospital admissions (527 episodes in the high-flux group versus 518 episodes in the low-flux group) or infection-related admissions (74 episodes in the high-flux group versus 82 episodes in the low-flux group).

Quality of life

Quality of life outcomes were reported in two studies (Churchill 1993; HEMO 2002; Table 4). Churchill 1993 evaluated quality of life in 22 people over four months, using the Time Trade Off (TTO) index, Sickness Impact Profile (SIP) and the Haemodialysis Quality of Life Questionnaire (HQoL). In HEMO 2002, quality of life was analysed using three tools: the Index of Well-Being, Kidney Diseases Quality of Life Long-Form Questionnaire, and the Short Form-36 Questionnaire, in 1813 people over three years of follow-up. In general, neither of the studies identified statistical or clinical differences between high-flux and low-flux membranes for effects on quality of life.

Manifestations of dialysis-related amyloidosis and predialysis serum beta-2 microglobulin

High-flux membranes resulted in higher predialysis beta-2 microglobulin clearance ([Analysis 1.6](#) (6 studies, 2071 participants): MD -12.17 mg/L, 95% CI -15.83 to -8.51 mg/L) but as expected not urea (equilibrated Kt/V_{urea}) ([Analysis 1.7](#) (3 studies, 1968 participants): MD -0.00, 95% CI -0.03 to 0.02). One study that included few events, reported the effect of treatment on the clinical complications of beta-2 microglobulin-mediated amyloidosis, finding significant reductions in carpal tunnel syndrome ([Analysis 1.8.1](#) (1 study, 20 participants): RR 0.06, 95% CI 0.00 to 0.90) and dialysis-associated arthropathy ([Analysis 1.8.2](#) (1 study, 20 participants): RR 0.06, 95% CI 0.00 to 0.90). [Brown 1989](#), a small study published in abstract form only, reported improvement in shoulder movement, but no differences in walking time, grip strength, or fist closure, in 18 people with established dialysis-arthropathy after six months of high-flux haemodialysis.

Symptoms related to dialysis (hypotension, nausea, vomiting, and muscle cramps)

One study found no difference between high-flux and low-flux dialysis membranes for intradialytic hypotension ([Analysis 1.9](#) (1 study, 84 participants): RR 3.00, 95% CI 0.13 to 71.61). [Skroeder 1993](#) reported no difference between membrane types in the incidence of symptomatic hypotension, headache, and pruritus among patients in the high-flux and low-flux groups.

Dialysis adequacy

There were no differences between high-flux and low-flux groups with respect to numbers of patients who withdrew due to dialysis inadequacy ([Analysis 1.10](#) (1 study, 155 participants): RR 0.58, 95% CI 0.13 to 2.71).

Lipids

There were no differences between high-flux and low-flux haemodialysis membranes with respect to total cholesterol levels ([Analysis 1.11.1](#) (4 studies, 124 participants): MD -0.16 mmol/L, 95% CI -0.59 to 0.27 mmol/L); high-density lipoprotein (HDL) cholesterol ([Analysis 1.11.2](#) (4 studies, 154 participants): MD -0.04 mmol/L, 95% CI -0.14 to 0.05 mmol/L); low density lipoprotein (LDL) cholesterol ([Analysis 1.11.3](#) (4 studies, 154 participants): MD 0.06, 95% CI -0.20 to 0.31 mmol/L); very low density lipoprotein (VLDL) cholesterol ([Analysis 1.11.3](#) (2 studies, 64 participants): MD -0.11 mmol/L; 95% CI -0.39 to 0.17 mmol/L) and serum triglycerides ([Analysis 1.11.4](#) (4 studies, 124 participants): MD -0.21 mmol/L; 95% CI -0.48 to 0.05 mmol/L).

Residual renal function

[Lang 2001](#) reported that RRF at the end of study period was significantly higher in high-flux group participants ([Analysis 1.12](#) (1 study, 30 participants): MD 1.10 mL/min, 95% CI 0.80 to 1.40) compared with the low-flux group. [Hartmann 1997](#) reported data on rate of decline of RRF. Participants in the high-flux group had a significantly slower decline in RRF ([Analysis 1.13](#) (1 study, 20 participants): MD -0.13 mL/min/mo, 95% CI -0.17 to -0.09 mL/min/mo).

Adverse events

Adverse events reported in the included studies are summarised in [Table 5](#). Generally, adverse events were not systematically sought by investigators in most trials. The reported adverse events were also heterogeneous between included studies. Adverse events were reported by 13 investigators ([Acchiardo 1989](#); [Churchill 1993](#); [Collins 1993](#); [Hartmann 1997](#); [House 1999](#); [Jeloka 2001](#); [Kuchle 1996](#); [Lang 2001](#); [Li 2010](#); [Locatelli 1996](#); [Locatelli 2000](#); [Mohini 1989](#); [Rizvi 1995](#)) which included adverse reactions (unspecified), hypotension during dialysis, vomiting, cramping, hospital admissions, infections, graft thrombosis, symptoms during dialysis, treatment inadequacy, reaction to dialysis membrane, arthritis-like symptoms, vascular access failure, and intracranial haemorrhage.

Subgroup and publication bias analysis

Due to the small number of studies that reported individual outcomes of interest we did not perform a funnel plot analysis of publication bias or subgroup analyses.

DISCUSSION

Summary of main results

We identified 33 studies that evaluated the effects of membrane flux on clinical and biochemical outcomes in people on haemodialysis for this review. Collectively, the 33 studies included nearly 4000 people, and the median follow-up period of participants was three months. Of these, 10 studies that included about 3000 participants, reported mortality data. Although membrane flux had no effect on all-cause mortality, in meta-analyses limited by few studies, cardiovascular mortality was reduced by approximately 17% in people who received high-flux haemodialysis compared to low-flux haemodialysis. In absolute terms, treating 100 people with high-flux haemodialysis membranes for two years may prevent approximately three deaths from cardiovascular causes. We found no evidence that membrane flux altered infection-related mortality; there were insufficient data to understand treatment effects on hospitalisation due to infection; and few studies systematically reported adverse events. There was insufficient information identified to reliably determine the effects of membrane flux on dialysis-related arthropathy; carpal tunnel syndrome; quality of life; or admission to hospital for any cause. As expected, high-flux dialysis was found to remove beta-2 microglobulin better than low-flux dialysis, but it had no clinical effect on lipid clearance.

Overall completeness and applicability of evidence

The strengths of the current analysis include the comprehensive and systematic review of randomised studies, a published and peer-reviewed protocol, and a systematic search strategy of MEDLINE, EMBASE, and the Cochrane Renal Group's Specialised Register. Despite the strengths of the current review, several limitations should be noted.

First, most studies were small and had heterogeneous enrolment criteria. Particularly, there were few studies that reported the effects of membrane flux on important patient-relevant outcomes, including mortality, symptoms, and functional status. Data for treatment effects on mortality relied heavily on a single study ([HEMO 2002](#)) that dominated (contributed over 80% of the weight)

these meta-analyses. Based on the cardiovascular death rate of approximately 9%/year observed in the low-flux membrane group, we calculated that a study of approximately 4000 participants followed for two years would be necessary to achieve 80% power needed to confirm the 17% risk reduction in cardiovascular mortality observed with high-flux dialysis.

Second, data were particularly sparse for risks of adverse events. Most studies did not report adverse events systematically. As a consequence, the relative safety of high-flux compared to low-flux dialysis is incompletely understood.

Third, to provide summary estimates, we combined a study with participants commencing dialysis (incident) with studies in which participants were already on dialysis (prevalent). Although we found no heterogeneity in the analyses for mortality, which suggested that the findings were generalisable among different dialysis populations regardless of time already on dialysis at enrolment, the small number of studies meant we could not be sure that important differences in treatment effects were not influenced by treatment effects carried over from previous dialysis modalities or survivor bias. Insufficient study data for mortality also precluded subgroup analyses to understand the effects of other specific study and participant characteristics on outcomes. It is unclear if membrane type (synthetic versus modified and unmodified cellulose), or biocompatibility, modified the effects of flux on cardiovascular mortality. It was however observed that membranes were synthetic and generally more biocompatible in both the high-flux and low-flux treatment groups in recent, larger studies. Additionally, the effects of membrane reuse on treatment effects or duration of follow-up could not be explored.

Consistency in the treatment effect between studies suggests that the findings may be generalisable to all people on haemodialysis. However, the small number of studies in the mortality analyses, combined with the dominance of two large studies (HEMO 2002; MPO 2009), means that possible differences exist in the effects of membrane flux on people with specific clinical characteristics.

Quality of the evidence

Importantly, data from individual studies in the review combined with the number of studies reporting specified outcomes indicate that evidence for the benefits and safety of high-flux and low-flux dialysis has marked limitations that should be taken into account when interpreting the results of this review. Nearly all studies were at high risk of bias from most elements considered essential in the conduct of a randomised trial that may have unpredictable effects on the summary treatment effects.

Potential biases in the review process

While the review was completed according to standardised Cochrane methodology, potential biases in the review process should be considered. We completed a formal search designed by a specialist information manager including data from wide sources including handsearching, to limit the potential for omission of potentially relevant studies. There were insufficient studies included in most meta-analyses to allow us to examine for potential publication bias. Inspection of the funnel plot for mortality indicated asymmetry suggesting smaller studies with smaller treatment effects for high-flux membranes were not available for analysis. Most studies did not systematically report all relevant

patient-centred outcomes, suggesting that data for mortality and other clinical outcomes were incomplete, and summary estimates were potentially unreliable.

Agreements and disagreements with other studies or reviews

Larger membrane pore sizes in high-flux dialysis membranes may increase back-transport of dialysis impurities, including endotoxin fragments, from dialysate to bloodstream. Accordingly, high-flux membranes may theoretically increase adverse effects in the event of dialysate contamination, although contrasting data suggests that reduced transport of endotoxins occurs across synthetic high-flux membranes (Schindler 2003).

The mechanism for lowering cardiovascular mortality by high-flux membrane dialysis was unclear. Larger membrane pore size resulted in increased transport of retention solutes by both diffusion and convection, and may enable greater clearance of circulating molecules and fluid that are potentially pathogenic for cardiovascular disease. However, the identity of such cleared molecules has not been determined. Alternatively, high-flux membranes may reduce cardiovascular deaths because of greater biocompatibility or reduced pro-inflammatory properties, although these hypotheses could not be tested using the current data.

We noted that in the dialysis population, cardiovascular, but not all-cause mortality was improved by high-flux haemodialysis. There are two possible main reasons for this discrepancy between cardiovascular mortality (which was reduced by 17%) and all-cause mortality (no effect). First, due to the small number of studies, a type II statistical error may have occurred (that is, not finding a difference between treatment groups when a difference exists) due to insufficient statistical power. This is despite inclusion of over 1000 fatal events in nearly 3000 individuals in our analysis, making this possibility less likely. Alternatively, high-flux membrane dialysers may specifically reduce deaths due to cardiovascular disease (such as atherosclerotic vascular occlusion, heart failure, or sudden death) in people on haemodialysis, but not deaths from non-vascular causes, about which we have little information. Because cardiovascular deaths accounted for approximately 50% of deaths in the included studies, a reduction in cardiovascular events may not have been sufficient to reduce the mortality rate for high-flux membranes overall.

RCTs of membrane flux analysed in this review do not confirm the large reductions in all-cause mortality associated with high-flux dialysis in observational cohort studies (Hornberger 1992; Port 2001; Woods 2000). The discrepancy in the magnitude of mortality benefit for high-flux dialysis membranes between observational data and RCTs is most likely due to the risks of bias by confounding that are present in uncontrolled cohort analyses that may exaggerate treatment effects. High-flux dialysis membranes enable greater clearance of larger retention molecules than standard flux membranes, including the potentially amyloidogenic beta-2 microglobulin. While observational analyses suggest evidence that high-flux dialysis is associated with fewer complications related to beta-2 microglobulin accumulation (Chanard 1989; Koda 1997; van Ypersele de Strihou 1991) only two RCTs have so far reported the effects of membrane flux on the incidence of carpal tunnel syndrome or dialysis-related arthropathy (Brown 1989; Kuchle 1996). Current randomised data are therefore

insufficient to reliably inform clinicians and patients about the effects of high-flux membrane dialysis on amyloid-related complications. Assessing dialysis technologies with respect to beta-2 microglobulin amyloidosis is especially problematic due to the requirement for a long follow-up duration to allow for appearance of clinical manifestations. Observational studies show that amyloid-related complications occur in only in 5% to 10% of patients by 5 years, and in 15% to 30% by 10 years (Schwarz 1984) making randomised studies evaluating these outcomes arduous and expensive. Despite the paucity of data, it should be noted that the lack of evidence that high-flux membranes reduce amyloid-related complications does not necessarily indicate a lack of efficacy. A beneficial effect for high-flux haemodialysis on arthropathy and carpal tunnel syndrome is possible, but remains unproven.

The current meta-analyses support, in part, clinical guideline statements for membrane flux (Table 1), although the KDOQI 2006 and CARI 2005 guidelines now predate the release of results from MPO 2009, and the latter are currently being updated. Although the present meta-analysis supports the suggestion by the EBPG 2002 to consider use of high-flux membranes for haemodialysis patients to reduce cardiovascular risk, and that high-flux membranes might be considered in all patients who need haemodialysis, the data cannot confirm that membrane flux is an important factor when considering prevention of beta-2 microglobulin amyloidosis, as suggested by KDOQI 2006 and EBPG 2002.

To our knowledge, this is the first systematic review of RCTs that has specifically evaluated membrane flux for haemodialysis. A previous systematic review evaluated the effects of types of dialysis membrane (synthetic versus cellulose (modified and unmodified)) on outcomes and found no evidence of clinical benefit for synthetic membranes, despite including 32 studies (MacLeod 2005). Insufficient data for health-related outcomes, including mortality, were available in that review. Similarly, a systematic review that compared haemodiafiltration, haemofiltration, and acetate-free biofiltration, which are potentially more effective processes than haemodialysis in removing high molecular weight solutes, did not find evidence indicating any benefit of convective strategies on mortality, hospitalisation, or dialysis-related hypotension (Rabindranath 2005).

AUTHORS' CONCLUSIONS

Implications for practice

The currently available trial evidence has not demonstrated superiority of high-flux membranes with respect to important

clinical outcomes such as all-cause mortality, quality of life and hospital admission. It is not possible to recommend the use of these membranes in preference to low-flux membranes. A larger confirmatory RCT is required before high-flux membranes can be recommended to reduce cardiovascular mortality. Current RCT data cannot confirm that high-flux dialysis prevents amyloid-related arthropathy or carpal tunnel syndrome in people on long-term haemodialysis.

Implications for research

Further evidence from larger RCTs is needed to confirm the benefit of high-flux membranes with respect to dialysis-related amyloidosis. The MPO 2009 study has reported that the use of high-flux membranes are associated with significantly lower mortality in patients with both diabetes and low albumin (< 4 g/dL). A larger study conducted specifically in people with ESKD and higher comorbidities (diabetes, low serum albumin, pre-existing cardiovascular disease) is necessary to confirm these findings.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Acchiardo 1989

Methods	<ul style="list-style-type: none"> Study design: Parallel RCT Time frame: NS Follow-up period: 9 months Lost to follow-up: 2/20
Participants	<ul style="list-style-type: none"> Country: USA Setting: University, single centre Patients: Prevalent haemodialysis Duration on dialysis <ul style="list-style-type: none"> * Treatment group: 76.5 ± 48 months * Control group: 39.7 ± 30 months Number (treatment/control): 11/9 Mean age (treatment/control): 48.6 (29 to 72) to 49.5 (36 to 70) Sex (M/F) <ul style="list-style-type: none"> * Treatment group: 8/3 * Control group: 6/3 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Severe organ involvement, active haemolysis, or gastrointestinal bleeding; aluminium intoxication
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> Polysulphone high-flux dialysis: (Hemoflux F60 or F80) Blood flow rate 469 ± 3 mL/min Dialysate flow rate 800 mL/min Time 126.9 ± 10 min Kt/V 1.01 ± 0.1 <p>Low-flux</p> <ul style="list-style-type: none"> Regenerated cellulosic membranes (C-DAK; 90 SCE or 135 SCE) Blood flow rate 297 ± 10 mL/min Dialysate flow rate 500 mL/min Time 193.2 ± 39 min Kt/V 1.05 ± 0.1
Outcomes	<ul style="list-style-type: none"> Haematocrit Blood urea nitrogen Biochemistry
Notes	<ul style="list-style-type: none"> Imbalance in time on dialysis at baseline Exclusions post-randomisation but pre-intervention: 0 Stop or end point/s: Nil Additional data requested from authors: Clinical outcomes, risks of bias

Risk of bias

Acchiardo 1989 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (20); analysed (18); 90% followed
Selective reporting (reporting bias)	High risk	Primary and secondary outcomes were not reported
Other bias	Unclear risk	ITT not reported

Ayli 2005

Methods	<ul style="list-style-type: none"> Study design: Parallel RCT Time frame: NS Follow-up period: 6 months Lost to follow-up: 0/48
Participants	<ul style="list-style-type: none"> Country: Turkey Setting: University hospital Patients on chronic HD; could not achieve Hb > 11 g/dL despite EPO of at least 200 IU/kg/wk in 3 divided doses/wk for 6 months Duration on dialysis (median) <ul style="list-style-type: none"> * Treatment group: 48 months (range 20 to 96) * Control group: 44 months (range 18 to 96) Number (treatment/control): 24/24 Mean age (treatment/control): 58.3/59.9 years Sex (M/F) <ul style="list-style-type: none"> * Treatment group: 14/10 * Control group: 12/12 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Iron deficiency; chronic blood loss; acute or chronic infection; malignancy; haemoglobinopathies; malnutrition; B₁₂ or folate deficiency; patients on ACEi or ARB
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> High-flux polysulfone membrane (Fresenius F60) Blood flow: 300 mL/min

Ayli 2005 (Continued)

- Dialysate: 500 mL/min

Low-flux

- Low-flux polysulfone membrane (Fresenius F6)
- Blood flow: 300 mL/min
- Dialysate: 500 mL/min

Outcomes	<ul style="list-style-type: none"> • Kt/V • URR • Predialysis beta-2 microglobulin levels
Notes	<ul style="list-style-type: none"> • Exclusions post-randomisation but pre-intervention: NS • Stop or end point/s: NS • Additional data requested from authors: Method of randomisation; details regarding blinding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (48); analysed (48); 100% followed
Selective reporting (reporting bias)	Low risk	Primary outcome (mortality) some secondary outcomes reported
Other bias	Unclear risk	ITT not clearly described

Blankestijn 1995

Methods	<ul style="list-style-type: none"> • Design: Parallel RCT • Time frame: NS • Follow-up period: 6 weeks • Lost to follow-up: 0/28
Participants	<ul style="list-style-type: none"> • Country: The Netherlands • Setting: University hospital • Chronic, stable HD patients • Median duration on HD: 24 months (range 6 to 176 months)

High-flux versus low-flux membranes for end-stage kidney disease (Review)

Blankestijn 1995 (Continued)

- Number: 28
- Median age: 63 years (range 22 to 80 years)
- Sex (M/F): NS

Exclusion criteria

- Diabetes; on drugs that affect cholesterol levels

Interventions	<p>High-flux</p> <ul style="list-style-type: none"> • High-flux polysulfone membrane (Fresenius F60) • Bicarbonate dialysate containing 11 mmol/L glucose • Time 11 ± 1.4 h/wk <p>Low-flux</p> <ul style="list-style-type: none"> • Low-flux cuprophan membrane • Bicarbonate dialysate containing 11 mmol/L glucose • Time 11 ± 1.4 h/wk
Outcomes	<ul style="list-style-type: none"> • Lipid profile including: total cholesterol, VLDL cholesterol, LDL cholesterol, HDL cholesterol, triglycerides • Kt/V
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: None • Stop or end point/s: NS • Additional data requested from authors: Method of randomisation, blinding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Low risk	Adequate, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (28); analysed (28); followed (100%)
Selective reporting (reporting bias)	High risk	Only some secondary outcomes reported
Other bias	Unclear risk	ITT not clearly described

Brown 1989

Methods	<ul style="list-style-type: none"> Study design: Parallel RCT Time frame: NS Follow-up period: 6 months Lost to follow-up: Unclear
Participants	<ul style="list-style-type: none"> Country: United Kingdom Setting: Charing Cross Hospital Patients: Patients requiring haemodialysis with dialysis arthropathy Duration on dialysis: 12.3 ± 3 years Number: 18 Mean age: 55 ± 10 years Sex (M/F):14/4 <p>Exclusion criteria: NS</p>
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> Polyacrylonitrile or polysulphone <p>Low-flux</p> <ul style="list-style-type: none"> Cuprophane
Outcomes	<ul style="list-style-type: none"> Predialysis beta-2 microglobulin Dialysis arthropathy C-reactive protein
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: Unclear Stop or end point/s: Unclear Additional data requested from authors: Clinical outcomes, risks of bias Abstract publication only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Enrolled/randomised (18); analysed (unclear); followed (unclear)

Brown 1989 (Continued)

Selective reporting (re-reporting bias)	High risk	Only some secondary outcomes reported; unable to include in meta-analyses
Other bias	Unclear risk	ITT not clearly described; study reported in abstract form only

Chu 2006

Methods	<ul style="list-style-type: none"> Study design: Parallel RCT Time frame: NS Follow-up period: 2 months Lost to follow-up: 2/40 (5%)
Participants	<ul style="list-style-type: none"> Country: Taiwan Setting: Single centre Patients: Individuals on maintenance HD > 6 months and > 20 years Duration on dialysis <ul style="list-style-type: none"> * Treatment group: 82.2 ± 125 months * Control group: 69.1 ± 87.6 months Number (treatment/control): 21 Mean age (treatment/control): 19 Sex (M/F) <ul style="list-style-type: none"> * Treatment group: 11/9 * Control group: 9/9 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Active infection, obvious inflammation, malignancy, or intolerance to dialysers
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> FX80 (KUF 59 mL/h/mm Hg) Inline steam sterilisation Surface area 1.8 m² Minimum blood flow rate 250 mL/min Dialysate flow rate 500 mL/min <p>Low-flux</p> <ul style="list-style-type: none"> F8 HPS (KUF 18 mL/h/mm Hg) Inline steam sterilisation Surface area 1.8 m² Minimum blood flow rate 250 mL/min Dialysate flow rate 500 mL/min
Outcomes	<ul style="list-style-type: none"> Oxidative stress Insulin resistance Inflammation Dialysis efficiency
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: 2/40 Stop or end point/s: None reported Additional data requested from authors: Clinical outcomes, risks of bias

Chu 2006 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (40); analysed (38); followed (95%)
Selective reporting (reporting bias)	High risk	Only some secondary outcomes reported; unable to meta-analyse
Other bias	Unclear risk	ITT not clearly described

Churchill 1993

Methods	<ul style="list-style-type: none"> Design: Cross-over RCT Time frame: NS Follow-up period: 8 months Lost to follow-up: 8/30
Participants	<ul style="list-style-type: none"> Country: Canada Setting: University hospital Patients on chronic HD for at least 3 months Number (enrolled/reported): 30/24 Age (mean): 52 years (range: 21 to 72 years) Sex (M/F): 13/9 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Inability to complete the QoL tests; inability to complete the neuropsychological evaluation; allergy to ethylene oxide; elective live donor transplant within 8 months
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> High-flux cellulose acetate (UFR15 mL/h/mm Hg) Beta-2 microglobulin clearance: -11.4 mL/min Bicarbonate dialysis <p>Low-flux</p> <ul style="list-style-type: none"> Low-flux cellulose acetate (UFR: 3.5 to 5 mL/h/mm Hg)

High-flux versus low-flux membranes for end-stage kidney disease (Review)

Churchill 1993 (Continued)

- Beta-2 microglobulin clearance: No clearance at all
- Bicarbonate dialysis

Outcomes	Quality of life measures including: <ul style="list-style-type: none"> • HD-QOL • TTO index • SIP
Notes	<ul style="list-style-type: none"> • Exclusions post-randomisation but pre-intervention: 8 patients, no details of dropouts given • Stop or end point/s: NS • Additional data requested from authors: Method of randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Enrolled/randomised (30); analysed (22); followed (73.3%)
Selective reporting (reporting bias)	High risk	Only one secondary outcome reported; unable to meta-analyse
Other bias	Unclear risk	ITT not clearly described

Collins 1993

Methods	<ul style="list-style-type: none"> • Design: Cross-over RCT • Time frame: NS • Follow-up period: 6 months • Lost to follow-up: 5/40
Participants	<ul style="list-style-type: none"> • Country: USA • Setting: University hospital • Patients on chronic HD using CU membranes • Number (treatment/control): 17/18 • Mean age (treatment/control): 50/55 years

Collins 1993 (Continued)

- Sex (M/F)
 - * Treatment group: 7/10
 - * Control group: 3/14
- Race (Blacks/other)
 - * Treatment group: 16/1
 - * Control group: 15/3

Exclusion criteria: NS

Interventions	<p>High-flux</p> <ul style="list-style-type: none"> • High-flux PAN membrane (Hospal F16, 1.55 m²; Kuf-44 mL/mm Hg/h) 3 times/wk • Dialysate flow: 500 mL/min • Blood flow rate: 300 to 400 mL/min • Dialysis duration: 3.25 hours <p>Low-flux</p> <ul style="list-style-type: none"> • Low-flux cuprophane membrane (Gambro 9, 1.6 m²; Kuf-8 mL/mm Hg/h) 3 times/wk • Dialysate flow: 500 mL/min • Blood flow rate: 300 to 400 mL/min • Dialysis duration: 3.3 hours
Outcomes	<p>Quality of life measures including:</p> <ul style="list-style-type: none"> • HD-QOL • TTO index • SIP
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: NS • Stop or end point/s: NS • Additional data requested from authors: Method of randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Enrolled/randomised (40); analysed (35); followed (87.5%)

Collins 1993 (Continued)

Selective reporting (reporting bias)	High risk	Only secondary outcomes reported; unable to meta-analyse
Other bias	High risk	ITT: All participants not included in analyses

De Vriese 2003

Methods	<ul style="list-style-type: none"> Study design: Cross-over RCT Time frame: NS Follow-up period: 1 month (first cross-over phase) Lost to follow-up: 2 patients withdrew (1 had presumed reaction to superflux membrane; 1 received a kidney transplant during the study)
Participants	<ul style="list-style-type: none"> Country: Belgium Setting: AZ Sint-Jan AV haemodialysis unit (single unit) Patients: Haemodialysis Duration on dialysis: NS Number (treatment/control): 15/15 Mean age: 69.0 ± 18 years (range 36 to 89) Sex (M/F): NS <p>Exclusion criteria</p> <ul style="list-style-type: none"> Acute illness, life expectancy < 3 months, problems with vascular access, excessive interdialytic weight gains requiring regular addition dialyses and inability to provide informed consent
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> Triacetate dialyser (FB-150U, Nipro) UF coefficient 29.8 mL/h/mm Hg Sieving coefficient beta-2 microglobulin 0.88 Treatment duration, blood flow, dialysate flow and ultrafiltration determined by attending nephrologist <p>Low-flux</p> <ul style="list-style-type: none"> Triacetate dialyser (Sureflux-150L, Nipro) UF coefficient 12.8 mL/h/mm Hg Sieving coefficient beta-2 microglobulin 0.36 Treatment duration, blood flow, dialysate flow and ultrafiltration determined by attending nephrologist
Outcomes	<ul style="list-style-type: none"> Plasma homocysteine
Notes	<ul style="list-style-type: none"> Additional data requested from authors: Clinical outcomes, risks of bias Had a superflux treatment arm (Sureflux-150FH, ultrafiltration coefficient 66.9 ml/L/mm Hg)

Risk of bias

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

De Vriese 2003 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Enrolled/randomised (30); analysed (unclear); followed (unclear)
Selective reporting (reporting bias)	High risk	Primary and secondary outcomes not reported
Other bias	Unclear risk	ITT not clearly described

Fishbane 1997

Methods	<ul style="list-style-type: none"> Study design: Parallel RCT Time frame: Unclear Follow-up period: 2 months Lost to follow-up: 5/30 (2/16 high-flux and 3/14 low-flux)
Participants	<ul style="list-style-type: none"> Country: USA Setting: Winthrop-University Hospital Dialysis Center Patients: Long term haemodialysis > 6 months with diabetes Duration on dialysis <ul style="list-style-type: none"> * Treatment group: 17.4 (4.0) months * Control group: 18.0 (4.0) months Number (treatment/control): 13 Mean age (treatment/control): 12 Sex (M/F) <ul style="list-style-type: none"> * Treatment group: 8/5 * Control group: 6/6 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Lack of stable dialysis access, URR < 60%, hospitalisation within one month for marked changes in metabolic control and concomitant treatment with an angiotensin converting enzyme inhibitor or lipid lowering medication
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> AN69 Fitral 16 Dialyzer (Hospal Inc, Lyon, France) <p>Low-flux</p> <ul style="list-style-type: none"> F8 dialysis membrane (Fresenius Inc, Germany)
Outcomes	<ul style="list-style-type: none"> Advanced glycation end products

High-flux versus low-flux membranes for end-stage kidney disease (Review)

Fishbane 1997 (Continued)

- Notes
- Exclusions post randomisation but pre-intervention: None
 - Stop or end point/s: None
 - Additional data requested from authors: Clinical outcomes, risks of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	High risk	Enrolled/randomised (30); analysed (25); followed (83%)
Selective reporting (reporting bias)	High risk	Primary and secondary outcomes not reported
Other bias	High risk	ITT: All participants not included in analyses

Gardinali 1994

Methods	<ul style="list-style-type: none"> • Design: Parallel RCT • Time frame: NS • Follow-up period: 3 months • Lost to follow-up: 0/36
Participants	<ul style="list-style-type: none"> • Country: Italy • Setting: University hospital • Patients undergoing regular HD • Number: 36 • Age: NS • Sex (M/F): NS <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Recurrent bacterial infections; diabetes; autoimmune diseases and/or myeloma
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> • High-flux, polysulfone and polyacrylonitrile membranes <p>Low-flux</p>

Gardinali 1994 (Continued)

- Low-flux, cuprophane membranes

Outcomes	<ul style="list-style-type: none"> • Predialysis beta-2 microglobulin values
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: NS • Stop or end point/s: NS • Additional data requested from authors: Method of randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (36); analysed (36); followed (100%)
Selective reporting (reporting bias)	High risk	Only one secondary outcome reported
Other bias	Unclear risk	ITT not clearly described

Goldberg 1996

Methods	<ul style="list-style-type: none"> • Design: Cross-over RCT • Time frame: NS • Follow-up period: 1 month • Lost to follow-up: 0/29
Participants	<ul style="list-style-type: none"> • Country: USA • Setting: University hospital • Patients undergoing regular HD • Number: 29 • Age: NS • Sex (M/F): NS <p>Exclusion criteria: NS</p>
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> • High-flux, polysulfone membrane (Fresenius F-80)

Goldberg 1996 (Continued)

- Duration: 3 months

Low-flux

- Low-flux, polysulfone membrane (Fresenius F8)

Outcomes	<ul style="list-style-type: none"> • Lipid profiles
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: NS • Stop or end point/s: NS • Additional data requested from authors: Method of randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (29); analysed (29); followed (100%)
Selective reporting (reporting bias)	High risk	Only one secondary outcome reported
Other bias	Unclear risk	ITT not clearly described

Hartmann 1997

Methods	<ul style="list-style-type: none"> • Design: Parallel RCT • Time frame: NS • Follow-up period: 12 months • Lost to follow-up: 0/20
Participants	<ul style="list-style-type: none"> • Country: Germany • Setting: University hospital • Tubulo-interstitial disease as cause for ESKD; CrCl (10 to 15 mL/min); no previous RRT; repeatedly recorded normotensive values (BP consistently < 140/90 mm Hg, no antihypertensive medication); no comorbidity and no drugs other than for the prevention of secondary hyperparathyroidism or water soluble vitamins • Number (treatment/control): 10/10 • Mean age (treatment/control): 52/51 years

Hartmann 1997 (Continued)

- Sex (M/F)
 - * Treatment group: 7/3
 - * Control group: 7/3

Exclusion criteria

- Already on RRT; presence of comorbidity; on drugs for indications other than hyperparathyroidism and water soluble vitamins

Interventions	<p>High-flux</p> <ul style="list-style-type: none"> • High-flux biocompatible polysulfone membrane (Fresenius F 60, UF coefficient 40 mL/mm Hg/h), 3 times/wk for 4 to 5 hours • Blood pump speed: 200 to 250 mL/min • Dialysate flow speed: 500 mL/min <p>Low-flux</p> <ul style="list-style-type: none"> • Low-flux cellulose acetate membrane (CT-130 Baxter, UF coefficient 5.6 mL/mm Hg), 3 times/wk for 4 to 5 hours • Blood pump speed: 200 to 250 mL/min • Dialysate flow speed: 500 mL/min
Outcomes	<ul style="list-style-type: none"> • Death • Number hospitalised • Number hospitalised for infection • Hypotensive episodes • Kt/V • RRF
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: None • Stop or end point/s: NS • Additional data requested from authors: Method of randomisation, blinding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (20); analysed (20); followed (100%)

Hartmann 1997 (Continued)

Selective reporting (re-reporting bias)	Low risk	Primary and secondary outcomes reported
Other bias	Low risk	ITT analysis performed

HEMO 2002

Methods	<ul style="list-style-type: none"> Design: Parallel RCT Time frame: NS Follow-up period: 6 years Lost to follow-up: 0/1846 <ul style="list-style-type: none"> * 392 patients did not continue the study, of whom 194 received a transplant and 198 switched to other methods of dialysis or moved to non-participating dialysis centres
Participants	<ul style="list-style-type: none"> Country: USA Setting: Multicentre study Adults (18 to 80 years); in-centre HD thrice weekly; on dialysis for > 3 months; achieve equilibrated Kt/V of 1.3 within 4.5 hours on 2/3 consecutive attempts during baseline to be randomised Number (treatment/control): 921/925 Mean age (treatment/control): 57.7/57.6 years Sex (M/F) <ul style="list-style-type: none"> * Treatment group: 43.3%/56.7% * Control group: 44.2%/55.8% Race (Blacks/other) <ul style="list-style-type: none"> * Treatment group: 62.6%/37.4% * Control group: 62.6%/37.4% Diabetics (treatment/control): 44.7%/44.7% <p>Exclusion criteria</p> <ul style="list-style-type: none"> Currently in acute care or chronic care at time of randomisation; interdialytic 24 h urine collection with a urea clearance > 1.5 mL/min/35 L urea volume; current pregnancy; scheduled living donor transplant within period of study; returned to HD after kidney transplantation within 6 months; active malignancies requiring current chemo or radiotherapy; severe CCF (NYHA Class IV) after maximal therapy; unstable angina, new onset angina, recent exacerbation of frequency, duration, or severity of angina pectoris; symptomatic AIDS according to CDC classification; active systemic infections such as TB or systemic fungal infection; CPD requiring supplemental oxygen; cirrhosis with encephalopathy or abnormal PT; severe malnutrition (serum albumin < 2.6 g/dL for 2/3 baseline measurements); expected geographic unavailability for > 20 dialysis treatments/y; use of investigational drugs or involvement in other interventional protocols; unable to follow protocol due to mental incompetence or other reason; unwillingness to participate in the procedures of the protocol
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> High-flux HD thrice weekly; 17 types of high-flux dialysers used, most common were Fresenius F80 (43% of sessions) and Baxter CT190 (48%). Reprocessing methods included Renalin without bleach, formaldehyde, or glutaraldehyde, with bleach, or heated citric acid Two-by-two factorial design target equilibrated Kt/V achieved by manipulating duration of treatment session UF coefficient >14 mL/h/mm Hg, mean beta-2 microglobulin clearance > 20 mL/min <p>Low-flux</p> <ul style="list-style-type: none"> Low-flux HD thrice weekly; 8 types of low-flux dialysers used, most common were Fresenius F8 (46% of sessions) and Baxter CT 210 (43%). To possibly eliminate bio-incompatibility confounding flux, the authors excluded unsubstituted cellulose membranes from the study

HEMO 2002 (Continued)

	<ul style="list-style-type: none"> Reprocessing methods included Renalin without bleach, formaldehyde, or glutaraldehyde, with bleach, or heated citric acid Two-by-two factorial design target equilibrated Kt/V achieved by manipulating duration of treatment session Ultrafiltration coefficient > 14 mL/h/mm Hg, mean beta-2 microglobulin clearance > 20 mL/min
Outcomes	<ul style="list-style-type: none"> Mortality (all-cause, cardiovascular, infectious) Beta-2 microglobulin clearance rate Hospitalisation (all-cause, cardiovascular, infectious)
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: NS Stop or end point/s: NS Additional data requested from authors: Method of randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Performed centrally using random permuted blocks, with stratification according to clinical centre, age and diabetic status
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (1846); analysed (1846); followed (100%)
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported
Other bias	Low risk	ITT analysis performed

House 1999

Methods	<ul style="list-style-type: none"> Design: Cross-over RCT Time frame: NS Follow-up period: 3 months Lost to follow-up: 3/48
Participants	<ul style="list-style-type: none"> Country: Canada Setting: University Hospital Adults (18 to 80 years); HD duration ≥ 3 but ≤ 18 months

House 1999 (Continued)

- Time on dialysis (mean)
 - * Treatment group: 9.1 months
 - * Control group: 9.8 months
- Number: 48
- Mean age (treatment/control): 56.7/55.7 years
- Sex (M/F)
 - * Treatment group: 70.8%/21.2%
 - * Control group: 66.7%/33.3%

Exclusion criteria

- Diabetes mellitus; use of lipid lowering drugs; recent coronary artery syndrome; adverse reaction to polysulfone; life expectancy < 6 months; imminent kidney transplantation or major surgery; hypercoagulable state; malabsorption; refusal or inability to provide informed consent

Interventions	<p>High-flux</p> <ul style="list-style-type: none"> • High-flux polysulfone (Fresenius F80) • Bicarbonate-based dialysate was used and dialysis was carried out 3 times/wk • Dialysis membranes were single use only <p>Low-flux</p> <ul style="list-style-type: none"> • Low-flux polysulfone (Fresenius F8) • Bicarbonate based dialysate was used and dialysis was carried out 3 times/wk • Dialysis membranes were single use only
Outcomes	<ul style="list-style-type: none"> • Lipid profiles
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: None • Stop or end point/s: NS • Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Random number generator
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (48); analysed (45); followed (93.75%)
Selective reporting (reporting bias)	High risk	Only one secondary outcome reported

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House 1999 (Continued)

Other bias	High risk	ITT analysis not performed
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INFLUX 2008

Methods	<ul style="list-style-type: none"> Study design: Parallel RCT Time frame: Unclear Follow-up period: 4 weeks Lost to follow-up: Unclear
Participants	<ul style="list-style-type: none"> Country: France Setting: Multicentre Patients: Regular HD ≥ 12 hours/wk, Kt/V 1.2, no reuse for ≥ 6 months and CRP levels 5 to 50 mg/L confirmed twice within 4 week inclusion period (HD low permeability membrane, Polyflux L) Duration on dialysis: NS Number (treatment/control): 79/72 Mean age (treatment/control): 60.3 ± 14.5 years/65.5 ± 10.1 years Sex (M/F) <ul style="list-style-type: none"> * Treatment group: 49/30 * Control group: 41/31 <p>Exclusion criteria: NS</p>
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> Polyflux H membrane <p>Low-flux</p> <ul style="list-style-type: none"> Polyflux L membrane
Outcomes	<ul style="list-style-type: none"> Beta-2 microglobulin CRP Prealbumin Advanced glycation end-products Asymmetric dimethyl arginine
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: Not clear Stop or end point/s: NS Additional data requested from authors: Clinical outcomes, risks of bias Number of patients randomised was not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias)	High risk	Not blinded

High-flux versus low-flux membranes for end-stage kidney disease (Review)

INFLUX 2008 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Enrolled/randomised (not reported); analysed (151); followed (unclear)
Selective reporting (reporting bias)	High risk	Only secondary outcomes reported; unable to include in meta-analyses
Other bias	Unclear risk	ITT : not clearly described

Jeloka 2001

Methods	<ul style="list-style-type: none"> Study design: Parallel RCT Time frame: NS Follow-up period: 12 weeks Lost to follow-up: NS
Participants	<ul style="list-style-type: none"> Country: India Setting: Maulana Azad Medical College, New Delhi Patients: 20 Duration on dialysis: 7.1 ± 2.57 years (range 3 to 12 years) Number (treatment/control): 10/10 Mean age (treatment/control): 49.1 ± 15.44 years/ 45 ± 9.28 years Sex (M/F) <ul style="list-style-type: none"> * Treatment group: 3:2 ratio * Control group: 3:2 ratio <p>Exclusion criteria</p> <ul style="list-style-type: none"> AIDS; lymphoproliferative disorders; inflammatory disorders such as systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease; viral hepatitis; cirrhosis of the liver; tuberculosis; chronic osteomyelitis; primary amyloidosis
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> Polysulphone membranes <p>Low-flux</p> <ul style="list-style-type: none"> Cuprophane membrane
Outcomes	<ul style="list-style-type: none"> Beta-2 microglobulin Arthritis like symptoms
Notes	<ul style="list-style-type: none"> Exclusions post-randomisation but pre-intervention: Unclear Stop or end point/s: NS Additional data requested from authors: Clinical outcomes, risks of bias

Risk of bias

Jeloka 2001 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generation
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Enrolled/randomised (20); analysed (unclear); followed (unclear)
Selective reporting (reporting bias)	High risk	Only secondary outcomes reported; unable to include in meta-analyses
Other bias	Unclear risk	ITT: not clearly described

Klemm 2004

Methods	<ul style="list-style-type: none"> Study design: Cross-over RCT Time frame: Unclear Follow-up period: 6 weeks Lost to follow-up: 3/29 (10%)
Participants	<ul style="list-style-type: none"> Country: Germany Setting: Friedrich Schiller University and Fresenius Medical Care Patients: Stable chronic HD Duration on dialysis: NS Number (treatment/control): NS Mean age (treatment/control): NS Sex (M/F): NS <p>Exclusion criteria: NS</p>
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> FX60 Helixone Surface area of 1.4 m² Haemodialysis 3 times weekly 4 to 5.5 hours/session Blood flow rate 500 mL/min Dialysate flow rate and ultrafiltration determined by attending nephrologist Ultrafilter U 8000S <p>Low-flux</p>

Klemm 2004 (Continued)

- F 6 HPS polysulfone
- Surface area 1.3 m²
- Haemodialysis 3 times weekly
- 4 to 5.5 hours/session
- Blood flow rate 500 mL/min
- Dialysate flow rate and ultrafiltration determined by attending nephrologist
- Ultrafilter U 8000S

Outcomes	<ul style="list-style-type: none"> • Oxidative stress • Homocysteine metabolism
Notes	<ul style="list-style-type: none"> • Exclusions post-randomisation but pre-intervention: NS • Stop or end point/s: NS • Additional data requested from authors: Clinical outcomes, risks of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants: not blinded Investigators: not clearly described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (29); analysed (26); followed (90%)
Selective reporting (reporting bias)	High risk	Only secondary outcomes reported; unable to include in meta-analyses
Other bias	High risk	ITT: randomised participants not all included in analyses

Krieter 2002

Methods	<ul style="list-style-type: none"> • Study design: Parallel RCT • Time frame: NS • Follow-up period: 4 weeks • Lost to follow-up: 4/12 (33%)
Participants	Stable HD
Interventions	High-flux <ul style="list-style-type: none"> • Polyethersulfone membranes (DIAPES(R) HF8 surface area 1.4 m²; Arylane H4, 1.35 m²)

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Krieter 2002 (Continued)

	Low-flux <ul style="list-style-type: none"> Hemophan (1.3 m²)
Outcomes	<ul style="list-style-type: none"> Inflammatory markers CRP
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: NS Stop or end point/s: NS Additional data requested from authors: Clinical outcomes, risks of bias Abstract report only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	High risk	Drawn by lots
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	High risk	Enrolled/randomised (12); analysed (8); followed (66%)
Selective reporting (reporting bias)	Unclear risk	Only secondary outcomes reported; unable to include in meta-analyses
Other bias	Unclear risk	ITT: not described

Kuchle 1996

Methods	<ul style="list-style-type: none"> Design: Parallel RCT Time frame: NS Follow-up period: 6 years Lost to follow-up: 0/30 * 2 patients received kidney transplants; 2 died
Participants	<ul style="list-style-type: none"> Country: Germany Setting: University Hospital Patients on long-term haemodialysis Number (treatment/control): 12/12 Mean age (treatment/control): 50/52

Kuchle 1996 (Continued)

- Sex (M/F)
 - * Treatment group: 6/4
 - * Control group: 6/4

Exclusion criteria: NS

Interventions	<p>High-flux</p> <ul style="list-style-type: none"> • High-flux, polysulfone (Fresenius F60S, 1.2 m²) • Blood flow rate: 200 to 250 mL/min • Dialysate flow rate: 500 mL/min <p>Low-flux</p> <ul style="list-style-type: none"> • Low-flux (Disscap 160E, 1.0-1.2 m²) • Blood flow rate: 200 to 250 mL/min • Dialysate flow rate: 500 mL/min
Outcomes	<ul style="list-style-type: none"> • Mortality • Beta-2 microglobulin • Carpal tunnel syndrome; arthropathy
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: None • Stop or end point/s: NS • Additional data requested from authors: Method of randomisation, blinding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (24); analysed (20); followed (100%)
Selective reporting (reporting bias)	Low risk	Primary (mortality) and secondary outcomes reported
Other bias	Unclear risk	ITT: not clearly described

Lang 2001

Methods	<ul style="list-style-type: none"> Design: Parallel RCT Time frame: NS Follow-up period: 2 years Lost to follow-up: 0/30
Participants	<ul style="list-style-type: none"> Country: Germany Setting: University Hospital Patients started on HD electively; stable clinical condition Number (treatment/control):15/15 Mean age (treatment/control): 45/43 years Sex (M/F) <ul style="list-style-type: none"> * Treatment group: 10/5 * Control group: 9/6 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Severe comorbidity; on nephrotoxic drugs; rapidly progressive GN; RRF < 2 mL/min; predictable follow-up of < 24 months in the same dialysis facility
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> High-flux, polysulfone (Fresenius F60, UF coefficient 40 mL/mm Hg /h, 1.3 m²) Blood flow rate: 200 to 280 mL/min Dialysate flow rate: 500 mL/min <p>Low-flux</p> <ul style="list-style-type: none"> Low-flux (Disscap 160E, UF coefficient 6.25 mL/mm Hg/h, 1.22 m²) Blood flow rate: 200 to 280 mL/min Dialysate flow rate: 500 mL/min
Outcomes	<ul style="list-style-type: none"> RRF Mortality
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: None Stop or end point/s: NS Additional data requested from authors: Method of randomisation, blinding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Alternate order
Allocation concealment (selection bias)	High risk	Alternate order
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described

Lang 2001 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Enrolled/randomised (30); analysed (30); followed (100)
Selective reporting (reporting bias)	High risk	One primary outcome and 1 secondary outcome reported
Other bias	Unclear risk	ITT: not clearly described

Li 2007a

Methods	<ul style="list-style-type: none"> Study design: Parallel RCT Time frame: September 2004 to January 2005 Follow-up period: 5 months Lost to follow-up: Unclear
Participants	<ul style="list-style-type: none"> Country: China Setting: University Hospital, Shanghai Patients: Maintenance haemodialysis 1.5 to 5 years Duration on dialysis: 3.2 ± 1.1 years (1.5 to 5.0 years) Number (treatment/control): 23/20 Mean age (treatment/control): 55.4 ± 9.7 years (29 to 75 years) Sex (M/F): 25/18 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Lung, liver, neurological disease, malignant tumour
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> F60 polysulfone dialyser Ultrafiltrate coefficient 40 mL/h/mm Hg Surface area 1.3 m² Fresenius 4008S capacity controlled dialyser Bicarbonate dialysate 4 hours 3 times per week Dialysate flow rate 500 mL/min Blood flow 190 to 250 mL/min <p>Low-flux</p> <ul style="list-style-type: none"> F6 polysulphone dialyser ultrafiltrate coefficient 5.5 mL/h/mm Hg Surface area 1.3 m² Fresenius 4008S capacity controlled dialyser Bicarbonate dialysate 4 hours 3 times per week Dialysate flow rate 500 mL/min Blood flow 190 to 250 mL/min
Outcomes	<ul style="list-style-type: none"> Beta-2 microglobulin
Notes	<ul style="list-style-type: none"> Exclusions post-randomisation but pre-intervention: Unclear Stop or end point/s: Unclear

High-flux versus low-flux membranes for end-stage kidney disease (Review)

Li 2007a (Continued)

- Additional data requested from authors: Clinical outcomes, risks of bias
- Reported in Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Unclear risk	Not clearly described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Enrolled/randomised (43); analysed (unclear); followed (unclear)
Selective reporting (reporting bias)	High risk	Only one secondary outcome reported; data unable to be meta-analysed
Other bias	Unclear risk	ITT: not clearly described

Li 2010

Methods	<ul style="list-style-type: none"> • Study design: Cross-over RCT • Time frame: NS • Follow-up period: 24 weeks • Lost to follow-up: 0%
Participants	<ul style="list-style-type: none"> • Country: Hong Kong, China • Setting: Prince of Wales Hospital (Hong Kong China) and Alice Ho Miu Ling Nethersole Hospital (Hong Kong China) • Patients: Stable anuric maintenance HD patients who were on a dialyser reuse program using low-flux polysulfone membrane (F6HPS) and bicarbonate dialysate for ≥ 3 months and had satisfactory vascular access • Duration on dialysis <ul style="list-style-type: none"> * Treatment group: 4.2 ± 3.7 years * Control group: 5.1 ± 3.1 years • Number (treatment/control): 19/23 • Mean age (treatment/control): 57 ± 11 years/55.7 ± 13.8 years • Sex (M/F) <ul style="list-style-type: none"> * Treatment group: 8/11 * Control group: 8/15 <p>Exclusion criteria</p>

Li 2010 (Continued)

- Patients > 75 years; those with a history of active infection, inflammatory disease, ongoing malignancy, active phase immune disease, immunosuppressive drugs, planned renal transplantation in the subsequent year, baseline measured CRP > 50 mg/L

Interventions	<p>High-flux</p> <ul style="list-style-type: none"> • Polyamide membrane (Polyflux 14S) • Surface area 1.4 m² • Ultrafiltration coefficient 62 mL/h/mm Hg • Vitamin B₁₂ clearance 125 mL/min • Sterilised using Puristeril 340 • All individuals underwent their usual protocol (blood flow, dialysate flow, dialysis treatment time, anticoagulation type, dosage) • Sieving coefficient for beta-2 microglobulin > 0.6 and UF coefficient ≥ 20 mL/mm Hg/h <p>Low-flux</p> <ul style="list-style-type: none"> • Polyamide membrane (Polyflux 6L) • Surface area 1.4 m² • Ultrafiltration coefficient 8.6 mL/h/mm Hg • Vitamin B₁₂ clearance 85 mL/min • Sterilised using Puristeril 340 • All individuals underwent their usual protocol (blood flow, dialysate flow, dialysis treatment time, anticoagulation type, dosage) • Sieving coefficient for beta-2 microglobulin >0 and UF coefficient ≤ 10 mL/mm Hg/h
Outcomes	<ul style="list-style-type: none"> • Mortality; cardiovascular mortality • Cholesterol; triglycerides • Inflammatory response
Notes	<ul style="list-style-type: none"> • Exclusions post-randomisation but pre-intervention: 0 • Stop or end point/s: None reported • Additional data requested from authors: Clinical outcomes, risks of bias • Data for first phase of cross-over provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation table
Allocation concealment (selection bias)	Low risk	Consecutively numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias)	Low risk	Enrolled/randomised (46); analysed (45); followed (98%)

High-flux versus low-flux membranes for end-stage kidney disease (Review)

Li 2010 (Continued)

All outcomes

Selective reporting (re-reporting bias)	Low risk	Primary and some secondary outcomes reported
Other bias	High risk	ITT: patients randomised not all included in analyses

Locatelli 1996

Methods	<ul style="list-style-type: none"> Design: Parallel RCT Time frame: NS Follow-up period: 2 years Lost to follow-up: 0/155 <ul style="list-style-type: none"> * Patient numbers in the high-flux, low-flux bioincompatible membrane and low-flux biocompatible membrane arms of the study given * Numbers of patients who left the study: 24 for kidney transplant, 5 for acute clinical reasons, 4 for fistula related problems, 12 for treatment inadequacy and 50 for technical reasons
Participants	<ul style="list-style-type: none"> Country: Italy Setting: Multicentre study Adults (18 to 70 years); RRT for at least 2 months; on dialysis for > 3 months; regular thrice weekly HD; stable clinical condition Number (treatment/control): 51/104 Mean age (treatment/control): 56/52.1 years Sex (M/F) <ul style="list-style-type: none"> * Treatment group: 70.6%/29.4% * Control group: 69.1%/30.9% <p>Exclusion criteria</p> <ul style="list-style-type: none"> Presence of malignant disease; myocardial Infarction in the previous 12 months; stroke or TIA in the previous 6 months; severe heart failure (NYHA Class III or IV)
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> High-flux, polysulfone 3 times/wk <p>Low-flux</p> <ul style="list-style-type: none"> Low-flux, polysulfone or cuprophane 3 times/wk
Outcomes	<ul style="list-style-type: none"> Mortality Kt/V Hospital admission Days spent in hospital Beta-2 microglobulin values
Notes	<ul style="list-style-type: none"> Exclusions post-randomisation but pre-intervention: None Stop or end point/s: NS Additional data requested from authors: None

Risk of bias

Locatelli 1996 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly described
Allocation concealment (selection bias)	Low risk	Centralized at the Nephrology department in Lecce - not otherwise described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (155); analysed (83); followed (53.5%). Patients were accounted for (24 for kidney transplant, 5 for acute clinical reasons, 4 for fistula related problems, 12 for treatment inadequacy and 50 for technical reasons).
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported
Other bias	Low risk	ITT performed

Locatelli 2000

Methods	<ul style="list-style-type: none"> Design: Parallel RCT Time frame: NS Follow-up period: 12 weeks Lost to follow-up: 0/84
Participants	<ul style="list-style-type: none"> Country: Italy Setting: Multicentre study Adult (> 18 years); conventional thrice weekly HD for at least 6 months with cellulose dialyser; negligible RRF (average estimated urea and CrCl < 1 mL/min/1.73 m²); no change in EPO, iron, folic acid, vit B₁₂, ACEi in the previous 3 months; dialysis dosage > 1.2 or > 1.4 (respectively estimated by means of equilibrated or non-equilibrated Kt/V) Number (treatment/control): 35/39 Mean age (treatment/control): 64/65 years Sex (M/F) <ul style="list-style-type: none"> * Treatment group: 19/16 * Control group: 20/19 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Patients whose clinical condition had been unstable during the previous 3 months; patients on treatment with erythropoiesis related drugs (steroids, cyclophosphamide, azathioprine, or androgen hormones); severe cardiac, hepatic, bone marrow, connective tissue or neoplastic diseases; plasma transferrin saturation < 25% or serum ferritin < 200 ng/mL; MCV < 83 m³ or > 100 m³; hyperparathyroidism defined as n-amino terminal PTH > 500 mU/mL, with ionised Ca 1.15 to 1.37 mmol/L; use of aluminium based binders at a dose of > 2 g/d for at least 1 year before study entry; clinical or laboratory findings of aluminium toxicity; use of a dialyser with a synthetic membrane or use of a convective dialyser technique in the previous 6 months

Locatelli 2000 (Continued)

Interventions	<p>High-flux</p> <ul style="list-style-type: none"> High-flux BK-F PMMA membrane 3 times/wk <p>Low-flux</p> <ul style="list-style-type: none"> Low-flux cellulose-based membrane 3 times/wk
Outcomes	<ul style="list-style-type: none"> Mortality Intradialytic hypo- and hypertension Equilibrated Kt/V
Notes	<ul style="list-style-type: none"> Exclusions post randomisation but pre-intervention: 10 Stop or end point/s: NS Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (84); analysed (74); followed (88.09%). All patients accounted for.
Selective reporting (reporting bias)	Unclear risk	Only 1 primary outcome reported
Other bias	Low risk	ITT performed

Mohini 1989

Methods	<ul style="list-style-type: none"> Study design: Parallel RCT Time frame: NS Follow-up period: 6 months Lost to follow-up: NS
Participants	<ul style="list-style-type: none"> Country: USA Setting: Henry Ford Hospital, Detroit, MI

High-flux versus low-flux membranes for end-stage kidney disease (Review)

Mohini 1989 (Continued)

- Patients: Clinical stable patients treated with recombinant human EPO and on HD
- Duration on dialysis: NS
- Number (treatment/control): 16/18
- Mean age (treatment/control): NS
- Sex (M/F): NS

Exclusion criteria: NS

Interventions	<p>High-flux</p> <ul style="list-style-type: none"> • Polysulfone <p>Low-flux</p> <ul style="list-style-type: none"> • Cellulosic
Outcomes	<ul style="list-style-type: none"> • Haematocrit
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: NS • Stop or end point/s: None reported • Additional data requested from authors: Clinical outcomes, risks of bias • Abstract presentation only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Enrolled/randomised (34); analysed (unclear); followed (unclear)
Selective reporting (reporting bias)	High risk	No primary or secondary outcomes reported
Other bias	Unclear risk	ITT not described

MPO 2009

- Methods
- Study design: Parallel RCT
 - Time frame: December 1998 to June 2006
 - Follow-up period: Mean observation time (3.0 years); maximum (7.5 years)

High-flux versus low-flux membranes for end-stage kidney disease (Review)

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MPO 2009 (Continued)

	<ul style="list-style-type: none"> Lost to follow-up: 191/738
Participants	<ul style="list-style-type: none"> Country: Italy Setting: Multicentre study All new ESKD patients of both sexes, admitted for dialysis, willing to cooperate, gave informed consent and fulfil the following inclusion criteria: aged 18 to 75 years; RRT < 1 month; at risk, originally defined as serum albumin < 4.0 g/dL (subsequently changed to include those with albumin > 4.0 g/dL as the investigators could not find sufficient numbers of patients with the lower albumin level (< 4.0 g/dL) Mean time on dialysis prior to enrolment: 31 days Number (treatment/control): 360/378 Mean age (treatment/control): 59.4/60.2 years % Male (treatment/control): 62.9/65.3 % Diabetic (Treatment/control): 26.1/22.5 <p>Exclusion criteria</p> <ul style="list-style-type: none"> AKI; pregnancy; previous leg amputation; scheduled for kidney transplantation from a living donor within the study period; HD after kidney transplantation; nephrotic syndrome (proteinuria > 6 g/24 h/1.73 m²); active malignancies; current therapy with immunosuppressive agents; severe CHF after maximal therapy (NYHA class IV); unstable angina pectoris; active systemic infections (TB, systemic fungal infection, AIDS, hepatitis with ALT > twice the upper normal value); CPD requiring supplementary oxygen; cirrhosis with encephalopathy; CVC as intended permanent vascular access; involvement in other intervention protocols; inability to follow the main requirements of the present protocol; unwillingness to undergo the protocol procedures
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> High-flux synthetic or substituted cellulose membranes High-flux was defined as sieving coefficient beta-2 microglobulin > 0.6 and ultrafiltration coefficient ≥ 20 mL/mm Hg/h Haemodialysis 3 times per week with bicarbonate haemodialysis with a minimum treatment time of 180 minutes and a minimum spKt/V of 1.2 Dialyser reuse was not allowed Treatment parameters (treatment time, blood flow rate, dialysis fluid flow rate, dialyser surface area) adjusted locally by the investigator to reach the Kt/V target <p>Low-flux</p> <ul style="list-style-type: none"> Low-flux synthetic, substituted cellulose or unsubstituted cellulose membranes Haemodialysis 3 times/wk with bicarbonate haemodialysis with a minimum treatment time of 180 minutes and a minimum spKt/V of 1.2 Dialyser reuse was not allowed Treatment parameters (treatment time, blood flow rate, dialysis fluid flow rate, dialyser surface area) adjusted locally by the investigator to reach the Kt/V target
Outcomes	<ul style="list-style-type: none"> Mortality Hospitalisation Beta-2 microglobulin levels
Notes	<ul style="list-style-type: none"> Exclusions post-randomisation but pre-intervention: 91 Stop or end point/s: End of study period was set to be 3 years from the date of last patient recruitment Additional data requested from authors: None
Risk of bias	
Bias	Authors' judgement Support for judgement

MPO 2009 (Continued)

Random sequence generation (selection bias)	Low risk	Centralised randomisation using a separate list for each participating centre divided into blocks of eight
Allocation concealment (selection bias)	Low risk	Centralised randomisation using a separate list for each participating centre divided into blocks of eight
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (738); analysed (647); followed (86.31%). All patients accounted for.
Selective reporting (reporting bias)	Low risk	Primary and one secondary outcome reported.
Other bias	Low risk	ITT performed

Opatrny 2002

Methods	<ul style="list-style-type: none"> Design: Cross-over RCT Time frame: NS Follow-up period: 8 weeks Lost to follow-up: 0/25
Participants	<ul style="list-style-type: none"> Country: Czech Republic Setting: University hospital Patients on HD for ESKD Mean time on dialysis (treatment/control): 28/19 months Number (treatment/control): 12/13 Mean age (treatment/control): 71/69 years Sex (M/F) <ul style="list-style-type: none"> * Treatment group: 6/6 * Control group: 7/6 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Diabetes mellitus; active liver disease; manifest signs of bleeding; clinical or laboratory signs of infection; received blood transfusions
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> High-flux, polysulfone (Fresenius F60S, UF coefficient 40 mL/mm Hg/h, 1.3 m²) Blood flow rate: 200 to 350 mL/min Dialysate flow rate: 500 mL/min <p>Low-flux</p> <ul style="list-style-type: none"> Low-flux, polysulfone (Fresenius 7HPS, UF coefficient 9.8 mL/mm Hg/h, 1.6 m²)

Opatrny 2002 (Continued)

- Blood flow rate: 200 to 350 mL/min
- Dialysate flow rate: 500 mL/min

Outcomes	<ul style="list-style-type: none"> • Kt/V • Beta-2 microglobulin levels
Notes	<ul style="list-style-type: none"> • Exclusions post-randomisation but pre-intervention: None • Stop or end point/s: NS • Additional data requested from authors: Method of randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Provided by authors - record of method not available
Allocation concealment (selection bias)	High risk	Patients names were written in a piece of paper put in a bag and taken out without looking at the names (information obtained by contacting the authors)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (25); analysed (25); followed (100%)
Selective reporting (reporting bias)	High risk	Secondary outcomes reported; unable to include in meta-analyses
Other bias	Unclear risk	ITT not described

Ottosson 2001

Methods	<ul style="list-style-type: none"> • Design: Parallel RCT • Time frame: NS • Follow-up period: 12 weeks • Lost to follow-up: 3/42
Participants	<ul style="list-style-type: none"> • Country: Sweden • Setting: Multicentre • Patients on chronic stable HD for at least 3 months • Mean time on dialysis (treatment/control): 16.6/20.4 months • Number (treatment/control): 19/23 • Mean age (treatment/control): 67.9/70.2 years

Ottosson 2001 (Continued)

- Sex (M/F)
 - * Treatment group: 9/10
 - * Control group: 15/8

Exclusion criteria

- ACEi; lipid lowering therapy; oestrogen therapy; planned major surgery; kidney transplantation within the study follow-up period

Interventions	<p>High-flux</p> <ul style="list-style-type: none"> • High-flux, PAN (AN-69, 1.65 m², B₁₂ clearance: 115 mL/min) • Blood flow: 200 to 300 mL/min • Dialysate flow: 500 mL/min <p>Low-flux</p> <ul style="list-style-type: none"> • Low-flux, cellulose diacetate (FB170T, NISSHO Corp, Japan, 1.7 m². B₁₂ clearance 77 mL/min) • Blood flow: 200 to 300 mL/min • Dialysate flow: 500 mL/min
Outcomes	<ul style="list-style-type: none"> • Lipid profile
Notes	<ul style="list-style-type: none"> • Exclusions post randomisation but pre-intervention: None • Stop or end point/s: NS • Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (42); analysed (39); followed (92.58%)
Selective reporting (reporting bias)	High risk	Only secondary outcomes reported
Other bias	Unclear risk	ITT not described

Rizvi 1995

Methods	<ul style="list-style-type: none"> Study design: Cross-over RCT Time frame: Unclear Follow-up period: 1 month Lost to follow-up: 0%
Participants	<ul style="list-style-type: none"> Country: India Setting: Single medical college centre Patients: Stable adult individuals with ESKD aged 18 to 61 years Duration on dialysis: Unclear Number (treatment/control): 10/10 Mean age (treatment/control): 34.5 ± 11.6 years Sex (M/F) <p>Exclusion criteria: NS</p>
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> Polysulphone (Fresenius) UF rate 15 mL/h/mm Hg Time 2 hours/session Acetate dialysis <p>Low-flux</p> <ul style="list-style-type: none"> Polysulphone (Fresenius) Ultrafiltration rate 4.0 mL/h/mm Hg Time 4 hours/session Acetate dialysis
Outcomes	<ul style="list-style-type: none"> Serum creatinine, blood urea, calcium, alkaline phosphatase, electrolytes Complications and intradialytic symptoms Cost
Notes	<ul style="list-style-type: none"> Exclusions post-randomisation but pre-intervention: Unclear Stop or end point/s: None reported Additional data requested from authors: Clinical outcomes, risks of bias Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Not described

Rizvi 1995 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (20); analysed (20); followed (100%)
Selective reporting (reporting bias)	Unclear risk	Only secondary outcomes reported; unable to include in meta-analyses
Other bias	Unclear risk	ITT not described

Sawaya 1989

Methods	<ul style="list-style-type: none"> Study design: Parallel RCT Time frame: Unclear Follow-up period: 18 months Lost to follow-up: Unclear
Participants	<ul style="list-style-type: none"> Country: USA Setting: Single hospital centre Patients: Stable haemodialysis patients Duration on dialysis: NS Number (treatment/control): NS Mean age (treatment/control): NS Sex (M/F): NS <p>Exclusion criteria: NS</p>
Interventions	<p>High-flux</p> <ul style="list-style-type: none"> Polysulfone <p>Low-flux</p> <ul style="list-style-type: none"> Saponified cellulose ester
Outcomes	<ul style="list-style-type: none"> Visual evoked potentials
Notes	<ul style="list-style-type: none"> Exclusions post-randomisation but pre-intervention: Unclear Stop or end point/s: None reported Additional data requested from authors: Clinical outcomes, risks of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Low risk	Participants not blinded Investigators blinded

High-flux versus low-flux membranes for end-stage kidney disease (Review)

Sawaya 1989 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Enrolled/randomised (8); analysed (unclear); followed (unclear)
Selective reporting (reporting bias)	High risk	No relevant outcomes reported
Other bias	Unclear risk	ITT not described

Simon 1993

Methods	<ul style="list-style-type: none"> Design: Parallel RCT Time frame: NS Follow-up period: 48 months Lost to follow-up: 0/54
Participants	<ul style="list-style-type: none"> Country: France Setting: University teaching hospital HD 3 times/ wk, 4 hours/session; agree to blood sample collection every month; agree to have treatment in the dialysis centre conducting the study Number (treatment/control): 32/22 Age: NS Sex (M/F) <ul style="list-style-type: none"> * Treatment group: 13/19 * Control group: 14/8 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Systemic disease; chronic respiratory failure; hepatic dysfunction; neoplasm; chronic infectious disease; uncontrolled hypertension
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> High-flux, polysulfone (AN 69) <p>Control group</p> <ul style="list-style-type: none"> Low-flux, cuprophane
Outcomes	<ul style="list-style-type: none"> Hospitalisation (all-cause, infectious, cardiac) Mortality (all-cause, infectious, cardiac)
Notes	<ul style="list-style-type: none"> Exclusions post-randomisation but pre-intervention: None Stop or end point/s: NS Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
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Simon 1993 (Continued)

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Enrolled/randomised (54); analysed (54); followed (100%)
Selective reporting (reporting bias)	Low risk	Primary outcomes reported
Other bias	Unclear risk	ITT not described

Skroeder 1993

Methods	<ul style="list-style-type: none"> Design: Cross-over RCT Time frame: NS Follow-up period: 84 HD sessions Lost to follow-up: 4/20 <ul style="list-style-type: none"> * The authors mention that only 16/20 completed the study, and that 4 did not complete < 40% of planned treatment sessions and 13 randomly selected patients underwent some duplicate treatments to increase statistical validity
Participants	<ul style="list-style-type: none"> Country: Sweden Setting: University hospital Patients on maintenance HD; stable condition for at least 3 months Mean time on dialysis: 1.7 years Number: 20 Sex (M/F): 16/4 Mean age: 61 years (range 40 to 80) <p>Exclusion criteria</p> <ul style="list-style-type: none"> Signs of inflammatory disease; liver disease; myeloproliferative or lymphoproliferative disease; diabetes mellitus; immunosuppressive therapy; anticoagulants; signs of acute infection or malignancy
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> High-flux polyamide membranes (Polyflux, area 1.0 or 1.6 m²) Blood flow: 200 or 400 mL/min Dialysis duration: 2 or 4 hours Dialysate flow: 500 mL/min <p>Control group</p>

Skroeder 1993 (Continued)

- Low-flux hemophane (GF 120 Plus, are 1.2 or 2 m²)
- Blood flow: 200 or 400 mL/min
- Dialysis duration: 2 or 4 hours
- Dialysate flow: 500 mL/min

Outcomes	<ul style="list-style-type: none"> • Intradialytic symptoms (headache, pruritus, hypotension) • Dialysate beta-2 microglobulin concentration • Post-dialysis serum beta-2 microglobulin concentration
Notes	<ul style="list-style-type: none"> • Exclusions post-randomisation but pre-intervention: None • Stop or end point/s: NS • Additional data requested from authors: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Enrolled/randomised (20); analysed (16); followed (80%). The authors mention that only 16/20 completed the study, and that 4 did not complete < 40% of planned treatment sessions and 13 randomly selected patients underwent some duplicate treatments to increase statistical validity
Selective reporting (reporting bias)	High risk	Only secondary outcomes reported; unable to include in meta-analysis
Other bias	High risk	ITT not performed

Takasawa 2005

Methods	<ul style="list-style-type: none"> • Study design: Parallel RCT • Time frame: NS • Follow-up period: 6 months • Lost to follow-up: Unclear
Participants	<ul style="list-style-type: none"> • Country: Japan • Setting: Three hospitals • Patients: Stable HD • Duration on dialysis: NS • Number (treatment/control): 9/10

High-flux versus low-flux membranes for end-stage kidney disease (Review)

Takasawa 2005 (Continued)

- Sex (M/F): NS

Exclusion criteria: NS

Interventions	<p>High-flux</p> <ul style="list-style-type: none"> • Polysulfone (APS-E) membrane <p>Low-flux</p> <ul style="list-style-type: none"> • FPS-16M membrane
Outcomes	<ul style="list-style-type: none"> • Haematocrit • Beta-2 microglobulin
Notes	<ul style="list-style-type: none"> • Exclusions post-randomisation but pre-intervention: Unclear • Stop or end point/s: None reported • Additional data requested from authors: Clinical outcomes, risks of bias • Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Enrolled/randomised (19); analysed (unclear); followed (unclear)
Selective reporting (reporting bias)	High risk	Only one secondary outcome reported; unable to include in meta-analyses
Other bias	Unclear risk	ITT not described

ACEi - angiotensin converting enzyme inhibitor; AIDS - acquired immunodeficiency syndrome; AKI - acute kidney injury; ALT - alanine aminotransferase; ARB - angiotensin receptor blocker; BP - blood pressure; Ca - calcium; CCF - congestive cardiac failure; CHF - chronic heart failure; CPD - cardiopulmonary disease; CrCl - creatinine clearance; CRP - C-reactive protein; CVC - central venous catheter; EPO - erythropoietin; ESKD - end-stage kidney disease; GN - glomerulonephritis; Hb - haemoglobin; HD - haemodialysis; HDL - high density lipoprotein; HD-QoL - Haemodialysis Quality of Life Questionnaire; ITT - intention-to-treat; MCV - mean corpuscular volume; NS - not stated; LDL - low density lipoprotein; NYHA - New York Heart Association; PT - prothrombin time; PTH - parathyroid hormone; QoL - quality of life; RCT - randomised controlled trial; RRF - residual renal function; RRT - renal replacement therapy; TB - tuberculosis; TIA - transient ischaemic attack; TTO - time trade-off; UF - ultrafiltration; UFR - ultrafiltration rate; URR - urea reduction rate; VLDL - very low density lipoprotein

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

Study	Reason for exclusion
Abe 2008	Cross-over RCT comparing 3 high-flux membranes in diabetic patients
Abe 2009	Cross-over RCT comparing 2 high-flux membranes in diabetic patients
Alarcon 1994	Not RCT
Albertazzi 1999	Not RCT
Amadori 1983	Not RCT
Andreoli 2007	Cross-over RCT comparing low-flux membranes
Arakawa 1991	Not RCT
Arnadottir 2002	Outcomes not relevant to the review
Becker 1999	Not CKD
Bergamo 1991	Short duration (< 1 month exposure)
Bonomini 1994	Not RCT
Bonomini 1996	Short duration (< 1 month exposure)
Bordoni 2006	Short duration
Bosc 1997	Compared 2 high-flux membranes
Boudville 2009	Cross-over RCT comparing high-flux membranes
Branger 1988	Not RCT
Campbell 1987	Not appropriate exposure
Caramelo 1994	Outcomes not relevant to the review
Cases 1993	Outcomes not relevant to the review
Chanard 1989	Not RCT
Chaveau 1992	Compared 5 high-flux membranes
Chen 2005c	Not RCT
Churchill 1995	Review article
Civati 1991	Not RCT
Combe 1994	Outcomes not relevant to the review
CONTRAST (Dutch) 2005	Cross-over RCT comparing online HF with low-flux HD

Study	Reason for exclusion
Danielson 1986	Interventions not relevant to review
Daugirdas 1994a	Review article
De Francisco 1994	Outcomes not relevant to the review
De Precigout 1996	Not RCT
Dellanna 1999	Not appropriate exposure
Demirtas 2002	Not RCT
Descamps-Latscha 1991	Outcomes not relevant to the review
Dhakal 1999	Not RCT
Ding 1998	Not RCT
Diop 2000	Not RCT
Docci 1992	Outcomes not relevant to the review
Docci 1995	Not RCT
Domrongkitchaiporn 1997	Not RCT
Donovan 1992	Outcomes not relevant to the review
Falkenhagen 1987	Not RCT
Ferreira 1995	Outcomes not relevant to the review
Fourtunas 2001	Outcomes not relevant to the review
Fox 1993	Outcomes not relevant to the review
Franke 2002	Not appropriate exposure
Gascón 1993	Not appropriate exposure
Girndt 1999	Outcomes not relevant to the review
Gonella 1994	Outcomes not relevant to the review
Grekas 1985	Outcomes not relevant to the review
Grooteman 1995	Outcomes not relevant to the review
Grooteman 1995b	Compared 2 high-flux membranes
Grooteman 1997	Outcomes not relevant to the review
Grooteman 2005	Not appropriate exposure
Grooteman 2007	Not appropriate exposure

Study	Reason for exclusion
Haag-Weber 1994	Outcomes not relevant
Hakim 1995	Review article
Hakim 1996	Not RCT
Haque 1994	Outcomes not relevant to the review
Hardouin 2000	Not RCT
Haufe 2001	Outcomes not relevant to the review
Heisel 1995	Not RCT
Hernandez 2007a	Not appropriate exposure
Himmelfarb 1993	Outcomes not relevant to the review
Himmelfarb 1998	Compared 2 low-flux membranes
Hoenich 1994	Compared 3 high-flux membranes
Hoenich 1995	Not RCT
Hoenich 1997	Outcomes not relevant to the review
Hoenich 2000	Compared 2 high-flux membranes
Hoenich 2000a	Review, commentary, or editorial
Hornberger 1992	Not RCT
Hornych 1996	Outcomes not relevant to the review
Huraib 2000	Outcomes not relevant to the review
Ingram 1998	Compared 2 low-flux membranes
Iorio 1997	Not RCT
Ivanovich 1983	Not RCT
Josephson 1992	Not RCT
Kasama 1996	Outcomes not relevant to the review
Kato 2001	Not RCT
Kim 2009	Cross-over RCT comparing HDF with online endogenous perfusion with low-flux HD
Kino 1995	Outcomes not relevant to the review
Kirschbaum 1994	Not RCT
Klemm 1997	Outcomes not relevant to the review

Study	Reason for exclusion
Klinkmann 1998	Compared 4 low-flux membranes
Koda 1997	Not RCT
Kramer 1992	Compared 4 high-flux membranes
Krieter 2008	Cross-over RCT compared 2 high-flux membranes
Krieter 2010	Cross-over RCT comparing high-flux HD and online post-dilution HDF
Lee 2009b	Cross-over RCT comparing high cut-off versus high-flux dialysis membranes
Leitienne 1991	Not appropriate exposure
Levin 1993	Not RCT
Lin 1996	Not RCT
Linnenweber 2001	Outcomes not relevant to the review
Locatelli 1996b	Review article and protocol of future trial
Locatelli 1997	Not RCT
Locatelli 1999	Design of ongoing study
Locatelli 2000b	Review article
Locatelli 2001a	Review article
Locatelli 2001b	Review article
Locatelli 2002	Review article
Locatelli 2003	Review article
Lonnenmann 2003	Not RCT
Lundberg 1994	Compared 2 low-flux membranes
MacGinley 2001	Not RCT
Mahuet 2001	Not RCT
MAMHEBI Study 2006	FX high-flux versus standard high-flux
Mandolfo 2008	Haemodiafiltration versus high-flux dialysis
Mann 2003	Not RCT
Martin-Malo 1991	Not RCT
Martin-Malo 1993	Not RCT
Martinez Ara 1994	Outcomes not relevant to the review

Study	Reason for exclusion
Martos 1997	Outcomes not relevant to the review
Matthews 1994	Review article
Matzkies 2000	Not RCT
McCarthy 1997	Not RCT
Mehrotra 2009	Cross-over RCT comparing high-normal with low-normal arterial pH
Memoli 2000	Outcomes not relevant to the review
Memoli 2002	Outcomes not relevant to the review
Memoli 2003	Outcomes not relevant to the review
Merello Godino 2002	Not RCT
Mioli 1994	Not RCT
Mishkin 2002	Haemodiafiltration versus high-flux dialysis
Moreno 1996	Not RCT
Moshfegh 2002	Outcomes not relevant to the review
Mudge 2005	Superflux versus high flux
Muller 1998	Comparison of sterilization techniques
Munger 2000	Short duration (< 1 month)
Navarro 1994	Not RCT
Navarro 1997	Not RCT
Nensel 1994	Not RCT
Ohi 2001	Outcomes not relevant to the review
Opatrny 1993	Short duration
Opatrny 1995	Not RCT
Opatrny 2006	Compared 2 high-flux membranes
Otti 2001	Outcomes not relevant to the review
Ouseph 2008	Compared 2 high-flux membranes
Panichi 1995	Not RCT
Parker 1996	Compared 2 low-flux membranes
Pellicano 2008	Super-flux versus high-flux

Study	Reason for exclusion
Pengloan 1991	Not RCT
Pereira 1996	Interventions not relevant to review
Pickett 2002	Interventions not relevant to review
Ponikvar 2001	AKI patients
Quellhorst 1979	Outcomes not relevant to the review
Riegel 2001	Outcomes not relevant to the review
Risler 1994	Not RCT
Ritz 1994	Outcomes not relevant to the review
Robles 1993	Not RCT
Robles 1995	Not RCT
Ronco 1995	Compared 2 high-flux membranes
Sa 2002	Not RCT
Schaefer 1987	Outcomes not relevant to the review
Schaefer 1993	Outcomes not relevant
Schaefer 1994	Compared 3 high-flux membranes
Schauer 1991	Outcomes not relevant to the review
Schiffl 2000	Not RCT
Schindler 2000	Outcomes not relevant to the review
Schindler 2003	Outcomes not relevant to the review
Schonermarck 2006	Compared 2 high-flux membranes
Schouten 1997	Outcomes not relevant to the review
Schouten 2000	Outcomes not relevant to the review
Schroder 2001	Not RCT
Schultze 1987	Outcomes not relevant to the review
Schwalbe 1987	Outcomes not relevant
Sethi 1988	Not RCT
Sevillano 1990	Not RCT
Singh 2003	Compared 2 low-flux membranes

Study	Reason for exclusion
Sirolli 1999	Outcomes not relevant to the review
Sirolli 2000	Short duration (< 1 month)
Sirolli 2002	Outcomes not relevant to the review
Sklar 1998	Outcomes not relevant to the review
Sklar 1999	Compared 2 low-flux membranes
Skroeder 1990	Not RCT
Sombolos 1997	Not RCT
Sreeharan 1982	Outcomes not relevant to the review
Stefanovic1998	Outcomes not relevant to the review
Stegmayr 1992	Outcomes not relevant to the review
Stegmayr 1998	Compared 2 low-flux membranes
Stegmayr 1999	Interventions not relevant to review
Stein 2001	Not RCT
Stuard 1996	Outcomes not relevant to the review
Sultan 1990	Not RCT
Takenaka 2001a	Outcomes not relevant to the review
Takenaka 2001b	Not RCT
Tayeb 2000	Not RCT
Taylor 1992	Not RCT
Tessitore 2000	Not high flux versus low flux
Tessitore 2004	Not RCT
Thalhammer 1998	Outcomes not relevant to the review
Thijs 2007	Not high flux versus low flux
Tonelli 2009	Cross-over RCT comparing 2 high-flux dialysers in parallel to 3 other dialysis modalities (4 hours of standard HD, 4.5 hours of HD, and 4 hours of HD with increased dialysate flow)
Traut 2007	Irrelevant outcomes - not clearly RCT
Tridon 1987	Not RCT
Valentijn 1998	Outcomes not relevant to the review

Study	Reason for exclusion
Van Stone 1995	Not RCT
Van Ypersele 1991a	Not RCT
Van Ypersele 1991b	Not RCT
Vanherweghem 1988	Outcomes not relevant to the review
Vanholder 1988	Outcomes not relevant to the review
Vanholder 1991	Interventions not relevant to review.
Vanholder 1992a	Outcomes not relevant to the review
Vanholder 1999	Review article
Varela 2001	Outcomes not relevant to the review
Vaslaki 1998	Outcomes not relevant to the review
Velasquez 1988	Outcomes not relevant to the review
Verbeelen 1991	Outcomes not relevant to the review
Verresen 1990	Not RCT
Verresen 1994	Outcomes not relevant to the review
Wakasa 1995	Outcomes not relevant to the review
Wanner 2004	Not high flux versus low flux intervention
Ward 1993	Not appropriate intervention
Ward 1997	Compared 4 low-flux membranes
Ward 2000	Compared 2 high-flux membranes
Ward 2003	Outcomes not relevant to the review
Wei 1994	Interventions not relevant
Wens 1992	Outcomes not relevant to the review
Woffindin 1992	Outcomes not relevant to the review
Woo (Tx) 2002	AKI patients
Woods 2000	Not RCT
Wright 1999a	Outcomes not relevant to the review
Wright 2000	Outcomes not relevant to the review
Yasuhiro 1998	Not RCT

Study	Reason for exclusion
Zaoui 1990	Outcomes not relevant to the review
Zaoui 1991	Outcomes not relevant to the review
Zaoui 1993	Outcomes not relevant to the review
Zhang 2011	Outcomes not relevant to the review

AKI - acute kidney injury; CKD - chronic kidney disease; HD - haemodialysis; HDF - haemodiafiltration; HF - haemofiltration

Characteristics of ongoing studies [ordered by study ID]

NCT00004285

Trial name or title	Phase II Randomized Study of Standard vs High Amount of Hemodialysis Using Low vs High Flux Dialyzer Membranes for End Stage Renal Disease. http://www.clinicaltrials.gov/ct2/show/NCT00004285
Methods	
Participants	<p>Disease Characteristics</p> <ul style="list-style-type: none"> End stage renal disease that requires in-centre hemodialysis 3 times/week On hemodialysis for at least 3 months (6 months following renal transplant) No scheduled renal transplant from living donor <p>Prior/Concurrent Therapy</p> <ul style="list-style-type: none"> No concurrent intervention studies unless ancillary to this protocol No concurrent investigational drugs <p>Patient Characteristics</p> <ul style="list-style-type: none"> Hepatic: Albumin at least 2.6 g/dL by nephelometry No cirrhosis with encephalopathy or abnormal PT Renal: Urea clearance (interdialytic) no greater than 1.5 mL/min per 35 litres total urea volume Cardiovascular: No New York Heart Association class IV congestive heart failure despite maximal therapy No unstable angina No new onset angina No recent exacerbation of frequency, duration, or severity of angina Pulmonary: No chronic pulmonary disease requiring supplemental oxygen Other: Not hospitalised in acute or long term care facility at entry No active malignancy requiring chemotherapy or radiotherapy No AIDS No active systemic infection, e.g., tuberculosis or fungal infection No mental incompetence or other contraindication to protocol therapy Not pregnant Geographically available for treatment at participating institution No more than 20 missed treatments/year
Interventions	<p>Patients are randomly assigned to 1 of 4 groups: moderate dose dialysis, low flux membrane; high dose dialysis, low flux membrane; moderate dose dialysis, high flux membrane; or high dose dialysis, high flux membrane. Moderate dose is a target eKt/V of 1.05 and high dose is 1.45. The dose and delivery of dialysis are measured monthly by the equilibrated fractional clearance of urea (eKt/V) calculated with double pool kinetics.</p> <p>Patients are dialyzed 3 times a week in the shortest possible time (minimum 2.5 hours), adjusted for adequate fluid removal. General medical care, protein and calorie intake, and dialyzer reuse and other aspects of dialysis therapy are standardized. The protocol document lists approved dialyzers; no unsubstituted cellulosic membranes are permitted.</p>

NCT00004285 (Continued)

The intervention phase of this study is 5 years.

Outcomes	Patients are followed for survival
Starting date	October 1992
Contact information	Study Chair: Daniel B Ornt, University of Rochester
Notes	Available at http://www.clinicaltrials.gov/ct2/show/NCT00004285 Accessed 26 June 2012. Study completed, no publications identified

DATA AND ANALYSES

Comparison 1. High-flux versus low-flux membranes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	10	2915	Risk Ratio (IV, Random, 95% CI)	0.95 [0.87, 1.04]
2 Death due to infection	3	2547	Risk Ratio (IV, Random, 95% CI)	0.90 [0.71, 1.14]
3 Cardiovascular mortality	5	2612	Risk Ratio (IV, Random, 95% CI)	0.83 [0.70, 0.99]
4 Hospitalisation	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1 Any cause	2	74	Risk Ratio (IV, Random, 95% CI)	0.79 [0.52, 1.20]
4.2 Cardiovascular cause	1	54	Risk Ratio (IV, Random, 95% CI)	0.92 [0.23, 3.70]
4.3 Infectious cause	1	20	Risk Ratio (IV, Random, 95% CI)	0.33 [0.02, 7.32]
5 Hospital admissions/year	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Predialysis beta-2 microglobulin	6	2071	Mean Difference (IV, Random, 95% CI)	-12.17 [-15.83, -8.51]
7 Equilibrated Kt/V _{urea}	3	1968	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.03, 0.02]
8 Dialysis-associated amyloid-related complications	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8.1 Carpel tunnel syndrome	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Dialysis-associated arthropathy	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9 Intradialytic hypotension	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
10 Withdrawal due to treatment inadequacy	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

High-flux versus low-flux membranes for end-stage kidney disease (Review)

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Lipid profile	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 Total cholesterol	4	124	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.59, 0.27]
11.2 HDL cholesterol	4	154	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.14, 0.05]
11.3 LDL cholesterol	4	154	Mean Difference (IV, Random, 95% CI)	0.06 [-0.20, 0.31]
11.4 VLDL cholesterol	2	64	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.39, 0.17]
11.5 Triglycerides	4	124	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.48, 0.05]
12 Residual renal function at end of study period	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13 Average rate of loss of residual renal function	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 High-flux versus low-flux membranes, Outcome 1 All-cause mortality.

Analysis 1.2. Comparison 1 High-flux versus low-flux membranes, Outcome 2 Death due to infection.

Analysis 1.3. Comparison 1 High-flux versus low-flux membranes, Outcome 3 Cardiovascular mortality.

Analysis 1.4. Comparison 1 High-flux versus low-flux membranes, Outcome 4 Hospitalisation.

Analysis 1.5. Comparison 1 High-flux versus low-flux membranes, Outcome 5 Hospital admissions/year.

Analysis 1.6. Comparison 1 High-flux versus low-flux membranes, Outcome 6 Predialysis beta-2 microglobulin.

Analysis 1.7. Comparison 1 High-flux versus low-flux membranes, Outcome 7 Equilibrated Kt/V_{urea}.

Analysis 1.8. Comparison 1 High-flux versus low-flux membranes, Outcome 8 Dialysis-associated amyloid-related complications.

Analysis 1.9. Comparison 1 High-flux versus low-flux membranes, Outcome 9 Intradialytic hypotension.

Analysis 1.10. Comparison 1 High-flux versus low-flux membranes, Outcome 10 Withdrawal due to treatment inadequacy.

Analysis 1.11. Comparison 1 High-flux versus low-flux membranes, Outcome 11 Lipid profile.

Analysis 1.12. Comparison 1 High-flux versus low-flux membranes, Outcome 12 Residual renal function at end of study period.

Analysis 1.13. Comparison 1 High-flux versus low-flux membranes, Outcome 13 Average rate of loss of residual renal function.

ADDITIONAL TABLES

Table 1. Current guidelines on membrane flux for individuals requiring haemodialysis

Guideline	Country	Year	Recommendation/suggestion
KDOQI 2006	USA	2003; 2006	The use of poorly biocompatible, unmodified cellulose dialyser membranes for haemodialysis is discouraged. In patients with evidence of, or at risk for beta-2 microglobulin amyloidosis, non-cuprophane (EVIDENCE), high-flux dialysers (OPINION) should be used
CARI 2005	Australia	2005 (being up-dated)	No recommendations possible based on Level I or II evidence (Level I evidence is a systematic review of randomised controlled trials and Level II evidence is evidence from randomised controlled trials)
Kidney Disease Improvement Global Outcomes			No recommendation
EBPG 2002	Europe	2007	<p>The use of synthetic high-flux membranes should be considered to delay long-term complications of haemodialysis therapy. Specific indications include: to reduce dialysis-related amyloidosis; to improve control of hyperphosphataemia; to reduce the increased cardiovascular risk; to improve control of anaemia.</p> <p><i>Position statement from the European Renal Best Practice Advisory Board (2009):</i> Strong recommendation that high-flux dialysis should be used in the case of high-risk patients (comparable to the low-albumin group in MPO 2009). In view of the small incremental extra cost of high-flux filters, the high prevalence of albumin < 40 g/L at the start of dialysis, and the substantial improvement in an intermediate marker (beta-2 microglobulin) in the high-flux group of the MPO, expanding the use of high-flux to all patients makes sense. The recommendation to use high-flux in all patients remains at 2B (weak recommendation, based on moderate quality evidence)</p>
Renal Association 2009	United Kingdom	2009	Suggest that high-flux dialysers should be used instead of low-flux dialysers to provide haemodialysis (weak recommendation, based on moderate quality evidence). Evidence of improved patient survival with the use of high-flux membranes is restricted to incident patients, who have lower serum albumin concentrations (< 40 g/L) or have diabetes mellitus, and prevalent patients, who have been on haemodialysis > 3.7 years

Table 2. Characteristics of included studies categorised according to type of high-flux membrane (Continued)

Study	No. of patients	Age (years)	Sex (%)	Time on dialysis (months)	Time on dialysis (%)	Membrane type		Membrane reuse	Study design	Kt/V urea	Follow-up	Primary outcome
						High-flux	Low-flux					
Polysulphone												
Acchiardo 1989	20	48.6 to 49.5	70	-	39.7 to 76.5	Polysulphone	Regenerated cellulose	Reuse	Parallel	1.01 to 1.05	9 mo	Haematocrit
Mohini 1989	34	-	-	-	-	Polysulfone	Cellulose	Reuse	Parallel	-	6 mo	Haematocrit
Sawaya 1989	16	-	-	-	-	Polysulfone	Cellulose	-	Parallel	-	18 mo	Visual evoked potentials
Blankestijn 1995	28	63 (22 to 80)	35.7	0†	-	Polysulfone	Cuprophane	Single use	Parallel	2.73 to 2.95/wk	1.5 mo	Lipids
Rizvi 1995	23	34.5 ± 11.6	-	-	-	Polysulfone	Polysulfone	-	Cross-over	-	1 mo	Biochemistry, complications and intradialytic symptoms
Goldberg 1996	29	-	-	-	-	Polysulfone	Cellulose acetate	-	Cross-over	-	1 mo	Lipids
Kuchle 1996	24	50 to 52	60	-	40 to 42	Polysulfone	Cuprophane	Single use	Parallel	-	6 y	Dialysis-related arthropathy
Locatelli 1996	155	50.5 to 56.0	69.6	-	-	Polysulfone	Polysulfone Cuprophane	-	Parallel	1.21 to 1.26	24 mo	Dialysis tolerance
Hartmann 1997	20	51 to 52	30	0†	-	Polysulfone	Cellulose acetate	Single use	Parallel	1.65	12 mo	Residual renal function

Table 2. Characteristics of included studies categorised according to type of high-flux membrane *(Continued)*

House 1999	48	55.7 to 56.7	68.8	0†	9.1 to 9.8	Polysulfone	Polysulfone	Single use	Parallel	-	3 mo	Plasma homocysteine
Jeloka 2001	20	45 to 49.1	-	-	85.2 ± 30.8	Polysulfone	Cuprophane	-	Parallel	-	3 mo	beta-2 microglobulin
Lang 2001	30	43 to 45	63.3	-	-	Polysulfone	Cuprophane	Single use	Parallel	-	24 mo	Residual renal function
Opatrny 2002	25	63 ± 15	52	0†	19.0 to 28.0	Polysulfone	Polysulfone	-	Cross-over	1.5 ± 0.3	2 mo	Anaemia
Klemm 2004	29	57 to 64	73.1	30.89 to 58		Polysulfone	Polysulfone	-	Cross-over	-	6 wk	Oxidative stress Homocysteine metabolism
Takasawa 2005	19	-	-	-	-	Polysulfone	Polysulfone	-	Parallel	-	6 mo	Haematocrit
Li 2007a	43	55.4 ± 9.7	58.1	-	18-60	Polysulfone	Polysulfone	-	Parallel	-	5 mo	beta-2 microglobulin
Chu 2006	40	54.4 to 60.4	52.6	39.59.1 to 82.2		Modified polysulfone	Polysulfone	Reuse	Parallel	1.33 to 1.40	2 mo	Oxidative stress, insulin resistance, inflammation, and dialysis efficiency
INFLUX 2008	151	60.3 to 65.5	60	-	-	Polysulfone	Polysulfone	Single use	Parallel	-	5 mo	C-reactive protein
Polyacrylonitrile												
Collins 1993	40	50 to 55	40	42.5		Polyacrylonitrile	Cuprophane	Single use	Cross-over	-	3 mo	Dialysis tolerance
Simon 1993	54	-	50	-	-	Polyacrylonitrile	Cuprophane	-	Parallel	1.05 to 1.30	12 mo	Mortality or first hospitalisation

Table 2. Characteristics of included studies categorised according to type of high-flux membrane (Continued)

Fishbane 1997	30	54 to 55	56	10017.4 to 18.0	Polyacrylonitrile	Polysulfone	-	Parallel	-	2 mo	Advanced glycation end product (AGE) peptide clearance
Ottosson 2001	42	69 (39 to 85)	57	- 18 (3 to 107)	Polyacrylonitrile	Cellulose diacetate	Single use	Parallel	-	3 mo	Lipids
Polysulphone or polyacrylonitrile											
Brown 1989	18	55 ± 10	77.7	- 151.2 ± 36	Polyacrylonitrile or polysulfone	Cuprophane	-	Parallel	-	6 mo	Dialysis arthropathy, beta-2 microglobulin and C-reactive protein
Gardinali 1994	36	27 to 72	63.9	0† 77 ± 69	Polyacrylonitrile or polysulfone	Cuprophane	-	Cross-over	-	3 mo	Anaphylotoxins
Polyamide											
Skroeder 1993	20	59 ± 13	80	0† -	Polyamide	Hemophane or cuprophane	Reuse	Cross-over	-	18 to 24 sessions	Beta-2 microglobulin clearance
Li 2010	46	57 to 60	38	16.01.2 to 98.4	Polyamide	Polyamide	Reuse	Cross-over	1.48 to 1.51	6 mo	Inflammatory response

Data are mean ± SD, mean (range) or proportion. Where baseline values were not reported for the entire cohort but for separate subgroups (e.g., high-flux or low-flux groups) the mean value for each treatment group is provided.

†Patients with diabetes mellitus were excluded.

Table 3. Dialysis prescription details in the included studies

Study	High-flux haemodialysis	Low-flux haemodialysis
Acchiardo 1989	Polysulphone membranes (F60 or F80). Blood flow rate 469 ± 3 mL/min, dialysate flow rate 800 mL/min, time 126.9 ± 10 min, Kt/V 1.01 ± 0.1	Cellulosic membranes (C-DAK: 90 SCE or 135 SCE). Blood flow rate 297 ± 10 mL/min, dialysate flow rate 500 mL/min, time 193.2 ± 39 minutes, Kt/V 1.05 ± 0.1
Brown 1989	Polyacrylonitrile or polysulfone	Cuprophane
Mohini 1989	Polysulfone membrane (Kd-urea 277 ± 13 mL/min, dialysis times 133 ± 4.8 min)	Cellulose membrane (Kd-urea 186 ± 8 mL/min, dialysis time 170 ± 7.8 min)
Sawaya 1989	Polysulfone	Cellulose ester
Churchill 1993	Cellulose acetate sterilised with ethylene oxide. Dialysate glucose-bicarbonate. Kt/V urea ≥ 1.0 . Dialyzer Duoflux High Performance Artificial Kidney. Beta-2 microglobulin clearance 11.4 mL/min. In vivo ultrafiltration rate 15 mL/h/mm Hg. Dialysis delivery system Cobe Centry 2000 Rx retrofitted to accommodate higher ultrafiltration requirements	Cellulose acetate sterilised with ethylene oxide. Dialysate glucose-bicarbonate. Kt/V urea ≥ 1.0 . Dialyzer CD3500 or CD4000. Beta-2 microglobulin clearance 0 mL/min. In vitro ultrafiltration rate 3.5 to 5.0 mL/h/mm Hg. Dialysis delivery system Cobe Centry 2000 Rx
Collins 1993	Non-cellulosic AN69 membrane (Hospal F16 hollow fibre). Dialyzer CGH Medical, Lakewood, CO. Surface area 1.55 m^2 . C_{urea} 269 mL/min, ultrafiltration coefficient 44 mL/h/mm Hg. Blood flow 400 mL/min, dialysis flow 500 mL/min. Volumetrically controlled machines (Fresenius 2008D)	Cuprophane membrane (Gambro 6N plate). Dialyzer CGH Medical, Lakewood, CO. Surface area 1.6 m^2 . C_{urea} 272 mL/min, ultrafiltration coefficient 8 mL/h/mm Hg. Blood flow 400 mL/min, dialysis flow 500 mL/min. Volumetrically controlled machines (Fresenius 2008D)
Simon 1993	AN69 membrane	Cuprophane
Skroeder 1993	Polyamine (Polyflux, area 1.0 or 1.6 m^2). Volume monitored bicarbonate haemodialysis 2 to 4 hours. Ethylene oxide sterilisation. Dialysate flow 500 mL/min. Blood flow 200 mL/min for 4 hours or 400 mL/min for 2 hours. Sterilised with ethylene oxide	Cuprophane (GF 120 H, area 1.2 or 2 m^2), hemophane (GF 120 Plus, area 1.2 or 2 m^2). Volume monitored bicarbonate haemodialysis 2 to 4 hours. Ethylene oxide sterilisation. Dialysate flow 500 mL/min. Blood flow 200 mL/min for 4 hours or 400 mL/min for 2 hours. Sterilised with ethylene oxide
Gardinali 1994	Polysulphone or polyacrylonitrile	Cuprophane
Blankestijn 1995	Polysulphone. Bicarbonate dialysate containing 11 mmol/L glucose. Time 11 ± 1.4 h/wk	Cuprophane. Bicarbonate dialysate containing 11 mmol/L glucose. Time 11 ± 1.4 h/wk
Rizvi 1995	Polysulphone (Fresenius). Ultrafiltration rate 15 mL/h/mm Hg. Time 2 hours/session. Acetate dialysis	Polysulphone (Fresenius). Ultrafiltration rate 4.0 mL/h/mm Hg. Time 4 hours/session. Acetate dialysis
Goldberg 1996	Polysulphone F80 (Fresenius)	Cellulose acetate (Terumo 220)
Kuchle 1996	Polysulphone F60 surface area 1.2 m^2 3 times/wk for 4 to 5 hours, MTS A 2008 C delivery system (Fresenius), dialysate flow rate 500 mL/min, blood flow rates 200 to 250 mL/min, acetate and bicarbonate dialysate	Cuprophane membrane, surface areas 1.0 to 1.2 m^2 (Hospal Germany), 3 times/wk for 4 to 5 hours, MTS A 2008 C delivery system (Fresenius), dialysate flow rate 500 mL/min, blood flow rates 200 to 250 mL/min, acetate and bicarbonate dialysate

Table 3. Dialysis prescription details in the included studies (Continued)

Locatelli 1996	Polysulfone, bicarbonate dialysate, Kt/V ≥ 1	Polysulfone or cuprophane, bicarbonate dialysate, Kt/V ≥ 1
Fishbane 1997	AN69 Fitral 16 dialyser	Polysulphone F8 dialyser
Hartmann 1997	Polysulphone F60 hollow fibre 1.25 m ² surface area, 3 times/wk for 4 to 5 hours (MTS 2008 C delivery system, blood pump speed 200 to 250 mL/min and the dialysate flow rate 500 mL/min, bicarbonate dialysate. Ultrafiltration coefficient 40 mL/h/mm Hg	CA-130 cellulose acetate hollow fibre 1.3 m ² surface area, 3 times/wk for 4 to 5 hours (MTS 2008 C delivery system, blood pump speed 200 to 250 mL/min and the dialysate flow rate 500 mL/min, bicarbonate dialysate. Ultrafiltration coefficient 5.6 mL/h/mm Hg
House 1999	Polysulphone. Prescription defined by nephrologist. Bicarbonate dialysate	Polysulphone. Prescription defined by nephrologist. Bicarbonate dialysate
Locatelli 2000	BK-F polymethyl methacrylate (PMMA)	Cellulose
Jeloka 2001	Polysulphone	Cuprophane
Lang 2001	Polysulphone F 60 hollow fibre, ultrafiltration coefficient 40 mL/mm Hg/h, surface area 1.3 m ² , urea clearance 185 mL/min at a blood flow rate of 200 mL/min, dialysis 3 times/ wk for 4 to 5 hours (MTS 4008 delivery system). Blood pump speed 200 to 280 mL/min and dialysate flow rate 500 mL/min	Disscap 160 E, ultrafiltration coefficient 6.25 mL/mm Hg/h, surface area 1.22 m ² , urea clearance 189 mL/min at a blood flow rate of 200 mL/min, dialysis 3 times/wk for 4 to 5 hours (MTS 4008 delivery system). Blood pump speed 200 to 280 mL/min and dialysate flow rate 500 mL/min
Ottosson 2001	Polyacrylonitrile AN69 membrane, surface area 1.65 m ² and urea clearance 190 mL/min. Prescribed blood flow set at 200 to 300 mL/min and dialysate flow set at 500 mL/min	Cellulose diacetate FB170T, surface area 1.7 m ² , urea clearance 190 mL/min. Prescribed blood flow set at 200 to 300 mL/min and dialysate flow set at 500 mL/min
Krieter 2002	Polyethersulfone DIAPES HF800 (1.4 m ²), Arylane H4 (1.35 m ²)	Hemophan (1.3 m ²)
HEMO 2002	Most commonly Fresenius F80 (43% of sessions) and Baxter CT190 (used in 48%). Reprocessing methods included Renalin without bleach, formaldehyde or glutaraldehyde, with bleach, or heated citric acid. Two-by-two factorial design target equilibrated Kt/V achieved by manipulating duration of treatment session. Ultrafiltration coefficient > 14 mL/mm Hg/h, mean beta-2 microglobulin clearance > 20 mL/min	Most commonly Fresenius F8 (46% of sessions) and Baxter CA210 (used in 43%). Reprocessing methods included Renalin without bleach, formaldehyde or glutaraldehyde, with bleach, or heated citric acid. Two-by-two factorial design target equilibrated Kt/V achieved by manipulating duration of treatment session. Ultrafiltration coefficient < 10 mL/mm Hg/h
Opatrny 2002	Steam sterilised F60S dialyser with surface area 1.3 m ² and urea clearance 185 mL/min. Blood flow rates 200 to 350 mL/min. Dialysate flow 500 mL/min. Dialysis 3 times/wk	Steam sterilised F7HPS dialyser with surface area 1.6 m ² and urea clearance 186 mL/min. Blood flow rates 200 to 350 mL/min. Dialysate flow 500 mL/min. Dialysis 3 times/wk
De Vriese 2003	Triacetate (FB-150U), surface area 1.5 m ² , ultrafiltration coefficient 29.8 mL/mm Hg/h, sieving coefficient beta-2 microglobulin 0.88. Treatment duration, blood flow, dialysate flow and ultrafiltration determined by attending nephrologist	Triacetate (Sureflux-150 L), surface area 1.5 m ² , ultrafiltration coefficient 12.8 mL/mm Hg/h, sieving coefficient beta-2 microglobulin 0.36. Treatment duration, blood flow, dialysate flow and ultrafiltration determined by attending nephrologist

Table 3. Dialysis prescription details in the included studies (Continued)

Klemm 2004	FX 60, Helixone, surface area 1.4 m ² , 3 times/wk for 4 to 5.5 hours, blood flow rate 500 mL/min, dialysate flow rate 500 mL/min, ultrafilter U 8000S	F 6 HPS polysulfone, surface area 1.3 m ² , 3 times/wk for 4 to 5.5 hours, blood flow rate 500 mL/min, dialysate flow rate 500 mL/min, ultrafilter U 8000S
Ayli 2005	Polysulphone F60 for 4 hours, 3 times/wk, blood flow 300 mL/min, dialysate flow rate 500 mL/min	Polysulphone F6 HPS for 4 hours, 3 times/wk, blood flow 300 mL/min, dialysate flow rate 500 mL/min
Takasawa 2005	Polysulfone (APS-E) membrane	Polysulfone (F7HPS) membrane
Bordoni 2006	Polysulphone and cellulose triacetate	Polysulphone and cellulose triacetate
Li 2007a	F60 polysulphone dialyser, ultrafiltration coefficient 40 mL/mm Hg/h, Fresenius 4008S capacity-controlled dialyser and bicarbonate dialysate for 4 hours, 3 times/wk, dialysate flow 500 mL/min, blood flow 190 to 250 mL/min	F6 polysulphone dialyser, ultrafiltration coefficient 5.5 mL/mm Hg/h, Fresenius 4008S capacity-controlled dialyser and bicarbonate dialysate for 4 hours 3 times/wk, dialysate flow 500 mL/min, blood flow 190 to 250 mL/min
Chu 2006	FX80 helixone, ultrafiltration coefficient 59 mL/mm Hg/h, inline steam sterilisation, surface area 1.8 m ² , minimum blood flow rate 250 mL/min and dialysate flow rate 500 mL/min	F8 HPS polysulphone, ultrafiltration coefficient 18 mL/mm Hg/h, inline steam sterilisation, surface area 1.8 m ² , minimum blood flow rate 250 mL/min and dialysate flow rate 500 mL/min
INFLUX 2008	Polyflux H membrane	Polyflux L membrane
MPO 2009	Synthetic (99%) or substituted cellulose membranes. Haemodialysis 3 times/wk with bicarbonate haemodialysis for a minimum treatment time of 180 minutes and a minimum spKt/V of 1.2. Treatment parameters (treatment time, blood flow rate, dialysis fluid flow rate, and dialyser surface area) were adjusted locally by the investigator to reach the spKt/V target	Synthetic (75%), substituted cellulose (22%) or unsubstituted cellulose membranes. Haemodialysis 3 times/wk with bicarbonate haemodialysis for a minimum treatment time of 180 minutes and a minimum spKt/V of 1.2. Treatment parameters (treatment time, blood flow rate, dialysis fluid flow rate, and dialyzer surface area) were adjusted locally by the investigator to reach the spKt/V target
Li 2010	High-flux polyamide membrane (Polyflux 14S) made of Polyamide S, surface area 1.4 m ² . Ultrafiltration coefficient 62 mL/h/mm Hg and vitamin B ₁₂ clearance 125 mL/min. Sterilised using Puristeril 340. All individuals underwent their usual prescriptions (blood flow, dialysate flow, dialysis treatment time, anticoagulation type, and dosage). Sieving coefficient for beta-2 microglobulin > 0.6 and ultrafiltration coefficient ≥ 20 mL/mm Hg/h	High-flux polyamide membrane (Polyflux 6L) made of Polyamide S, surface area 1.4 m ² . Ultrafiltration coefficient 8.6 mL/h/mm Hg and vitamin B ₁₂ clearance 85 mL/min. Sterilised using Puristeril 340. All individuals underwent their usual prescriptions (blood flow, dialysate flow, dialysis treatment time, anticoagulation type, and dosage). Sieving coefficient for beta-2 microglobulin > 0 and ultrafiltration coefficient ≤ 10 mL/mm Hg/h

Table 4. Summary of reported quality of life outcomes

Study	Quality of life instrument	Time of assessment	Method of reporting	Domains reported	Comments
Churchill 1993	1. TTO index 2. HQL 3. SIP	During the final 2 weeks of each treatment period	Compared scores for individual domains at be-	1. TTO 2. SIP: physical; psychological; total 3. HQL intradialytic symptoms (fatigue, washed out, thirst, bore-	1. TTO – no statistical difference 2. SIP – no statistical difference

Table 4. Summary of reported quality of life outcomes (Continued)

		(total 4 months treatment). If an acute event occurred, measurement was delayed until after 1 month of clinical stability	ginning and end of treatment	dom, pruritus, muscle cramps, back pain, dizziness, hypotension, muscle twitching, headache, nausea, irritability, chest pain)	3. HQL – intradialytic – dizziness, nausea and chest pain statistically better with high-flux dialysis (not statistically difference at the $P < 0.01$ level) 4. HQL – interdialytic – no statistical difference between groups
HEMO 2002	1. IWB 2. KDQOL-LF 3. SF-36	At baseline, and yearly at 1, 2, and 3 years of follow-up	Mean change in scores compared with baseline. Mean differences between high- and low-flux groups adjusted for baseline co-variables	IWB, physical functioning, role (physical), bodily pain, general health, vitality, social functioning, role (emotional), mental health, physical component summary score, mental component score, symptom/problem (effects, burden, cognitive function, sleep, social support, staff encouragement, patient satisfaction)	High-flux membranes were not associated with statistically significant differences in health-related quality of life

HQL, Haemodialysis Quality of Life questionnaire; IWB, Index of Well-Being; KDQOL-LF, Kidney Disease Quality of Life-Long Form; SF-36, Short Form-36 Health Survey; SIP, Sickness Impact Profile; TTO, time trade-off

Table 5. Adverse events

Study	Adverse events reported in studies
Acchiardo 1989	Hypertension, seizures, and clotted vascular access
Brown 1989	Not reported
Mohini 1989	“Adverse reactions were not greater with high flux dialysis”
Sawaya 1989	Not reported
Churchill 1993	Reported in quality of life analyses
Collins 1993	Hypotensive events, saline administration, emesis, cramping, symptom index reported. Cramping increased in high-flux group ($P < 0.05$). No significant differences in the occurrence of hospital admissions, infections, and graft thrombosis between groups
Simon 1993	Not reported
Skroeder 1993	Not reported
Cardinali 1994	Not reported
Blankestijn 1995	Not reported

Table 5. Adverse events *(Continued)*

Rizvi 1995	No statistically significant difference was observed as regards to frequency of complications and intradialytic symptoms during both therapies
Goldberg 1996	Not reported
Kuchle 1996	Not reported other than complications of dialysis-related arthropathy
Locatelli 1996	Drop-outs due to technical reasons, acute clinical reason, fistula-related, treatment inadequacy, transplant, death, and dialysis sessions with hypotension reported
Fishbane 1997	Not reported
Hartmann 1997	Hospitalisation and hypotensive episodes
House 1999	Reaction to dialysis membrane spontaneous rupture of oesophagus
Locatelli 2000	No major side-effects. No differences in blood pressure values during follow-up
Jeloka 2001	Arthritis-like symptoms on direct questioning
Lang 2001	Hypotension
Ottosson 2001	Not reported
Krieter 2002	Not reported
HEMO 2002	Not reported
Opatrny 2002	Not reported
De Vriese 2003	Not reported
Klemm 2004	Not reported
Ayli 2005	Not reported
Takasawa 2005	Not reported
Li 2007a	Unclear
Chu 2006	Not reported
INFLUX 2008	Not reported
MPO 2009	Not reported
Li 2010	Vascular access failure, myocardial infarction, intracranial haemorrhage

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	<ol style="list-style-type: none"> 1. MeSH descriptor Renal Dialysis explode all trees 2. MeSH descriptor Hemofiltration explode all trees 3. MeSH descriptor Kidney Failure, Chronic, this term only 4. (dialysis*):ti,ab,kw in Clinical Trials 5. (hemodialysis or haemodialysis):ti,ab,kw in Clinical Trials 6. (hemofiltration or haemofiltration):ti,ab,kw in Clinical Trials 7. (hemodiafiltration or haemodiafiltration):ti,ab,kw in Clinical Trials 8. (CAPD or CCPD or APD):ti,ab,kw in Clinical Trials 9. ("end-stage kidney" or "end-stage renal" or "endstage kidney" or "endstage renal"):ti,ab,kw in Clinical Trials 10.(ESKD or ESKF or ESRD or ESRF):ti,ab,kw in Clinical Trials 11.(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10) 12.MeSH descriptor Membranes, Artificial explode all trees 13.MeSH descriptor Kidney, Artificial, this term only 14.(high flux*):ti,ab,kw or (high-flux*):ti,ab,kw in Clinical Trials 15.(low flux*):ti,ab,kw or (low-flux*):ti,ab,kw in Clinical Trials 16.(membrane*):ti,ab,kw in Clinical Trials 17.(12 OR 13 OR 14 OR 15 OR 16) 18.(11 AND 17)
MEDLINE	<ol style="list-style-type: none"> 1. exp Renal Dialysis/ 2. exp Hemofiltration/ 3. Kidney Failure, Chronic/ 4. dialysis.tw. 5. (hemodialysis or haemodialysis).tw. 6. (hemofiltration or haemofiltration).tw. 7. (hemodiafiltration or haemodiafiltration).tw. 8. (CAPD or CCPD or APD).tw. 9. (end-stage kidney or end-stage renal or endstage kidney or endstage renal).tw. 10.(ESKD or ESKF or ESRD or ESRF).tw. 11.or/1-10 12.exp Membranes, Artificial/ 13.Kidney, Artificial/ 14.high-flux\$.tw. 15.low-flux\$.tw. 16.membrane\$.tw. 17.or/12-16 18.and/11,17
EMBASE	<ol style="list-style-type: none"> 1. exp Renal Replacement Therapy/ 2. (hemodialysis or haemodialysis).tw. 3. (hemofiltration or haemofiltration).tw. 4. (hemodiafiltration or haemodiafiltration).tw. 5. dialysis.tw. 6. (CAPD or CCPD or APD).tw. 7. Chronic Kidney Disease/ 8. Kidney Failure/ 9. Chronic Kidney Failure/ 10.(end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 11.(ESRF or ESKF or ESRD or ESKD).tw.

(Continued)

- 12.or/1-11
- 13.dialysis membrane/
- 14.artificial kidney/
- 15.(high flux\$ and (dialysis\$ or membrane\$)).tw.
- 16.(low flux\$ and (dialysis\$ or membrane\$)).tw.
- 17.or/13-16
- 18.and/12,17

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	<i>Low risk of bias:</i> 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). <i>High risk of bias:</i> 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. <i>Unclear:</i> 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	<i>Low risk of bias:</i> 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). <i>High risk of bias:</i> 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. <i>Unclear:</i> 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	<i>Low risk of bias:</i> 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. <i>High risk of bias:</i> 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. <i>Unclear:</i> Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	<i>Low risk of bias:</i> 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. <i>High risk of bias:</i> 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.

(Continued)

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.

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
20 January 2016	Amended	Amended study name House 2000 to House 1999

CONTRIBUTIONS OF AUTHORS

- KSR and SCP screened search results.
- GFMS and SCP advised about the review methodology.
- KSR and SCP assessed the risks of bias in the included studies and extracted data.
- PR gave advice on outcome measures, study inclusion criteria and will help with resolving differences in study inclusion and data extraction.
- SCP wrote the review.
- GFMS, PR, FL reviewed and approved the review.

DECLARATIONS OF INTEREST

- KSR received funding from the National Kidney Research Fund (UK) to conduct this systematic review.
- GFMS is the scientific director for Diaverum, a global provider of renal services
- SCP receives an unrestricted fellowship from the Consorzio Mario Negri Sud, provided by Amgen Dompe.
- FL was principal investigator of the MPO trial supported by an unrestricted grant by Fresenius Medical Care; has received lecture fees from Bellco, Fresenius Medical Care, and Gambro-Hospal.

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Internal sources

- No sources of support supplied

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- National Kidney Research Fund, UK.
- Consorzio Mario Negri Sud unrestricted grant from Amgen Dompe, Italy.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk of bias assessment tool has replaced the quality checklist.

INDEX TERMS

Medical Subject Headings (MeSH)

*Membranes, Artificial; Cardiovascular Diseases [mortality]; Kidney Failure, Chronic [mortality] [*therapy]; Randomized Controlled Trials as Topic; Renal Dialysis [*methods] [mortality]

MeSH check words

Humans