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Dialysate temperature reduction for intradialytic hypotension for people with chronic kidney disease requiring haemodialysis (Review)

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[Intervention Review]

Dialysate temperature reduction for intradialytic hypotension for people with chronic kidney disease requiring haemodialysis

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ABSTRACT

Background

Intradialytic hypotension (IDH) is a common complication of haemodialysis (HD), and a risk factor of cardiovascular morbidity and death. Several clinical studies suggested that reduction of dialysate temperature, such as fixed reduction of dialysate temperature or isothermal dialysate using a biofeedback system, might improve the IDH rate.

Objectives

This review aimed to evaluate the benefits and harms of dialysate temperature reduction for IDH among patients with chronic kidney disease requiring HD, compared with standard dialysate temperature.

Search methods

We searched Cochrane Kidney and Transplant's Specialised Register up to 14 May 2019 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal, and ClinicalTrials.gov.

Selection criteria

All randomised controlled trials (RCTs), cross-over RCTs, cluster RCTs and quasi-RCTs were included in the review.

Data collection and analysis

Two authors independently extracted information including participants, interventions, outcomes, methods of the study, and risks of bias. We used a random-effects model to perform quantitative synthesis of the evidence. We assessed the risks of bias for each study using the Cochrane 'Risk of bias' tool. We assessed the certainty of evidence using Grades of Recommendation, Assessment, Development and Evaluation (GRADE).

Main results

We included 25 studies (712 participants). Three studies were parallel RCTs and the others were cross-over RCTs. Nineteen studies compared fixed reduction of dialysate temperature (below 36°C) and standard dialysate temperature (37°C to 37.5°C). Most studies were of

unclear or high risk of bias. Compared with standard dialysate, it is uncertain whether fixed reduction of dialysate temperature improves IDH rate (8 studies, 153 participants: rate ratio 0.52, 95% CI 0.34 to 0.80; very low certainty evidence); however, it might increase the discomfort rate compared with standard dialysate (4 studies, 161 participants: rate ratio 8.31, 95% CI 1.86 to 37.12; very low certainty evidence). There were no reported dropouts due to adverse events. No study reported death, acute coronary syndrome or stroke.

Three studies compared isothermal dialysate and thermoneutral dialysate. Isothermal dialysate might improve the IDH rate compared with thermoneutral dialysate (2 studies, 133 participants: rate ratio 0.68, 95% CI 0.60 to 0.76; I^2 = 0%; very low certainty evidence). There were no reports of discomfort rate (1 study) or dropouts due to adverse events (2 studies). No study reported death, acute coronary syndrome or stroke.

Authors' conclusions

Reduction of dialysate temperature may prevent IDH, but the conclusion is uncertain. Larger studies that measure important outcomes for HD patients are required to assess the effect of reduction of dialysate temperature. Six ongoing studies may provide much-needed high quality evidence in the future.

PLAIN LANGUAGE SUMMARY

Dialysate temperature reduction for intradialytic hypotension for people with chronic kidney disease requiring haemodialysis

What is the issue?

An increasing number of patients with chronic kidney disease need haemodialysis (HD). When the kidneys are not able to remove enough waste from the blood, HD is used to clean the blood and to remove the excess water via a dialysis machine. Intradialytic hypotension (IDH) is a common complication of HD that is characterized by a sudden drop in blood pressure (BP) with hypotensive symptoms such as dizziness, weakness, nausea, and fatigue, and is a risk factor of cardiovascular morbidity and mortality. In general, a decrease in body temperature is associated with contraction of vessels, and an increase in BP. However, the widely used dialysate temperature is 37°C, and the body temperature is likely to increase during standard dialysis. Removal of heat with cool dialysate might be beneficial to haemodynamic stability. Additionally, fixed empirical reduction of dialysate temperature is simple and easy to adopt in daily practice, however it can increase patient discomfort such as cold sensations, shivering, and related symptoms.

What did we do?

We collected all data from studies of patients with CKD requiring HD that reported data on IDH, discomfort rate and other important outcomes. We included 25 studies comprising 712 participants in the review, and performed meta-analysis to estimate the effect of cooling dialysate.

What did we find?

The quality of included studies was generally very low due to the risk of bias, small sample size, and a lack of information.

We found very low quality evidence that fixed reduction of dialysate temperature decreased the incidence of IDH compared with standard dialysate and increased the discomfort rate. When patient discomfort is minimal, reduction of the dialysate temperature may be an option to reduce IDH. However, no study reported the long-term outcomes such as death or heart disorders.

Conclusions

There is limited data suggesting that the reduction of dialysate temperature may prevent IDH, but the conclusion is very uncertain. Larger studies that measure important outcomes such as IDH or mortality for HD patients are required to assess the effect of reducing dialysate temperature.

Summary of findings for the main comparison. Fixed reduction of dialysate temperature compared to standard dialysate temperature for patients requiring haemodialysis

Fixed reduction of dialysate temperature compared to standard dialysate temperature for patients requiring haemodialysis

Patient or population: patients requiring haemodialysis
Setting: dialysis centre
Intervention: fixed reduction of dialysate temperature
Comparison: standard dialysate temperature

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with standard dialysate temperature	Risk with fixed reduction of dialysate temperature			
Intradialytic hypotension rate follow up: median 3 weeks	251 episodes per 1,000 person-dialysis session	131 episodes per 1,000 person-dialysis session (85 to 201)	RR 0.52 (0.34 to 0.80)	153 (8)	⊕⊖⊖⊖ VERY LOW [1,2]
Discomfort rate Follow up: median 4 weeks	25 episodes per 1,000 person-dialysis session	208 episodes per 1,000 person-dialysis session (47 to 928)	Rate ratio 8.31 (1.86 to 37.12)	81 (4)	⊕⊖⊖⊖ VERY LOW [1,2]
Dropout due to adverse events Follow up: median 3 weeks	Nine studies (268 participants) reported there were no dropouts due to adverse events		-	268 (9)	Not graded
Death (all causes)	No studies reported the outcome		-	-	-
Acute coronary syndrome	No studies reported the outcome		-	-	-
Stroke	No studies reported the outcome		-	-	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

RR: risk ratio; **CI:** Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded two levels due to serious risk of bias: all included studies were randomised cross-over studies and carry-over effects could be biased the result. Additionally, all studies were rated high or unclear risk of bias in at least four domains
[2] Downgraded one level due to serious imprecision: the total sample size included in the analysis were less than optimal information size

Summary of findings 2. Isothermal dialysate compared to thermoneutral dialysate in patients requiring haemodialysis

Isothermal dialysate compared to thermoneutral dialysate in patients requiring haemodialysis

Patient or population: patients requiring haemodialysis
Setting: dialysis centre
Intervention: isothermal dialysate
Comparison: thermoneutral dialysate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with thermoneutral dialysate	Risk with Isothermal dialysate			
Intradialytic hypotension rate follow up: range 3 to 8 weeks	410 episodes per 1,000 person-dialysis session	279 episodes per 1,000 person-dialysis session (246 to 312)	Rate ratio 0.68 (0.60 to 0.76)	133 (2)	⊕⊖⊖⊖ Very low [1 2]
Discomfort rate Follow up: mean 3 weeks	One study reported that none of the patients allocated to isothermal or thermoneutral dialysate experienced shivering		-	17 (1)	Not graded
Dropout due to adverse event follow up: range 3 to 8 weeks	There were no reported dropouts due to adverse events in the 2 studies		-	133 (2)	Not graded
Death (all causes)	No study reported the outcome		-	-	-
Acute coronary syndrome	No study reported the outcome		-	-	-
Stroke	No study reported the outcome		-	-	-

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
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BACKGROUND

Description of the condition

Chronic kidney disease (CKD) is a global concern. According to the 2010 Global Burden of Disease study, CKD was ranked 27th in the list of causes of total number of global deaths in 1990 (age-standardized annual death rate of 15.7 per 100,000), but rose to 18th in 2010 (annual death rate 16.3 per 100,000) (Lozano 2012). The number of end-stage kidney disease (ESKD) patients receiving renal replacement therapy (RRT) was more than 2 million in 2011, and increased approximately 8% annually (Couser 2011; White 2008). Haemodialysis (HD) is the main modality of RRT, with almost 90% of dialysis patients under maintenance HD (Jain 2012). Patients with maintenance HD gain weight because of their inability to excrete urine. The excess water is removed by ultrafiltration during HD.

Intradialytic hypotension (IDH) is a common complication of HD. There is no consensus on the definition of IDH, but IDH is commonly defined as a drop in blood pressure during dialysis procedure and/or hypotensive symptoms such as dizziness, weakness, nausea, cramps, blurred vision, and fatigue (Assimon 2017; K/DOQI 2005; Santoro 2002). The pathophysiology of IDH is diverse. It could be the result of an inadequate cardiovascular response to the reduction in blood volume that occurs when the ultrafiltration volume is large (Leypoldt 2002). One process may involve an imbalance between a reduced effective circulating volume and the compensatory plasma refilling mechanism, wherein fluid from the interstitial and intracellular space is translocated into the intravascular compartment (Nesrallah 2013). Additionally, IDH can also be induced by several vasoactive substances such as adenosine or nitric oxide, which may be synthesized or released during dialysis (Sulowicz 2006). Recent studies have shown that haemodynamic instability is associated with impaired baroreflex sensitivity; a decrease in asymmetric dimethylarginine (ADMA), a naturally occurring nitric oxide synthase inhibitor, and inadequate vasopressin response (Chesterton 2010; Csiky 2008; Dubin 2011; Thompson 2009). Another study using echocardiography suggests that a blood pressure (BP) drop within a HD session is associated with HD-induced myocardial stunning (Burton 2009). Repeated decreases in organ perfusion due to IDH can introduce chronic organ injury over time (Nesrallah 2013). Moreover, several studies have shown an association between IDH and cardiovascular morbidity and mortality (Burton 2009; Sands 2014; Shoji 2004; Stefansson 2014; Tisler 2003). IDH is also associated with vascular access thrombosis, dysrhythmias, and mesenteric venous infarction (K/DOQI 2005). Risk factors associated with IDH include old age, female gender, Hispanic ethnicity, long dialysis vintage, high intradialytic weight gain, high dialysis dose, anaemia, diabetes, low predialysis BP, high osmolarity, and high body mass index (Mc Causland 2013; Mc Causland 2015; Sands 2014; Stefansson 2014; K/DOQI 2005).

Description of the intervention

Dialysate is heated by heating elements in the HD machine as the blood temperature decreases through an extracorporeal circuit. The widely used dialysate temperature is 37°C (Daugirdas 2007; K/DOQI 2005; Toth-Manikowski 2016). The body temperature is likely to increase during standard dialysis with the dialysate temperature of 37°C (Rosales 2000). The dialysis procedure itself affects body temperature regulation. There have been several clinical studies that investigated the effect of reduction of dialysate temperature for haemodynamic stability (Jost 1993; Maggiore 2002; van der Sande 2009; Zitt 2008). A simple intervention for lowering blood temperature is fixed empirical reduction of dialysate temperature. Alternative interventions are implemented by monitoring blood temperature (core temperature) in the arterial and venous bloodline (Selby 2006). This biofeedback system can adjust the dialysate temperature in response to the calculated body temperature and enable the implementation of isothermic dialysis, in which arterial temperature remains unchanged from the patient's baseline level (van der Sande 2009). In contrast, lower dialysate temperature may cause high frequency of discomfort, a cold sensation, or shivering (K/DOQI 2005).

How the intervention might work

Peripheral and cutaneous vasoconstriction is considered an important component for the ultrafiltration-induced decrease in blood volume (Schneditz 2003). HD patients tend to be hypovolaemic as ultrafiltration progresses during HD (Bos 2000; Leypoldt 2002). Hypovolaemia causes underfilling in the cardiac chambers, then cardiovascular response increases the arteriolar or venous tone. However, patients with impaired cardiovascular response cannot offset the volume reduction, and suffer a drop in BP (Santoro 2002). In general, a decrease in body temperature is associated with a decrease in blood flow to the compliant cutaneous circulation, an increase in total peripheral resistance, and an increase in BP (Schneditz 2003). One study reported that left ventricular contractility increased during cool dialysis (Levy 1992), while another observed that SBP was higher in the cool dialysate group but core temperature remained stable during dialysis (van der Sande 1999). Removal of heat with cool dialysate might activate autoregulatory mechanisms to preserve core temperature, which results in beneficial haemodynamic stability. In addition, a recent study showed the protective effect of cooling dialysate on dialysis-induced ischaemic brain injury (Eldehni 2015).

Why it is important to do this review

IDH remains an issue for chronic HD patients. The frequency of IDH was reported as 20% to 30% among patients undertaking HD (Davenport 2008a; Davenport 2008b). In addition, the incidence of IDH is likely to rise because an increasing number of older patients are expected to develop ESKD (K/DOQI 2005). Since IDH could introduce clinically relevant complications such as mortality and cardiovascular morbidity, evaluation of easy, cost-effective, and safe interventions should be evaluated to address this problem. Reduction of dialysate temperature could be an easy intervention for preventing IDH. The intervention could also be applied to patients in various settings because standard dialysis consoles have a dialysate temperature regulator; therefore, it can be applied universally and reduce the need for nursing involvement (Eldehni 2015; Toth-Manikowski 2016). Further, no additional cost is needed to conduct fixed reduction of dialysate temperature. While there are various methods of reducing dialysate temperature, optimal temperature or methods of temperature reduction to prevent IDH remain uncertain (Maggiore 2002; Santoro 2002; Selby 2006; Toth-Manikowski 2016). A recent systematic review has reported the effect of cooling dialysis on IDH; however, the study has several limitations, including non-reporting of the risk of bias judgment, assessment of the carry-over effect for the cross-over studies (if there was IDH in the session before cross-over, the patients and medical staffs would try to prevent it in the session after cross-over), exclusion of comparisons between different types of cooling

methods, and exclusion of children and modalities other than HD (Mustafa 2016). To that end, we conducted a systematic review of the effects and harms of reduction of dialysate temperature.

OBJECTIVES

This review aimed to evaluate the benefits and harms of dialysate temperature reduction for IDH among patients with CKD requiring HD, compared with standard dialysate temperature. In addition, we compared the benefits and harms of different types of dialysate temperature reduction for IDH.

METHODS

Criteria for considering studies for this review

Types of studies

We included all published, unpublished and ongoing randomised controlled trials (RCTs) to compare the reduction of dialysate temperature and normal temperature for IDH in HD patients.

Cluster RCTs were eligible if the number of clusters or the average size of each cluster, the outcome data regardless of cluster design for the total number of individuals, and an estimate of intracluster (or intraclass) correlation coefficient (ICC) were available.

We included data from cross-over RCTs.

We included quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) but excluded observational studies. No language restriction was applied.

Types of participants

Inclusion criteria

All patients undergoing maintenance HD, haemofiltration (HF) and haemodiafiltration (HDF) with minimum dialysis vintage of three months.

Exclusion criteria

- Patients on peritoneal dialysis
- Patients undergoing continuous RRT
- Patients undergoing sustained low-efficiency dialysis (SLED)
- Patients undergoing home HD.

Types of interventions

The experimental conditions were any methods of reduction of dialysate temperature. We considered the following comparisons.

1. Fixed reduction of dialysate temperature (below 36°C) versus standard dialysate temperature (37°C to 37.5°C)
2. Reduction of core temperature (below 36°C) using a biofeedback device versus standard dialysate temperature (37°C to 37.5°C)
3. Isothermic dialysis defined as maintenance of core temperature using a biofeedback device versus standard dialysate temperature (37°C to 37.5°C)
4. Reduction of arterial temperature using a biofeedback device versus fixed reduction of dialysate temperature (below 36°C)
5. Isothermic dialysis defined as maintenance of artery temperature using a biofeedback device versus fixed reduction of dialysate temperature (below 36°C)
6. Reduction of arterial temperature using biofeedback device versus isothermic dialysis defined as maintenance of arterial temperature using a biofeedback device
7. Any other methods of reduction of dialysate temperature versus standard dialysate temperature (37°C to 37.5°C).

Types of outcome measures

Primary outcomes

1. IDH rate (the proportion of dialysis sessions with episodes of IDH during follow-up) was defined as follows.
   - Intradialytic decrease in systolic blood pressure (SBP) by 20 mmHg or more, or a decrease in mean arterial pressure (MAP) by 10 mmHg associated with symptoms that include abdominal discomfort, yawning, sighing, nausea, vomiting, muscle cramps, restlessness, dizziness, and anxiety (K/DOQI 2005).
   - Decrease in SBP by 20 mmHg or more, or in MAP by 10 mmHg or more, associated with a clinical event and the need for nursing intervention (Kooman 2007).
   - Drop in SBP to < 90 mmHg or an absolute value > 30 mmHg, associated with symptoms of hypotension and lack of response to the supine position, but necessitating resuscitation with intravenous normotonic or hypertonic fluid administration (Tisler 2003).
   - Decrease in SBP of at least 10 mmHg or a SBP of < 100 mmHg, with symptoms such as cramps, nausea, vomiting, and dizziness (Fortin 2010).
   - Drop in SBP < 90 mmHg or of at least 20 mmHg with accompanying clinical symptoms (Maheshwari 2015).
   - Hypotensive episode requiring either saline infusion, lowering of the ultrafiltration rate (UF) or reduction in blood flow during the HD session (Mc Causland 2013).
   - Intradialytic decrease in SBP by > 30 mmHg to a level of < 90 mmHg (Sands 2014).
   - 40 mmHg drop in SBP (Shoji 2004).
   - We also accepted criteria that was similar to the above.
2. Death (all causes)
3. Discomfort rate defined as a cold sensation, shivering, and related symptoms.

Secondary outcomes

1. Acute coronary syndrome: diagnosis based on electrocardiographic changes, elevation of enzymes or confirmed during post-mortem examination.
2. All strokes: sudden focal neurologic deficit caused by cerebrovascular thrombosis, and categorized as ischaemic, haemorrhagic, or unspecified.
3. Quality of life (QoL) measured by a validated scale system such as Kidney Disease Quality of Life (KDQoL), or Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Health Experience Questionnaire (CHEQ) (Hays 1994; Wu 2001).
4. Dropout rate due to adverse events.
5. Rate of vasoconstrictor use (defined as any use of vasoconstrictor per dialysis session).

6. Lowest SBP during dialysis. If the authors reported any BP measure other than the lowest SBP during dialysis, we extracted it according to the following hierarchy: i) the lowest mean BP (MBP) during dialysis; ii) SBP at the end of dialysis; iii) MBP at the end of dialysis; iv) mean SBP during dialysis, and v) mean MBP during dialysis.
7. Lowest body temperature (BT) during dialysis.
8. Urea clearance-based dialysis adequacy (Kt/V_{urea}).
9. Vascular thrombosis defined as an access that has clotted, without blood flow in patients with arteriovenous fistula or graft.
10. New onset dysrhythmias.
11. Mesenteric venous thrombosis.
12. Post-HD fatigue measured by a validated scale system such as the Fatigue Severity Scale (Krupp 1989).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register up to 14 May 2019 through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from the following sources.

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

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the Cochrane Kidney and Transplant website.

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

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable; however, studies and reviews that might include relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts and, if necessary, the full text of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management

Two authors carried out data extraction independently using a structured, pilot-tested Excel data extraction form. Any disagreements were resolved by discussion with a further author acting as an arbiter. The data extraction form included the following items.

- General information: title, authors, year of publication, trial registration number, language, and country.
- Study characteristics: design and setting.
- Participants: total number, number of each age, sex, and comorbidity.
- Interventions and comparisons: types of reduction of dialysate, duration, and co-intervention.
- Outcome: definition of outcomes, number of participants allocated, number of missing participants, number of events (dichotomous outcomes), standard deviation and mean (continuous outcomes).
- Risk of bias and publication status.

We translated any studies reported in non-English language journals before assessment. Where more than one publication of one study existed, we grouped reports together and used the publication with the most complete data in the analyses. Where relevant outcomes were only published in earlier versions, the authors used these data. The authors also highlighted any discrepancies between published versions.

Assessment of risk of bias in included studies

Two authors independently assessed the following items using the risk of bias assessment tool (Higgins 2011) (Appendix 2).

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

Measures of treatment effect

Dichotomous outcomes results were expressed as risk ratios (RR) with 95% confidence intervals (CI). For rate outcomes, results were expressed as rate ratios with 95% CI. In the case of zero events, we added 0.5 to each count according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Where continuous scales of measurement were used to assess the effects of treatment (BP, body temperature, and heart rate), we used the mean difference (MD).

If the studies included in a review included a mixture of change-from-baseline and final value scores, we used the MD method in RevMan according to Chapter 9.4.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Unit of analysis issues

Cluster randomised studies

For dichotomous data, we applied the design effect and calculated effective sample size and number of events using ICC and the average cluster size, as described in chapter 16.3.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

If the ICC was not reported, we used the ICC of similar studies as a substitute. For continuous data, only the sample size was reduced; means and standard deviation remained unchanged (Higgins 2011).

Randomised cross-over studies

In the protocol, we planned to consider only data from the first period.

However, there was no study that reported first period data, and we could not obtain the data from any included studies by contacting the authors. We therefore used paired data that were potentially affected by carry-over effects, and judged the risk of bias due to carry-over effects in the other bias domain.

For multiple-arm studies, we included all intervention groups that were relevant to the review.

Dealing with missing data

We requested any further information required from the original author by written correspondence (e.g. emailing or writing to corresponding authors) and included any relevant information obtained in this manner in the review. We carefully evaluated important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population, and investigated attrition rates, e.g. drop-outs, losses to follow-up and withdrawals. The authors also critically appraised issues of missing data and imputation methods (e.g. last-observation-carried-forward) (Higgins 2011).

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. Heterogeneity was then analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.10 used for statistical significance, and with the I^2 test (Higgins 2003). We interpreted the I^2 values as follows.

- 0% to 40%: might not be important
- 30% to 60%: moderate heterogeneity
- 50% to 90%: might represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a CI for I^2) (Higgins 2011).

Assessment of reporting biases

We assessed heterogeneity by visual inspection of the forest plot.

If the number of eligible studies was 10 or more, we planned to use Egger's test to assess the potential existence of reporting bias (Higgins 2011).

Data synthesis

Data were pooled using the random-effects model.

Subgroup analysis and investigation of heterogeneity

Where possible, we used subgroup analyses for primary outcomes to explore possible sources of heterogeneity. We treated a study as a subgroup with a covariate if more than 80% of the included participants in a study had a covariate. We tested the following subgroups.

- Age: children (< 18 years), adults (18 to 75 years), and elderly (≥ 75 years)
- Comorbid conditions: history of diabetes mellitus, acute coronary syndrome, IDH, and current use of antihypertensive drugs
- Dialysis vintage: < 10 years and ≥ 10 years
- Dialysis modality: HD, HF, HDF
- We performed the following subgroup analysis for IDH outcome:
  * IDH definition: IDH defined by symptoms or intervention for hypotensive episode (e.g. saline flush, or lowering of the UF), and IDH defined by SBP irrespective of symptoms or intervention

Sensitivity analysis

Where possible, we performed sensitivity analyses in order to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis restricted to studies with low risk of selection bias (i.e. adequate random sequence generation and random allocation)
- Repeating the analysis excluding any very long or large studies to establish how much they dominated the results
- Repeating the analysis using a fixed-effect model instead of random-effects model
- Repeating the analysis restricted to a study protocol that excludes co-interventions for IDH, such as mannitol, hypertonic saline, or vasoconstrictors.

'Summary of findings' tables

We presented the main results of the review in 'Summary of findings' tables. These tables presented key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The 'Summary of findings' tables also included an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008).

The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of

effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schunemann 2011b).

We presented the following outcomes in the 'Summary of findings' tables.

- Death (all causes)
- Acute coronary syndrome
- Stroke
- IDH rate
- Rate of dropout due to adverse events
- Discomfort rate.

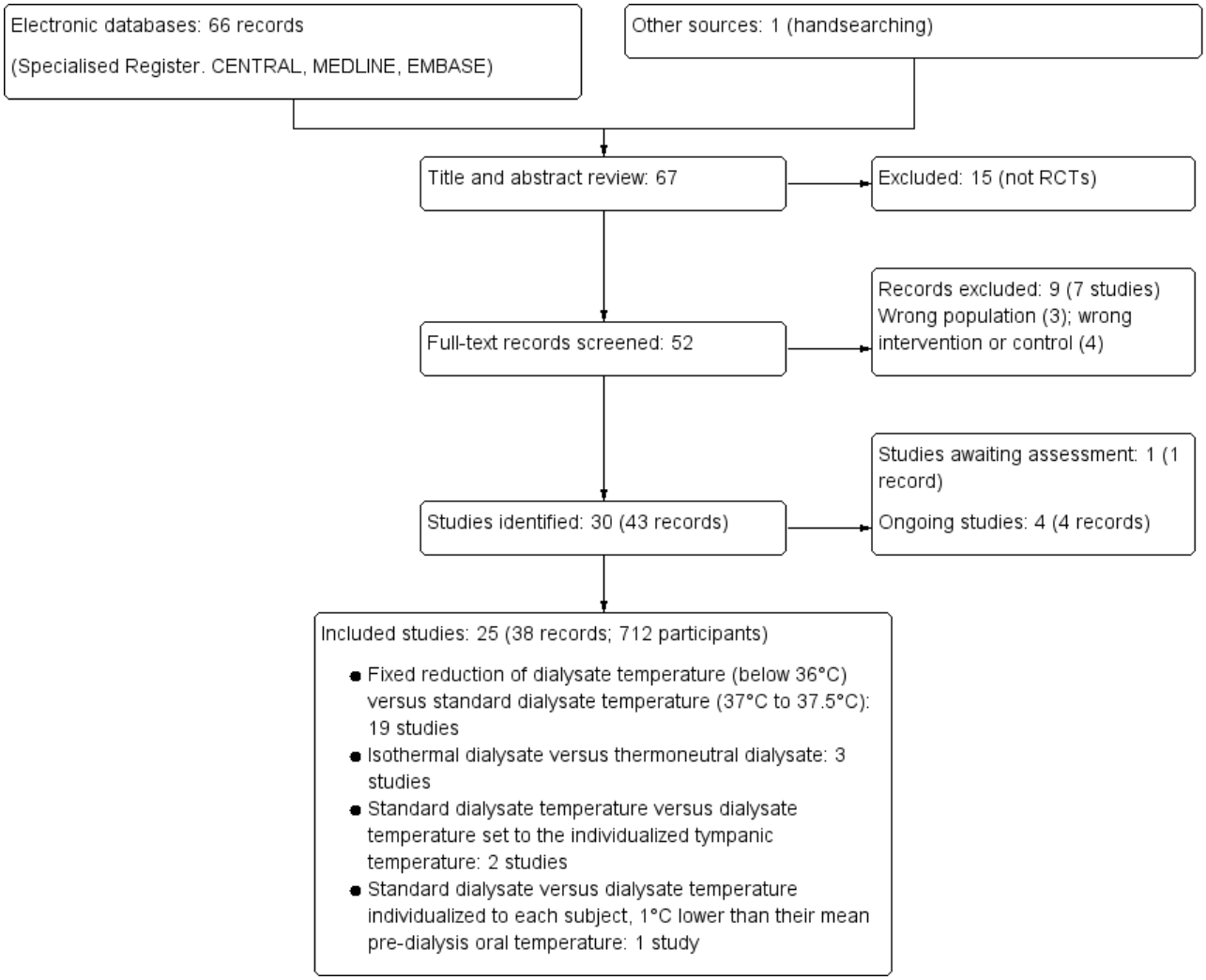
RESULTS

Description of studies

Results of the search

We identified 67 records. After screening titles and abstracts 52 records potentially met our inclusion criteria and after full-text review 25 studies (38 records) were included and 7 studies (9 records) were excluded. Four ongoing studies were identified (IRCT201306268140N2; IRCT2016060228219N1; Maheshwari 2015; MY TEMP 2017). One study (Kuhlmann 1996) was potentially eligible but has not been incorporated into the review due to a lack of information. These studies and will be assessed in a future update of this review (Figure 1).

Figure 1. Study flow diagram



Included studies

See Characteristics of included studies.

Study design

Three studies were parallel RCTs (Niyyar 2006; Odudu 2012; Rad 2017) and 22 were cross-over RCTs.

Sample size

Included studies were mainly small. Samples sizes ranged from 5 to 113 participants. Five studies included 50 or more participants (Ebrahimi 2017; Maggiore 2002; Odudu 2012; Rad 2017; Santoro 2002a).

Setting

Studies were mainly conducted in single centres. Twelve studies did not state the setting of participant recruitment (Beerenhout 2004; Gritters 2005; Manning 1995; Marants 2018; Niyyar 2006; Quereda 1988; Santoro 2002a; Selby 2006b; Shin 1994; Sterrett 1999; van der Sande 2009; Zitt 2008).

Participants

Different types of participants were included in different studies including stable, hypotension-prone, or those not taking α- or β-adrenergic blocking antihypertensive therapy. Eight studies did not report any eligibility criteria (Manning 1995; Marants 2018; Quereda 1988; Santoro 2002a; Sherman 1984; Sterrett 1999; van der Sande 2000; van der Sande 2001).

Interventions

Nineteen studies compared fixed reduction of dialysate temperature (below 36°C) and standard dialysate temperature (37°C to 37.5°C) (Ayoub 2004; Beerenhout 2004; Ebrahimi 2017; Gritters 2005; Jost 1993; Levy 1992; Manning 1995; Marants 2018; Odudu 2012; Parker 2007; Quereda 1988; Rad 2017; Sajadi 2016; Selby 2006b; Sherman 1984; Shin 1994; van der Sande 2000; van der Sande 2001; Zitt 2008). The differences in the prescribed dialysate temperature in the intervention and the control arms varied from 1°C to 2.2°C. Three studies used a biofeedback device and compared isothermal dialysate and thermoneutral dialysate (Maggiore 2002; Santoro 2002a; van der Sande 2009). In all studies, thermal balance was controlled by means of a Blood Temperature Monitor (BTM; Fresenius Medical Care, Bad Homberg, Germany). Of these, one study also compared reduction of arterial temperature using a biofeedback device, and isothermic dialysate and thermoneutral dialysate (van der Sande 2009). Two studies compared standard dialysate temperature and dialysate temperature set to the individualized tympanic temperature, measured by tympanic thermometer (Jefferies 2011; Sterrett 1999). One study compared standard dialysate and dialysate temperature individualized to each subject, 1°C lower than their mean pre-dialysis oral temperature (Niyyar 2006).

Outcomes

We requested further information, including the first phase data of cross-over studies such as baseline characteristics or outcomes, from the corresponding authors. The data were no longer available for Niyyar 2006, and we received no response from any other authors (Ayoub 2004; Beerenhout 2004; Ebrahimi 2017; Gritters 2005; Jefferies 2011; Jost 1993; Levy 1992; Maggiore 2002; Parker 2007; Quereda 1988; Sajadi 2016; Santoro 2002a; Selby 2006b; Sherman 1984; Shin 1994; Sterrett 1999; van der Sande 2000; van der Sande 2001; van der Sande 2009; Zitt 2008). The following reported outcomes included data based on paired comparisons.

- IDH: 10 studies (286 participants) (Ayoub 2004; Ebrahimi 2017; Gritters 2005; Jost 1993; Levy 1992; Maggiore 2002; Quereda 1988; Selby 2006b; Sherman 1984; van der Sande 2009). The definition of IDH varied across studies. Five studies used the definition of a fall of systolic BP below 90 to 100 mmHg or a decrease of systolic BP by more than 10 mmHg, accompanied with hypotensive symptoms (Ayoub 2004; Jost 1993; Maggiore 2002; Sherman 1984; van der Sande 2009). Two studies defined IDH as systolic blood pressure < 90 mmHg irrespective of symptoms (Levy 1992; Quereda 1988), and two studies used a composite of those definitions above (Ebrahimi 2017; Selby 2006b). Gritters 2005 did not describe the definition of IDH
- Discomfort rate due to cool dialysate: 7 studies (189 participants) (Ayoub 2004; Ebrahimi 2017; Jefferies 2011; Sajadi 2016; Selby 2006b; van der Sande 2000; van der Sande 2009).
- QoL: one study (10 participants) examined QoL (Selby 2006b)
- Dropout rate due to adverse events: 12 studies (412 participants) (Beerenhout 2004; Ebrahimi 2017; Jefferies 2011; Jost 1993; Levy 1992; Maggiore 2002; Odudu 2012; Parker 2007; Quereda 1988; Rad 2017; Selby 2006b; van der Sande 2009)
- Blood pressure: 18 studies (415 participants) (Ayoub 2004; Beerenhout 2004; Ebrahimi 2017; Gritters 2005; Jefferies 2011; Jost 1993; Levy 1992; Manning 1995; Maggiore 2002; Parker 2007; Quereda 1988; Selby 2006b; Sherman 1984; Shin 1994; Sterrett 1999; van der Sande 2000; van der Sande 2001; van der Sande 2009; Zitt 2008).
- Body temperature: 8 studies (205 participants) (Ayoub 2004; Beerenhout 2004; Jefferies 2011; Jost 1993; Maggiore 2002; van der Sande 2000; van der Sande 2001; van der Sande 2009).
- Kt/V_{urea}: 2 studies (Ayoub 2004; Maggiore 2002).
- Death (all causes), acute coronary syndrome, or all strokes were no reported by any of the included studies.

Excluded studies

Seven studies were excluded (see Characteristics of excluded studies).

Two studies (Lima 2006; Lima 2012) were of participants with acute kidney injury and one study (NCT02593526) was of HD-naive participants. One study had a co-intervention other than dialysate temperature in the intervention group (Veljancic 2011): one study (Maggiore 1987) compared standard dialysate and warmer dialysate, one study (Dheenan 2001) compared cold dialysate and different sodium concentration, and one study (Hecking 2012a) used blood volume-monitored regulation as an intervention.

Risk of bias in included studies

Most studies were of unclear or high risk of bias. See Figure 2 and Figure 3.

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

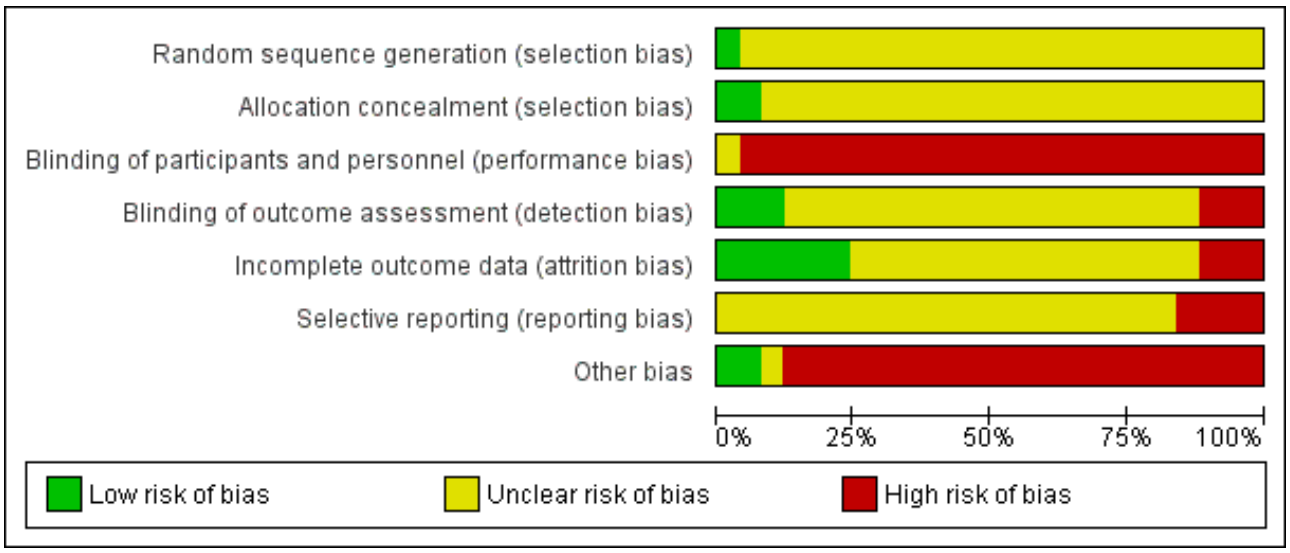


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

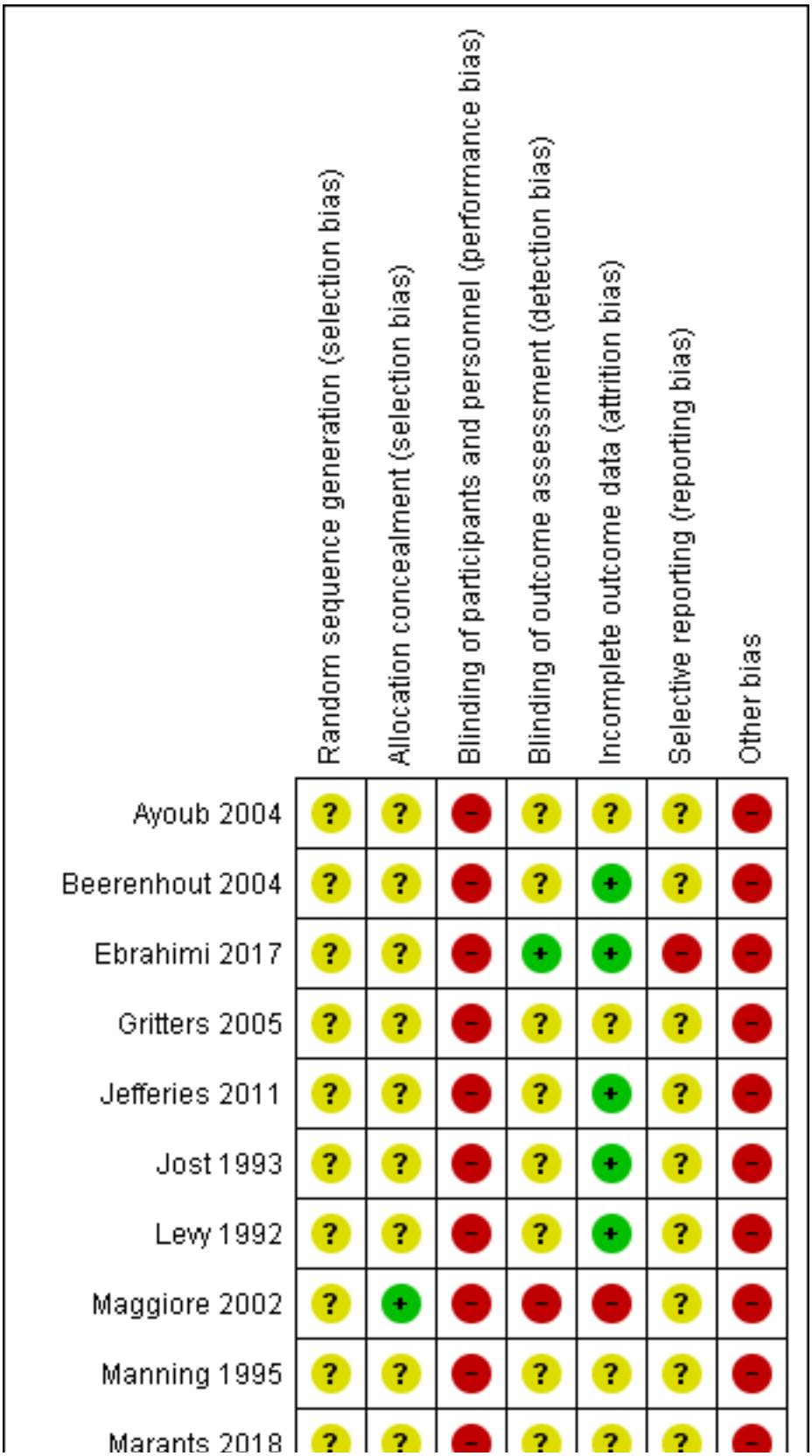
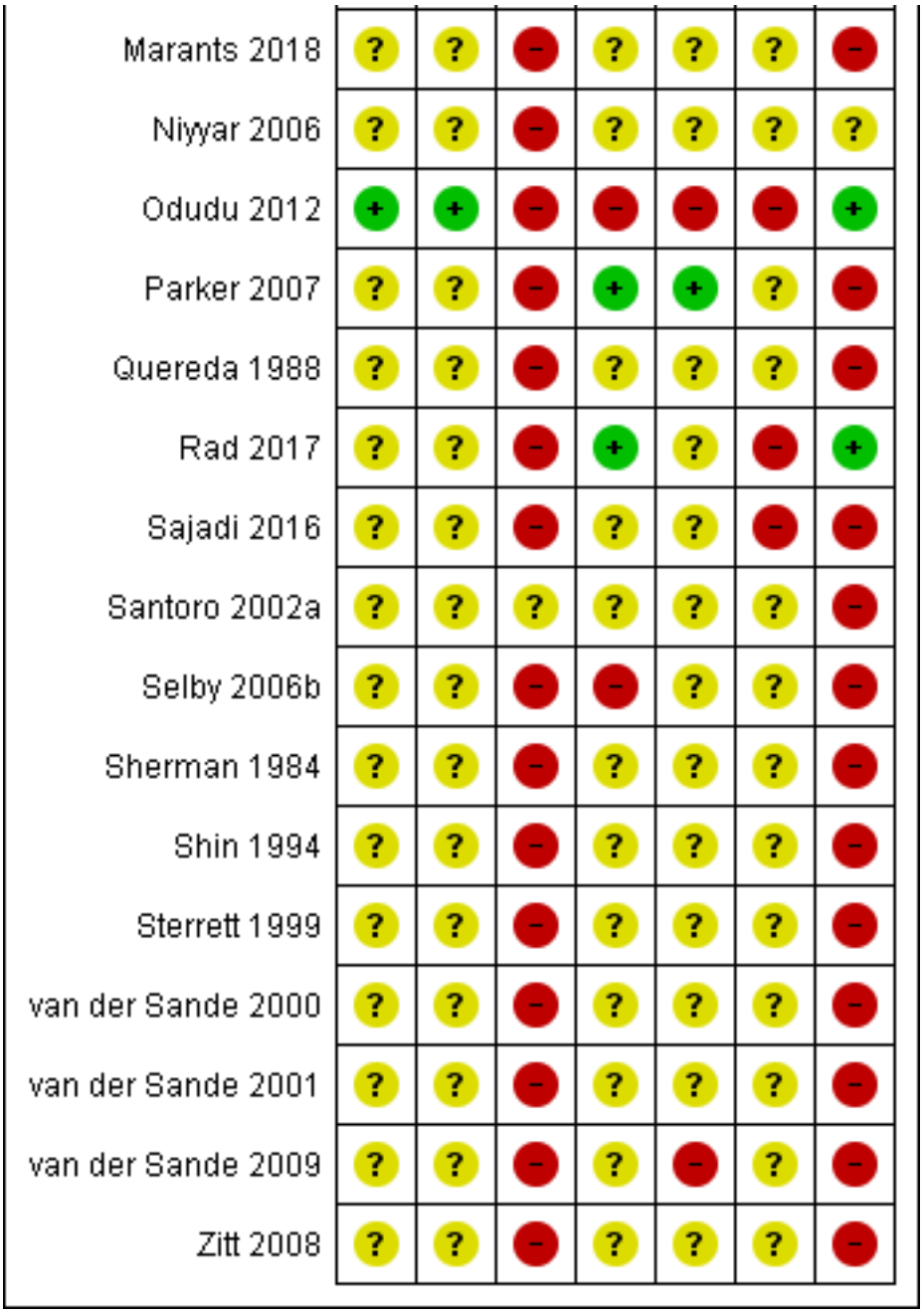


Figure 3. (Continued)



Allocation

Random sequence generation

One study (Odudu 2012) used a computer-generated random sequence. The other studies gave no indication or stated only "block randomisation" and were categorized as unclear.

Allocation concealment

One study (Maggiore 2002) used central randomisation, and one study (Odudu 2012) used sealed envelopes. The other studies gave no description and were categorized as unclear.

Blinding

Performance bias

We judged that blinding of the intervention was broken due to the nature of the intervention when studies compared fixed reduction of dialysate temperature (below 36°C) and standard dialysate temperature. Santoro 2002a compared energetically neutral dialysis (a net thermal energy transfer from the dialysate to the blood circuit equal to zero) and thermally neutral dialysis (the pre-dialysis patient core temperature was constant). This study was categorized as unclear because it was not clear whether the participants were aware of the intervention and there was no description about blinding.

Detection bias

Outcome assessors were blinded in two studies (Ebrahimi 2017; Rad 2017). Three studies were open label and were judged as high risk (Maggiore 2002; Odudu 2012; Selby 2006b). Other studies gave no description and were categorized as unclear.

Incomplete outcome data

Three studies were classified as high risk for incomplete outcomes because of the exclusion of more than 10% of participants from the final analysis (Maggiore 2002; Odudu 2012; van der Sande 2009). Six studies were classified as low risk (Beerenhout 2004; Ebrahimi 2017; Jefferies 2011; Jost 1993; Levy 1992; Parker 2007) as all or almost all participants were followed up, however, it should be noted that the first phase data of these studies were absent. Other studies were categorized as unclear.

Selective reporting

Five studies referred to their protocols (Ebrahimi 2017; Odudu 2012; Rad 2017; Sajadi 2016; Selby 2006b), but one was not accessible because the registry website was archived (Selby 2006b). Four studies with available protocols did not report pre-defined outcomes, and did not pre-define the cut-off or reported outcomes with multiple cut-offs (Ebrahimi 2017; Odudu 2012; Rad 2017; Sajadi 2016).

Other potential sources of bias

We judged cross-over RCTs to be at high risk of bias due to the carry-over effect. Moreover, we could not assess the baseline imbalance because these studies did not report the baseline characteristics classified by the interventions that the participants were allocated to in the first phase of the studies.

Effects of interventions

See: **Summary of findings for the main comparison** Fixed reduction of dialysate temperature compared to standard dialysate temperature for patients requiring haemodialysis; **Summary of findings 2** Isothermal dialysate compared to thermoneutral dialysate in patients requiring haemodialysis

The random effects and fixed effect models gave similar results, therefore only the random effects results have been presented.

See: Summary of findings for the main comparison and Summary of findings 2 for the main comparisons

Fixed reduction of dialysate temperature versus standard dialysate temperature

Intradialytic hypotension rate

Fixed reduction of dialysate temperature might improve IDH rate compared with standard dialysate (Analysis 1.1 (8 studies, 153 participants): rate ratio 0.52, 95% CI 0.34 to 0.80; I^2 = 19%; very low certainty evidence).

Discomfort rate

Fixed reduction of dialysate temperature might increase the discomfort rate compared with standard dialysate (Analysis 1.2 (4 studies, 161 participants): rate ratio 8.31, 95% CI 1.86 to 37.12; I^2 = 0%; very low certainty evidence). However, we could not incorporate Ebrahimi 2017 into the meta-analysis because it did not report the data but only mentioned that the discomfort rate did not differ between the cool dialysate and standard dialysate groups. The discomfort rate in the fixed reduction of the dialysate temperature group varied across the studies and ranged from 6.7% to 34.8%.

Death (all causes)

Death was no reported by any of the included studies.

Quality of life

Selby 2006b (10 participants) reported no differences in QoL between fixed reduction and standard dialysate as rated by the SF-36 questionnaire (median 62 (IQR 50 to 73) with 35°C and median 61 (IQR 39 to 78) with 37°C)

Dropouts due to adverse events

Nine studies (268 participants) reported the number of dropouts, and showed that there were no dropouts due to adverse events (Beerenhout 2004; Ebrahimi 2017; Jost 1993; Levy 1992; Odudu 2012; Parker 2007; Quereda 1988; Rad 2017; Selby 2006b).

Mean blood pressure at the end of haemodialysis

We used mean BP at the end of dialysis because it was the most frequently reported BP measure in the included studies. Fixed reduction of dialysate temperature might improve the mean BP at the end of dialysis (Analysis 1.3 (8 studies, 94 participants): MD 6.46 mmHg, 95% CI 2.84 to 10.08; I^2 = 0%; very low certainty evidence).

All seven studies that did not report the mean BP at the end of dialysis but reported other measures of BP, reported that systolic BP or mean BP was higher in the fixed reduction of dialysate temperature group (Beerenhout 2004; Ebrahimi 2017; Gritters 2005; Parker 2007; Quereda 1988; Selby 2006b; Shin 1994).

Change in body temperature during haemodialysis

We examined change in body temperature during dialysis because the lowest body temperature was not available. Fixed reduction of dialysate temperature might decrease body temperature (Analysis 1.4 (4 studies, 46 participants): MD -0.44°C, 95% CI -0.56 to -0.32; I^2 = 0%; very low certainty evidence). We could not incorporate the results from van der Sande 2000 as the data were only presented as a graph (Figure 1, page 1514).

Urea clearance-based dialysis adequacy (Kt/V_{urea})

Ayoub 2004 reported that there was no significant difference in Kt/V_{urea} between the cool dialysate and standard dialysate groups.

Post-haemodialysis fatigue

Sajadi 2016 (46 participants) reported isothermal dialysate might reduce post-HD fatigue scores using the Piper Fatigue Scale.

Ebrahimi 2017 (80 participants) reported no difference in fatigue between cool dialysate and standard dialysate (data not provided).

Isothermal dialysate versus thermoneutral dialysate

Intradialytic hypotension rate

Isothermal dialysate might improve the IDH rate compared with thermoneutral dialysate (Analysis 2.1 (2 studies, 133 participants):

rate ratio 0.68, 95% CI 0.60 to 0.76; I^2 = 0%; very low certainty evidence).

Discomfort rate

Maggiore 2002 (116 participants) reported that none of the participants allocated to isothermal or thermoneutral dialysate experienced shivering.

Death (all causes)

No study reported death.

Dropouts due to adverse events

Two studies (133 participants) reported there were no dropouts due to adverse events (Maggiore 2002; van der Sande 2009).

Changes in systolic blood pressure during haemodialysis

We used change in SBP during dialysis because it was the most frequently reported BP measures in the included studies. Isothermal dialysate might improve SBP during dialysis (Analysis 2.2 (2 studies, 133 participants): MD 6.59 mmHg, 95% CI 2.44 to 10.74; I^2 = 0%; very low certainty evidence).

Change in body temperature during haemodialysis

We examined change in body temperature during dialysis because the lowest body temperature was not available. Isothermal dialysate might decrease the body temperature compared with thermoneutral dialysate (Analysis 2.3 (2 studies, 133 participants); MD -0.40°C, 95% CI -0.60 to -0.21; I^2 = 95%; very low certainty evidence).

Urea clearance-based dialysis adequacy (Kt/V_{urea})

Maggiore 2002 (116 participants) reported isothermal dialysate did not decrease dialysis efficiency.

Reduction of arterial temperature using biofeedback device versus isothermal dialysate

van der Sande 2009 compared reduction of arterial temperature using biofeedback device and isothermal dialysate.

Intradialytic hypotension rate

There were three episodes of hypotension in the cooling group and three episodes in the isothermal group.

Discomfort rate

Three of 17 participants (17.6%) allocated to the reduction of arterial temperature group complained of shivering, however none of the participants allocated to the isothermal dialysate group reported shivering.

Lowest blood pressure during haemodialysis

It was unclear whether reduction of arterial temperature using a biofeedback device improved lowest BP during HD compared with isothermal dialysis.

Other methods of reduction of dialysate temperature versus standard dialysate temperature

Two studies evaluated the effect of dialysate temperature set to the individualized temperature of each individual participant compared with standard dialysate (Jefferies 2011; Sterrett 1999).

One study compared dialysate temperature individualized to each participant 1°C lower than their mean pre-dialysis oral temperature and standard dialysate temperature (Niyyar 2006).

One study compared reduction of arterial temperature using a biofeedback device with thermoneutral dialysis (van der Sande 2009).

Intradialytic hypotension rate

van der Sande 2009 reported one episode of hypotension in the cooling group and three episodes in the thermoneutral group.

Discomfort rate

van der Sande 2009 reported three patients in the reduction of arterial temperature group complained of shivering and no patients experienced shivering in the thermoneutral group.

Jefferies 2011 reported that 4/11 patients (36.4%) felt cold and used blankets or extra clothing at least once during the week in the individualized temperature group and 1/11 (9.1%) reported shivering, and no patients allocated to standard dialysate experienced discomfort.

Dropouts due to adverse events

Two studies reported that there were no dropouts due to adverse events (Jefferies 2011; van der Sande 2009).

Lowest blood pressure during haemodialysis

Jefferies 2011 and Sterrett 1999 only reported statistical significance or displayed BP in figures. Both studies reported that the SBP was higher among those with a dialysate temperature set to the individualized temperature of each individual patient.

It was unclear whether reduction of arterial temperature using a biofeedback device improved lowest BP during HD compared with thermoneutral dialysis (van der Sande 2009).

Lowest body temperature during haemodialysis

van der Sande 2009 reported reduction of arterial temperature using a biofeedback device might reduce body temperature compared with thermoneutral dialysis.

Jefferies 2011 reported that body temperature was decreased in the group allocated to dialysate temperature set to the individualized temperature of each individual participant, compared with the standard dialysate group (data not provided).

DISCUSSION

Summary of main results

We found very low quality evidence that fixed reduction of dialysate temperature decreased the incidence of IDH compared with standard dialysate and increased the discomfort rate compared with standard dialysate. However, no study reported the long-term

outcomes such as death (all causes) or coronary artery syndrome. Based on very low evidence, isothermal dialysate might reduce the IDH rate without discomfort. It should be noted that these results were not based on parallel comparisons. These results were drawn from comparisons between before and after data from cross-over studies.

Overall completeness and applicability of evidence

Seventeen of the 23 included studies were conducted over a decade ago. Practice in the treatment of patients undergoing HD has changed significantly over the years, and the difference in practice may lower external validity. Notably, dialysed patients with IDH risk factors such as older age, type II diabetes, and higher dialysate dose are increasing (Mc Causland 2013; National Kidney Foundation 2015; Pippias 2016; Sands 2014). For example, the incidence of patients older than 75 requiring HD has increased in Europe (Pippias 2016). The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) recommended a target single pool Kt/V (spKt/V) of 1.4/HD session for patients treated three times/week (Mc Causland 2013; National Kidney Foundation 2015). The changes in reimbursement policies might also affect the practice. In 2011, the Centers for Medicare & Medicaid Services (CMS) administered the End-Stage Renal Disease (ESRD) Quality Incentive Program (QIP) that proposed the target dialysis dose or anaemia level to promote high-quality care through outpatient dialysis centres (Centers for Medicare & Medicaid Services 2016). In Europe, age at the start of RRT has risen over the last decade and the prevalence of cardiovascular co-morbidities has decreased, while the prevalence of DM and malignancy has increased (Ceretta 2018).

Additionally, as shown in the Characteristics of included studies table, some studies did not report the eligibility criteria (Manning 1995; Marants 2018; Quereda 1988; Santoro 2002a; Sherman 1984; Sterrett 1999; van der Sande 2000; van der Sande 2001), and most studies did not report whether they used consecutive sampling. We therefore concluded that our evidence had low external validity.

Quality of the evidence

We graded the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (GRADE 2008). As shown in the Summary of findings for the main comparison, and Summary of findings 2 for the main comparison, we rated the overall certainty of evidence in this review as very low because of the serious issues with risks of bias, and the number of participants that comprised quantitative syntheses was less than the optimal information size of 400 (Guyatt 2011). As shown in Figure 3, most studies had high or unclear risks of bias for most domains of the study reporting that we assessed. The design, conduct, and analysis of the included studies were difficult to assess in most studies due to a lack of important methodological detail.

Potential biases in the review process

This review has several limitations. First, the results we have presented were not based on parallel group comparisons but a within-person comparison. We should note the presence of a carry-over effect when interpreting the results. For example, if there was an IDH in the first phase, clinicians or medical staff would attempt to prevent the event again. Most studies were cross-over RCTs and data from the first phase were not available, even though we tried to contact the authors three times. Secondly, as many of the included studies were old, we could not check whether unpublished studies existed, especially those conducted before the compulsory policy of trial registration adopted by the International Committee of Medical Journals in 2004 (De Angelis 2004). Additionally, most studies did not report any information about trial registration. Publication bias might potentially exist even though we performed a comprehensive systematic search strategy of the Cochrane Kidney and Transplant's Specialised Register.

Agreements and disagreements with other studies or reviews

Our findings showed similar results with the findings from a previous systematic review (Mustafa 2016). Cool dialysate might reduce the incidence of IDH, but it might increase the discomfort rate. Additionally, no study reported other serious adverse events, or dropouts due to adverse events. However, most studies that did not report IDH events introduced the effect of cool dialysate on IDH in their background section. From a clinical perspective, IDH events should be routinely noted in medical records, and reported in the publication. The frequency of IDH in the standard dialysate group of the included studies was consistent with previous reports (Davenport 2008a; Davenport 2008b).

AUTHORS' CONCLUSIONS

Implications for practice

Fixed reduction of dialysate temperature may be useful to reduce IDH when patient discomfort is minimal. On the other hand, isothermal dialysate may reduce IDH without less discomfort compared with thermoneutral dialysate. However, due to the need to prepare the biofeedback device, it may not be possible to routinely use isothermal dialysate. We should note the conclusion was based on very low certainty evidence. We found six ongoing studies that might provide much-needed high quality evidence in the future.

Implications for research

To avoid bias due to the carry-over effect, a parallel group RCT that evaluates patient-centred outcomes (e.g. IDH, discomfort rate, or mortality) is warranted. First period data should be presented to permit parallel comparison when cross-over design is employed. Additionally, evaluations must be carefully planned to ensure that random sequence generation, allocation concealment, and blinding of the outcome assessors are adequate, and sample sizes are appropriate to detect significant effects if they exist.

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Biostatistics, Western University, London, Ontario, Canada; Staff Nephrologist, London Health Sciences Center).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ayoub 2004

Methods	• Study design: cross-over RCT • Follow-up period: 3 months • Duration of study: April 2002 to June 2002
Participants	• Country: New Zealand • Setting: single centre • Inclusion criteria: not reported • Number: 10; hypotension-prone group (5); stable BP group (5) • Mean age ± SD: 59.8 ± 5.5 years • Sex: not reported • Exclusion criteria: recent surgical intervention; severe anaemia; problems related to vascular access; coronary artery disease; AKI; recent illnesses
Interventions	Treatment arm • Cool dialysate temperature (35℃) for 3 dialysis sessions Control arm • Standard dialysate temperature (36.5℃) for 3 dialysis sessions
Outcomes	• IDH rate • Discomfort rate defined as cold sensation, shivering, and related symptoms • Mean SBP during dialysis • Body temperature during dialysis • Urea clearance-based dialysis adequacy (Kt/V_{urea})
Notes	• Funding source: none • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement

Ayoub 2004 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients were informed about the temperature of each dialysis session, as they can feel the cool dialysis
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement: no description about the first phase data including missing values; dropouts not reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: the protocol was not available
Other bias	High risk	Carry-over effects potentially existed; no description for the assessment of the baseline imbalance of first period of the cross-over study

Beerenhout 2004

Methods	• Study design: cross-over RCT • Follow-up period: not reported • Duration of study: not reported
Participants	• Country: Netherlands • Setting: single centre • Inclusion criteria: not reported • Number: 12 • Mean age ± SD: 69 ± 6 years • Sex (M/F): 8/4 • Exclusion criteria: severe coronary, congestive heart failure (NYHA III or higher), or diabetes mellitus
Interventions	Treatment arm • HD using respective dialysate temperatures of 35.5°C Control arms • Pre-dilution on-line HF (infusate temperature 36.5°C) • HD using respective dialysate temperatures of 36.5°C
Outcomes	• Body temperature during dialysis • SBP change during dialysis
Notes	• Funding source: Gambro Health Care, Lund, Sweden • We requested further information but there was no response

Beerenhout 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Sessions were performed in random order": method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Insufficient information to permit judgement: No description about the first phase data including missing values but only 1 participants dropped out
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Ebrahimi 2017

Methods	• Study design: cross-over RCT • Follow-up period: not reported • Duration of study: not reported
Participants	• Country: Iran • Setting: single centre • Inclusion criteria: 18 to 75 years; undergoing HD using sodium bicarbonate solution 3 times/week; having a history of at least 6 months of HD treatment; having arteriovenous fistula vascular access, not suffering from severe anaemia (HCT < 20%) or coagulation disorders which could lead to bleeding during dialysis (as diagnosed by a physician); not taking high blood pressure medications; not taking any blood product during dialysis; and having no intention for migration and kidney transplantation • Enrolled: 80 • Age: 56.7 ± 14.4 • Sex (M/F): 44/36 • Exclusion criteria: death of patient, serious intradialytic complications such as seizures, and termination of dialysis sooner than the appointed time for any reason
Interventions	Treatment arm • Dialysate temperature 35°C; sodium concentration 138 mmol/L or 150 mmol/L Control arm • Dialysate temperature 37°C; sodium concentration 138 mmol/L or 150 mmol/L

Ebrahimi 2017 *(Continued)*

Outcomes	• IDH rate • Discomfort rate defined as cold sensation, shivering, and related symptoms • Mean SBP during dialysis • Post-HD fatigue
Notes	• Funding source: Tehran Medical Branch of Islamic Azad University • Factorial design to assess the effect of dialysate temperature and sodium concentration • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The researcher was in charge of measuring and recording blood pressure. The data collector and the data analyser were also unaware of this process
Incomplete outcome data (attrition bias) All outcomes	Low risk	Insufficient information to permit judgement: No description about the first phase data including missing values but there were no dropouts
Selective reporting (reporting bias)	High risk	IDH was not a pre-specified outcome but was reported in the publication
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Gritters 2005

Methods	• Study design: cross-over RCT • Follow-up period: not reported • Duration of study: not reported
Participants	• Country: Netherlands • Setting: not reported • Inclusion criteria: stable chronic HD patients • Enrolled: 10 • Age(M/F): not reported • Sex: not reported • Exclusion criteria: not reported
Interventions	Treatment arm

Gritters 2005 *(Continued)*

	• Dialysate temperature 35°C Control arm • Dialysate temperature 37°C
Outcomes	• IDH rate • Mean SBP during dialysis
Notes	• Abstract-only publication • Funding source: not reported • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement: no description about the first phase data including missing values
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Jefferies 2011

Methods	• Study design: cross-over RCT • Follow-up period: not reported • Duration of study: not reported
Participants	• Country: UK • Setting: a single hospital centre • Inclusion criteria: patients established on HD for 13 months • Enrolled: 11 • Mean age ± SD: 66 ± 12 years • Sex (M/F): not reported

Jefferies 2011 *(Continued)*

	• Exclusion criteria: those with pre-existing severe LV systolic dysfunction (NYHA IV) or cardiac transplant were excluded
Interventions	Treatment arm • HD with dialysate temperature set to the individualized temperature of each individual patient measured by tympanic thermometer Control arm • HD with dialysate temperature at 37°C
Outcomes	• Discomfort rate defined as cold sensation, shivering, and related symptoms • Mean SBP during dialysis • Body temperature during dialysis
Notes	• Funding source: The study was funded by a British Renal Society grant (No. 06-013) and has been adopted by the UKCRN portfolio (study 5822) • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Insufficient information to permit judgement: No description about the first phase data including missing values but there were no dropouts
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Jost 1993

Methods	• Study design: cross-over RCT • Follow-up period: 2 weeks • Duration of study: not reported
Participants	• Country: USA

Jost 1993 *(Continued)*

- Setting: single centre
- Inclusion criteria: not reported
- Enrolled: 12; hypotension-prone group (6), weight gainers group (6)
- Mean age ± SD: 62.5 ± 3.6 years
- Sex (M/F): 12/0
- Exclusion criteria: not reported

Interventions	Treatment arm • 35°C dialysate Control arm • 37°C dialysate
Outcomes	• IDH rate • Mean BP at end of HD • Body temperature during dialysis
Notes	• Funding source: not reported • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Insufficient information to permit judgement: No description about the first phase data including missing values but there were no dropouts
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of the first period of the cross-over study

Levy 1992

Methods	• Study design: cross-over RCT • Follow-up period: 15 weeks

Levy 1992 *(Continued)*

	• Duration of study: not reported
Participants	• Country: USA • Setting: single centre • Inclusion criteria: clinically stable on chronic HD; high quality echocardiograms; in sinus rhythm • Enrolled: 6 • Mean age ± SD: 55 ± 11 years • Sex (M/F): 6/0 • Exclusion criteria: not reported
Interventions	Treatment arm • Dialysate temperature of 35°C Control arm • Dialysate temperature of 37°C
Outcomes	• IDH rate • Mean BP at end of HD
Notes	• Funding source: not reported • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "The dialysis procedures were performed in random order..."; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No description about the first phase data including missing values but there were no dropouts
Selective reporting (reporting bias)	Unclear risk	The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Maggiore 2002

Methods	• Study design: cross-over RCT

Maggiore 2002 *(Continued)*

	• Follow-up period: 8 weeks • Duration of study: not reported
Participants	• Country: Italy • Setting: 27 centres in 9 European countries • Inclusion criteria: (1) symptomatic hypotensive episodes occurring in 25% or more of HD sessions; (2) minimum age of 18 years; (3) on HD therapy for at least 3 months; (4) treatment with standard HD 3 times weekly using bicarbonate buffer and with a treatment duration of at least 180 minutes • Randomised/analysed: 116/95 • Mean age: 66 ± 12 years • Sex (M/F): 37/58 • Exclusion criteria: recent surgical intervention; severe anaemia (HCT < 25%); intercurrent illnesses; problems related to vascular access; diffuse neoplastic disease; ascites; class IV heart failure according to the NYHA; obligatory use of a single needle or central venous catheter with single lumens; use of antihypotensive drugs; treatment with extracorporeal blood purification techniques other than HD; participation in another clinical study
Interventions	Treatment arm • Isothermic HD was designed to maintain constant body temperature throughout the dialysis sessions • Control arm • Thermoneutral HD that the target was to minimize heat exchange between extracorporeal blood and dialysate such that no heat energy was transferred to or from the patient
Outcomes	• IDH rate • Dropout rate due to adverse events • Maximum decrease of SBP during dialysis • Lowest body temperature during dialysis • Urea clearance-based dialysis adequacy (Kt/V_{urea})
Notes	• Funding source: Fresenius Medical Care AG • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was performed centrally in blocks of four patients, and separate randomisation lists were provided for each center." However, there was no description of random sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally in blocks of four patients, and separate randomisation lists were provided for each center."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias)	High risk	More than 15% of participants dropped out (21/116)

Maggiore 2002 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Manning 1995

Methods	• Study design: cross-over RCT • Follow-up period: 1 week • Duration of study: not reported
Participants	• Country: USA • Setting: not reported • Inclusion criteria: hypertensive-prone HD patients • Enrolled: 5 • Age: not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment arm • Dialysate temperature of 35°C Control arm • Dialysate temperature of 37°C
Outcomes	• Post-HD MAP
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Manning 1995 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Marants 2018

Methods	• Study design: cross-over RCT • Follow-up period: 2 visits • Duration of study: of study: not reported
Participants	• Country: Canada • Setting: not reported • Inclusion criteria: not reported • Enrolled: 16 • Age: not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment arm • Dialysate temperature of 35°C Control arm • Dialysate temperature of 36.5°C
Outcomes	• No outcome of interest was reported
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to permit judgement

Marants 2018 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Niyyar 2006

Methods	• Study design: parallel RCT • Follow-up period: 12 months • Duration of study: not reported
Participants	• Country: USA • Setting: not reported • Inclusion criteria: stable HD patients • Number: treatment group (11); control group (13) • Age: not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Dialysate temperature individualized to each subject, 1°C lower than their mean pre-dialysis oral temperature Control group • Dialysate temperature 37°C
Outcomes	• Dropout rate due to adverse events • Pre-dialysis SBP
Notes	• Abstract-only publication • Funding source: NINR-NR004340 • We requested further information but the data were no longer available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Blinding was not feasible because of the nature of the intervention

Niyyar 2006 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement: No description about the missing data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	Unclear risk	Insufficient information to permit judgement: No description for the assessment of the baseline imbalance

Odudu 2012

Methods	• Study design: parallel RCT • Follow-up period: 12 months • Duration of study: September 2009 to January 2013
Participants	• Country: UK • Setting: 4 centres • Inclusion criteria: patients having HD treatment at least 3 times/week; patients willing and able to provide consent; men and women age ≥ 16 years • Number (randomised/analysed: treatment group (36/26); control group (37/28) • Mean age ± SD: treatment group (60 ± 25); control group (60 ± 26) • Sex (M/F): treatment group (20/8); control group (19/7) • Exclusion criteria: exposure to HD for 180 days; contraindications for using MRI (e.g. patients with pacemakers and metal implants); inability to tolerate MRI because of claustrophobia; NYHA grade IV heart failure; pregnancy or lactating; mental incapacity to consent
Interventions	Treatment group • Individualised cooled dialysate temperature for 12 months. This was set at 0.5°C less than the patient's own temperature, determined from the mean of 6 prior treatment sessions with a tympanic thermometer, up to a maximum of 36°C, ensuring a minimum temperature separation of 1°C between groups Control group • Dialysate temperature of 37°C for 12 months
Outcomes	• Dropout rate due to adverse events
Notes	• Funding source: Research for Patient Benefit Grant from the UK National Institute of Healthcare Research (PB-PG-0408-16195)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised 1:1 by a computer-generated sequence placed into sealed envelopes by an independent statistician

Odudu 2012 *(Continued)*

Allocation concealment (selection bias)	Low risk	Patients were randomised 1:1 by a computer-generated sequence placed into sealed envelopes by an independent statistician
Blinding of participants and personnel (performance bias) All outcomes	High risk	Multicentre, prospective, randomised, unblinded, controlled study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Multicentre, prospective, randomised, unblinded, controlled study
Incomplete outcome data (attrition bias) All outcomes	High risk	73 patients were enrolled and randomised but 54 patients were analysed
Selective reporting (reporting bias)	High risk	IDH was the pre-specified outcome, but was not reported in the publication
Other bias	Low risk	No concern about baseline imbalance

Parker 2007

Methods	• Study design: cross-over RCT • Follow-up period: 9 months • Duration of study: not reported
Participants	• Country: USA • Setting: single centre • Inclusion criteria: not reported • Enrolled: 7 • Mean age ± SE: 42 ± 4.2 years • Sex (M/F): 3/4 • Exclusion criteria: patients with major chronic conditions associated with changes in sleep or BT, such as chronic infections, heart failure, chronic lung disease, arthritis, organic brain disease, drug/alcohol abuse; past psychiatric disorders requiring treatment
Interventions	Treatment arm • Dialysate bath temperature 35°C Control arm • Dialysate bath temperature 37°C
Outcomes	• Dropout rate due to adverse events • Mean SBP during dialysis
Notes	• Funding source: the National Institute of Health. National Institute of Nursing Research RO1 NR04340 and P20 NR007798. National Center for Research Resources M01 RR00039. EVS supported by EU FP6 Sensation Integrated Project (FP6- 507231) and projects SOW 014-90-001 and VIDI Innovation Grant 016.025.041 of the Netherlands Organization for Scientific Research, The Hague, The Netherlands • We requested further information but there was no response

Risk of bias

Parker 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	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
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The only measured outcome was "dropouts due to adverse events" and no dropouts was occurred
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Quereda 1988

Methods	• Study design: cross-over RCT • Follow-up period: 4 months • Duration of study: not reported
Participants	• Country: Spain • Setting: not reported • Inclusion criteria: not reported • Enrolled: 8 • Dropouts: 0 • Age: 58(9) • Sex (M/F): 2/6 • Exclusion criteria: not reported
Interventions	Treatment arms (48 sessions of each) 1. Cuprophan membrane (CU), dialysate sodium concentration (DNa) of 133mmol/L, dialysate temperature (DT) 37°C 2. CU, DNa133, DT35°C 3. CU, DNa139, DT37°C 4. CU, DNa 139, DT35°C 5. Polyacrylonitrile (PAN) membrane, DNa133, DT37°C 6. PAN, DNa133, DT35°C 7. PAN, DNa139, DT37°C 8. PAN, DNa 139, DT35°C

Quereda 1988 *(Continued)*

Outcomes	• IDH rate • Maximum decrease of SBP during dialysis
Notes	• Funding source: not reported • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement: No description about the first phase data including missing values
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Rad 2017

Methods	• Study design: parallel RCT • Follow-up period: 2 weeks • Duration of study: December 2014 to March 2015
Participants	• Country: Iran • Setting: multicentre (dialysis centre of Imam Reza Hospital and dialysis centres affiliated to Imam Reza hospital (Bentolhoda and AL- Muhammad) of Mashhad city) • Inclusion criteria: consent for participation in the study; aged 18 to 65 years; suffering from vision, hearing loss (deafness and dumbness); not suffering from clear mental disorders and severe emotional mood disorders, which prevent effective communication; patients with chronic renal failure (patients who 3 months have passed since their dialysis); patients who have arteriovenous fistulas for HD; patients receiving dialysis treatment 3 times/week and each session for 4 hours; patients who over the past 2 months, have a history of itching during HD; not suffering from endocrine disorders (such as hypothyroidism, hyperparathyroidism; not suffering from febrile illnesses (pneumonia, colds); no history of pruritic skin diseases; no use of medications or foods, causing itching; lack of pregnancy and liver problems; patients with a KT / V ≥ 1; patients with Hb of 10 to 11 mg/dL • Number: treatment group (30); control group (30) • Mean age ± SD: treatment group (53.10 ± 10.02); control group (55.83 ± 8.45)

Rad 2017 *(Continued)*

	• Sex (M/F): treatment group (17/13); control group (15/15) • Exclusion criteria: patients who develop acute complications during HD (disequilibrium syndrome, embolism, dysrhythmia, cardiac or respiratory arrest, coma); patients with skin disorders that feature itchiness (scabies, psoriasis); patients who discontinued their dialysis for any reason; patients who are referred for kidney transplants (patients who had kidney transplantations during the study); change in the frequency of HD, the patient's death, patients who cannot tolerate cold dialysis; female patients who become pregnant; HD with acetate; the incidence of fever; unwillingness to continue to participate in the study
Interventions	Treatment group • Temperature of HD fluid is regulated at 35.5°C and type of filter, coefficient of ultra- filtration, blood flow rate are not changed Control group • Temperature of HD fluid (dialysate) is regulated at 37°C. Type of filter, coefficient of ultra-filtration, blood flow rate and type of apparatus are constant during the study
Outcomes	• Dropout rate due to adverse events
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The random permuted block method was used, but there was no description how to generate the random sequence
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement: The only measured outcome was "dropouts due to adverse events" and no dropouts occurred
Selective reporting (reporting bias)	High risk	Insufficient information to permit judgement: The pruritus outcome was not measured by one of the pre-specified measures
Other bias	Low risk	No concern about the baseline imbalance

Sajadi 2016

Methods	• Study design: cross-over RCT • Follow-up period: 2 months • Duration of study: August 2014 to 31 October 2014

Sajadi 2016 *(Continued)*

Participants	• Country: Iran • Setting: single centre • Inclusion criteria: aged > 18 years old; experiencing some degree of fatigue (mild, moderate, and severe); referring consistently and regularly 3 times/week for receiving HD, receiving HD for at least 6 months, having haemodynamic stability, being able to listen and speak, having an acceptable level of alertness for responding to questions, having no dependence on narcotics, and no chronic anaemia (Hb < 8 g/dL) • Enrolled: 46 • Age: 58.46 ± 13.46 years • Sex (M/F): 25/21 • Exclusion criteria: not reported
Interventions	Treatment arm • 3 sessions of HD in the week (every other day) with a solution temperature of 35.5°C Control arm • 3 sessions of HD in the week (every other day) with a 37°C solution
Outcomes	• Discomfort rate defined as cold sensation, shivering, and related symptoms • Post-HD fatigue
Notes	• Funding source: Arak University of Medical Sciences • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement: No description about the first phase data including missing values
Selective reporting (reporting bias)	High risk	Primary outcome was reported with multiple cut-offs
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Santoro 2002a

Methods	• Study design: cross-over RCT • Follow-up period: 4 weeks • Duration of study: not reported
Participants	• Country: Italy • Setting: not reported • Inclusion criteria: not reported • Enrolled: 62 • Mean age ± SD: 65 ± 13 years • Sex (M/F): 24/38 • Exclusion criteria: not reported
Interventions	Treatment arm • Thermally neutral “cold HD”: the blood temperature monitor kept the pre-dialysis patient core temperature constant throughout the HD study session • Control arm • Energetically neutral: the blood temperature monitor was set in order to prevent a net thermal energy transfer from the dialysate to the blood circuit
Outcomes	• No outcomes of interest were reported
Notes	• Abstract-only publications • Funding source: not reported • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement: No description about the first phase data including missing values
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Selby 2006b

Methods	• Study design: cross-over RCT • Follow-up period: 2 weeks • Duration of study: not reported
Participants	• Country: UK • Setting: not reported • Inclusion criteria: patients who were on chronic, thrice-weekly, bicarbonate-based HD and prone to IDH were recruited. Criteria for the classification of IDH-prone patients included episodes of IDH in > 30% of dialysis sessions in the month before recruitment to the study. IDH was defined as SBP ≤ 100 mmHg, even in the absence of symptoms, or a fall in SBP > 10% of the predialysis reading in association with any of the classical symptoms of hypotension • Enrolled: 10 • Mean age ± SEM: 67.9 ± 2.6 years • Sex (M/F): 6/3 • Exclusion criteria: symptomatic severe heart failure (NYHA classification ≥ 3) or had previously received a heart transplant
Interventions	Treatment arm • Bicarbonate-based HD with a dialysate temperature of 35°C Control arm • Standard bicarbonate-based HD with a dialysate temperature of 37°C
Outcomes	• IDH rate • Discomfort rate defined as cold sensation, shivering, and related symptoms • Mean SBP during HD
Notes	• Funding source: the British Renal Society • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome assessors were not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement: No description about the first phase data including missing values

Selby 2006b *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Sherman 1984

Methods	• Study design: cross-over RCT • Follow-up period: 3 weeks • Duration of study: not reported
Participants	• Country: USA • Setting: single centre • Inclusion criteria: not reported • Enrolled: 17 • Mean age: 53.8 years • Sex (M/F): 9/8 • Exclusion criteria: not reported
Interventions	Treatment arms 1. Dialysate at 37.8°C 2. Dialysate at 36.7°C 3. Dialysate at 35.6°C
Outcomes	• IDH rate • Lowest mean BP during dialysis
Notes	• Funding source: not reported • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description about the first phase data including missing values

Sherman 1984 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Shin 1994

Methods	• Study design: cross-over RCT • Follow-up period: 2 weeks • Duration of study: not reported
Participants	• Country: USA • Setting: not reported • Inclusion criteria: low pre-HD BP or excessive interdialytic weight gain (details were unknown) • Enrolled: 10 • Age: not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment arm • 35°C dialysate Control arm • 37°C dialysate
Outcomes	• MAP during dialysis
Notes	• Abstract-only publication • Funding source: not reported • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient information to permit judgement: No description about the first phase data including missing values

Shin 1994 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Sterrett 1999

Methods	• Study design: cross-over RCT • Follow-up period: 2 weeks • Duration of study: not reported
Participants	• Country: USA • Setting: not reported • Inclusion criteria: not reported • Enrolled: 28 • Age: not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment arm • Dialysate temperature was set to match the patient's body temperature by ear thermometer Control arm • Dialysate temperature was set to 37
Outcomes	• Maximum decrease of MAP
Notes	• Abstract-only publication • Funding source: not reported • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Sterrett 1999 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement: No description about the first phase data including missing values
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

van der Sande 2000

Methods	• Study design: cross-over RCT • Follow-up period: 4 weeks • Duration of study: not reported
Participants	• Country: Germany • Setting: single centre • Inclusion criteria: not reported • Enrolled: 15 • Mean age (range): 55 years (21 to 77) • Sex (M/F): 7/8 • Exclusion criteria: not reported
Interventions	Treatment arms 1. 1 h of isolated ultrafiltration (i-UF) 2. UF+HD at a dialysate temperature of 37.5°C 3. UF+HD at a dialysate temperature of 35.5°C 4. UF+ HD in which the energy transfer was similar for that particular patient as during i-UF
Outcomes	• Discomfort rate defined as cold sensation, shivering, and related symptoms • SBP at the end of dialysis • Lowest body temperature during dialysis
Notes	• Funding source: not reported • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention

van der Sande 2000 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement: No description about the first phase data including missing values
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of the first period of the cross-over study

van der Sande 2001

Methods	• Study design: cross-over RCT • Follow-up period: 4 weeks • Duration of study: not reported
Participants	• Country: Netherlands • Setting: single centre • Inclusion criteria: not reported • Enrolled: 12 • Mean age ± SD: 56.67 ± 15.95 years • Sex (M/F): 7/5 • Exclusion criteria: not reported
Interventions	Treatment arms 1. Standard temperature HD (37.5°C) 2. Cool-temperature HD (35.5°C) 3. Postdilution HDF with a low amount of replacement fluid (exchange volume, 1 L/h) with the temperature of 37.5°C 4. HDF with an intermediate amount of replacement fluid (exchange volume, 2.5 L/h) with the temperature of 37.5°C
Outcomes	• Maximum decline in MAP • Lowest body temperature during dialysis
Notes	• Funding source: not reported • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

van der Sande 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement: No description about the first phase data including missing values
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

van der Sande 2009

Methods	• Study design: cross-over RCT • Follow-up period: 3 weeks • Duration of study: not reported
Participants	• Country: Canada • Setting: not reported • Inclusion criteria: on chronic HD treatment; experienced a drop in SBP of < 25 mmHg in at least 75% of dialysis sessions in the preceding 6 months; aged 18 to 85 years; ability to read and understand English • Enrolled: 17 • Mean age ± SD: 60.9 ± 10.6 years • Sex (M/F): 8/6 • Exclusion criteria: central venous catheter as vascular access for HD
Interventions	Treatment arms 1. Arterial temperature was set to decrease by 0.5°C at the individual patient's baseline level 2. Arterial temperature was set to remain unchanged at the individual patient's baseline level 3. Thermoneutral dialysis (during which no energy is added to or removed from the patient)
Outcomes	• IDH rate • Discomfort rate defined as cold sensation, shivering, and related symptoms • Lowest SBP during dialysis • Lowest body temperature during dialysis
Notes	• Funding source: no funding • We requested further information but there was no response

Risk of bias

Bias	Authors' judgement	Support for judgement

van der Sande 2009 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 15% (3/17) of participants were not included in the analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

Zitt 2008

Methods	• Study design: cross-over RCT • Follow-up period: 1 week • Duration of study: not reported
Participants	• Country: Austria • Setting: not reported • Inclusion criteria: not reported • Enrolled: 17 • Mean age ± SEM: 63.3 ± 3.2 years • Sex (M/F): 9/8 • Exclusion criteria: exclusion criteria for study participation were: known arrhythmia, α- or β-adrenergic blocking antihypertensive therapy, and severe peripheral artery disease
Interventions	Treatment arm • Dialysate temperature set at 35°C Control arm • Dialysate temperature set at 37°C
Outcomes	• SBP at the end of dialysis
Notes	• Funding source: an unrestricted research grant from the Dialysetrainings-Zentren GmbH, Nürnberg, Germany, and the Fonds zur Förderung der wissenschaftlichen Forschung und des wissenschaftlichen Nachwuchses, Land Tirol. • We requested further information but there was no response

Zitt 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised; method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not feasible because of the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement: No description about the first phase data including missing values
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement: The protocol was not available
Other bias	High risk	Carry-over effects potentially existed. No description for the assessment of the baseline imbalance of first period of the cross-over study

AKI - acute kidney injury; BP - blood pressure; BT- body temperature; Hb - haemoglobin; HCT - haematocrit; HD - haemodialysis; IDH - Intradialytic hypotension; M/F - male/female; MAP - mean arterial pressure; MRI - magnetic resonance imaging; NYHA - New York Heart Association; RCT - randomised controlled trial; SBP - systolic blood pressure; SD - standard deviation; SE; standard error; SEM - standard error of the mean

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

Study	Reason for exclusion
Dheenan 2001	Wrong interventions: cool dialysate versus dialysate with higher sodium concentration
Hecking 2012a	Wrong interventions: cool dialysate in combination with blood volume-monitored regulation
Lima 2006	Wrong population: patients with AKI
Lima 2012	Wrong population: patients with AKI
Maggiore 1987	Wrong interventions: warmer dialysate (39°C to 41°C) versus standard dialysate
NCT02593526	Wrong population: patients were HD naive (Patient may still enrol as long as no more than 12 weeks of in-centre HD have been performed prior to randomisation)
Veljancic 2011	Wrong interventions: wool dialysate in combination with blood volume monitoring

AKI - acute kidney injury; HD - haemodialysis

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

Kuhlmann 1996

Methods	• Study design: unclear • Follow-up period: not reported • Duration of study: not reported
Participants	• Country: Germany • Setting: not reported • Inclusion criteria: not reported • Enrolled: 28 • Age: not reported • Sex: not reported • Exclusion criteria: not reported
Interventions	Treatment arm • Intended maintenance of BT Control arm • Standard extracorporeal HD defined by a constant dialysate temperature of 37°C
Outcomes	• MAP
Notes	• We could not judge whether the study design was randomised to the limited information

BT - body temperature; HD - haemodialysis; MAP - mean arterial pressure

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

IRCT201306268140N2

Trial name or title	Effect of lowering dialysate temperature on the quality of haemodialysis in patients undergoing haemodialysis in 5t Azar hospital
Methods	Single-centre cross-over RCT
Participants	Inclusion criteria • The samples included the patients undergoing HD at 5th Azar Hospital having: hypotension in more than 30% of dialysis sessions (more than three sessions), during one month before the study; 3 times dialysis/week with sodium bicarbonate solution; patients did not receive analgesic, anti-hypertensive and anti-spasm during four hours before dialysis; no history of chronic infections, heart failure, chronic lung disease, drugs or alcohol abuse or required treatment for mental disorders, severe anaemia, coronary artery disease; aged > 18 years old and more than 3 month's dialysis treatment
Interventions	In cross-over study, patients are assessed during 24 dialysis sessions; the first group received HD for 12 sessions using cool dialysate (35.5°C) and the second group is on HD with standard dialysate temperature (37°C). Then the method of treatment is replaced in two groups for the next 12 sessions. Each patient gets dialysis once with routine temperature and once with cool dialysate. Patients are assessed during 24 dialysis sessions; the first group receives HD for 12 sessions using cool dialysate (35.5°C) and the second group is on HD with standard dialysate temperature (37°C). Then the method of treatment is replaced in two groups for the next 12 sessions. During the study, all the dialysis conditions are maintained the same, except temperature of dialysate (37°C or 35.5°C). All patients are on HD using GAMBRO AK96 HD machine

IRCT201306268140N2 *(Continued)*

Outcomes	• Dialysis adequacy • Blood pressure • Temperature
Starting date	22 June 2013
Contact information	Mollaei Einollah Kilometer 2 Goran-Sari, Golestan University of Medical Sciences, Gorgan Gorgan Golestan, Islamic Republic of Iran 00981714426900 Mollaei@goums.ac.ir
Notes	

IRCT2016060228219N1

Trial name or title	Effects of cool dialysate on sleep quality in patients undergoing haemodialysis
Methods	Single-centre cross-over RCT
Participants	Inclusion criteria • Consent for participation in the study; aged > 18 years and maximum 75 years; suffering from vision, hearing loss; not suffering from clear mental disorders and severe emotional mood disorders, which prevent effective communication; patients with chronic renal failure (patients who last had dialysis 6 months previously); patients receiving dialysis treatment 3 times/week and each session for 4 hours; not suffering from endocrine disorders (such as hypothyroidism, hyperparathyroidism); patients who have received scores higher than 5 Pittsburgh Sleep Quality Index; patients with haemoglobin levels > 8 mg/dL; lack of debilitating diseases and disorders such as severe chronic heart, respiratory, hepatic, history of seizures and severe neuropathy based on medical records and patient history; lack of psychiatric disorders (schizophrenia, anxiety, depression) or dementia, or stay in psychiatric wards because of the items listed; no history of kidney transplant Exclusion criteria • Patients who develop acute complications during HD (disequilibrium syndrome, embolism, dysrhythmia, cardiac, respiratory arrest, coma); patients who discontinued their dialysis for any reason; patients who are referred for kidney transplants (patients who receive kidney transplantations during the study); the patient's death, patients who cannot tolerate cold dialysis; the patient's unwillingness to continue to participate in the study
Interventions	Control • temperature of HD fluid (dialysate) is regulated at 37°C. Type of filter, coefficient of ultra-filtration, blood flow rate and type of apparatus are constant during the study Intervention • Temperature of HD fluid is regulated on (35.5°C) and type of filter, coefficient of ultra-filtration, blood flow rate are not changed
Outcomes	No outcome of interest was defined
Starting date	22 Sep 2016

IRCT2016060228219N1 *(Continued)*

Contact information	
Notes	

Maheshwari 2015

Trial name or title	Effect of cool vs. warm dialysate on toxin removal: rationale and study design
Methods	A single-centre, randomised cross-over study
Participants	Inclusion criteria • Adult patients male or female (aged 21 to 70 years) • Minimum dialysis vintage of 3 months • Stable on HD • Blood access capable of delivering the blood flow rate > 250 mL/min Exclusion criteria • History of recurring or persistent hypotension in the past 1 month • Pregnant woman • Severely hypertensive patients (SBP > 180 mmHg and/or DBP > 115 mmHg) • Severely hypotensive patients (SBP < 100 mmHg and/or DBP < 60 mmHg) • Paradoxically hypertensive patients whose BP increases by > 20% of baseline during dialysis (in the past 1 month) • History of recent myocardial infarction or unstable angina (within the past 6 months) • Significant valvular disease, i.e. severe aortic stenosis and moderate-severe mitral regurgitation • Patients with end-stage organ disease e.g. COPD, recent or debilitating CVA • Patients with left ventricular dysfunction, chronic heart failure and older age group more than 70 years • Patient with recent stroke (within the past 6 months) • History of known arrhythmia • Participation in another clinical intervention trial • Unable to consent
Interventions	Intervention • Cool dialysis with dialysate temperature at 35.5°C Control • Warm dialysis with dialysate temperature at 37°C
Outcomes	• IDH rate • Lowest SBP during dialysis • Urea clearance-based dialysis adequacy (Kt/V_{urea})
Starting date	July 2013
Contact information	Vaibhav Maheshwari LF Dialysis Center, National University Hospital, Singapore, SGN, Singapore, 298135
Notes	

MY TEMP 2017

Trial name or title	Major Outcomes With Personalized Dialysate TEMPerature (MyTEMP)
Methods	Cluster RCT
Participants	Patients undergoing HD in the dialysis centres that meet the following criteria Inclusion criteria • The medical director of the dialysis centre must provide informed consent and be willing to transition their patients to receive temperature-reduced personalized HD (if randomised to the intervention) or stay with the standard 36.5°C HD temperature during the course of the studies (if randomised to the control group); and • The centre must care for a minimum of 15 patients being treated with conventional in-centre HD 3 times/week. Exclusion criteria • The centre cares for less than 15 patients being treated with conventional in-centre HD 3 times/week
Interventions	Intervention • Dialysis centres randomised to the intervention arm provided temperature-reduced personalized HD. A nurse set the temperature of the dialysate to 0.5°C below each patient's body temperature measured just before starting the dialysis treatment. We are aware that some dialysis machines (e.g. Fresenius 5008) are only able to modify dialysate temperature by 0.5°C increments. For centres with those machines, the temperature should be lowered by a minimum of 0.5°C and a maximum of 0.9°C. Control • Dialysis centres in the control group provided usual care, which is standard dialysis using a fixed dialysate temperature of 36.5°C
Outcomes	Primary outcome • Composite outcome of all-cause mortality or major cardiovascular event rate Secondary outcomes • Cardiovascular-related mortality; Hospitalisation for non-fatal myocardial infarction; Hospitalisation for non-fatal ischaemic stroke; Hospitalisation for non-fatal congestive heart failure; Composite outcome of all-cause mortality or major cardiovascular event; and HD sessions complicated by IDH
Starting date	3 April, 2017
Contact information	Amit X Garg, London Health Sciences Centre, London, Ontario, Canada, N6A5W9
Notes	Trial registration: NCT02628366

HD - haemodialysis; IDH - intradialytic hypotension; RCT - randomised controlled trial

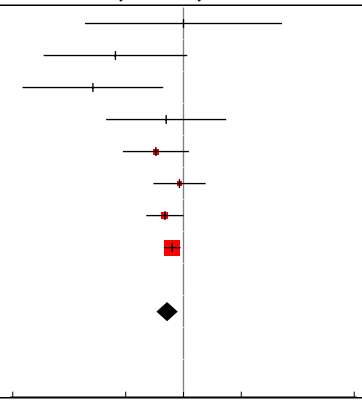
DATA AND ANALYSES

Comparison 1. Fixed reduction of dialysate temperature versus standard dialysate temperature

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Intradialytic hypotension	8		Rate Ratio (Random, 95% CI)	0.52 [0.34, 0.80]
2 Discomfort rate: cold sensation, shivering, and related symptoms	4		Rate Ratio (Random, 95% CI)	8.31 [1.86, 37.12]
3 Mean BP at the end of dialysis	8	188	Mean Difference (IV, Random, 95% CI)	6.46 [2.84, 10.08]
4 Change in body temperature during dialysis	5	102	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.56, -0.32]

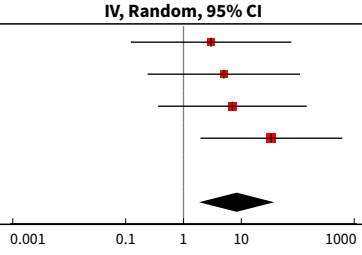
Analysis 1.1. Comparison 1 Fixed reduction of dialysate temperature versus standard dialysate temperature, Outcome 1 Intradialytic hypotension.

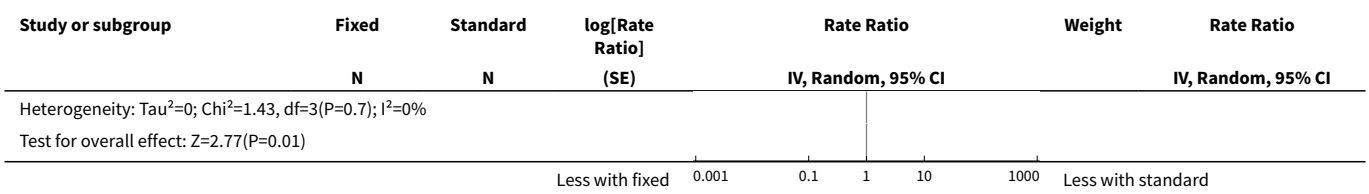
Study or subgroup	Fixed N	Standard N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
Levy 1992	0	0	0 (2)		1.16%	1[0.02,50.4]
Ayoub 2004	0	0	-2.7 (1.46)		2.14%	0.07[0,1.16]
Jost 1993	0	0	-3.6 (1.43)		2.23%	0.03[0,0.45]
Selby 2006b	0	0	-0.7 (1.22)		3.02%	0.5[0.05,5.48]
Gritters 2005	0	0	-1.1 (0.67)		9.06%	0.33[0.09,1.24]
Ebrahimi 2017	0	0	-0.2 (0.53)		13.38%	0.85[0.3,2.41]
Sherman 1984	0	0	-0.7 (0.38)		21.86%	0.48[0.23,1]
Quereda 1988	0	0	-0.4 (0.17)		47.16%	0.64[0.46,0.89]
Total (95% CI)					**100%**	**0.52[0.34,0.8]**
Heterogeneity: Tau^2=0.07; Chi^2=8.67, df=7(P=0.28); I^2=19.24%						
Test for overall effect: Z=3.01(P=0)						



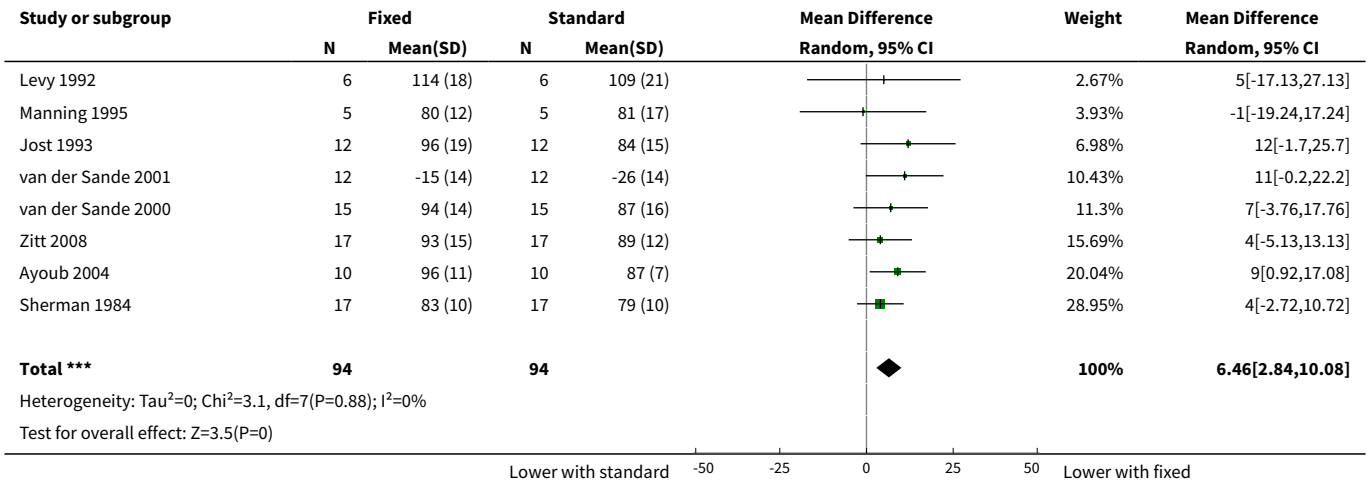
Analysis 1.2. Comparison 1 Fixed reduction of dialysate temperature versus standard dialysate temperature, Outcome 2 Discomfort rate: cold sensation, shivering, and related symptoms.

Study or subgroup	Fixed N	Standard N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
van der Sande 2000	0	0	1.1 (1.63)		21.97%	3[0.12,73.31]
Ayoub 2004	0	0	1.6 (1.55)		24.29%	5[0.24,104.37]
Selby 2006b	0	0	2 (1.51)		25.6%	7.03[0.36,135.58]
Sajadi 2016	0	0	3.5 (1.44)		28.15%	33.12[1.97,556.88]
Total (95% CI)					**100%**	**8.31[1.86,37.12]**

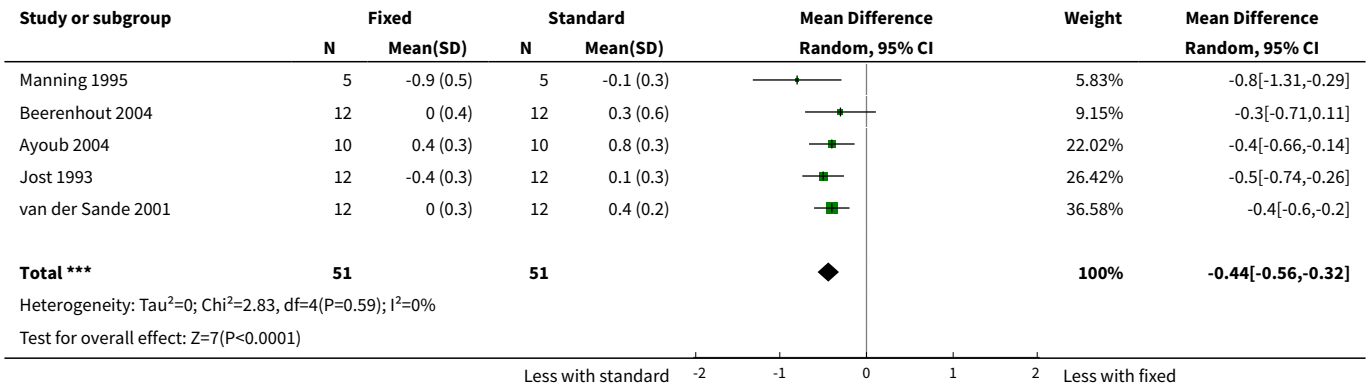




Analysis 1.3. Comparison 1 Fixed reduction of dialysate temperature versus standard dialysate temperature, Outcome 3 Mean BP at the end of dialysis.



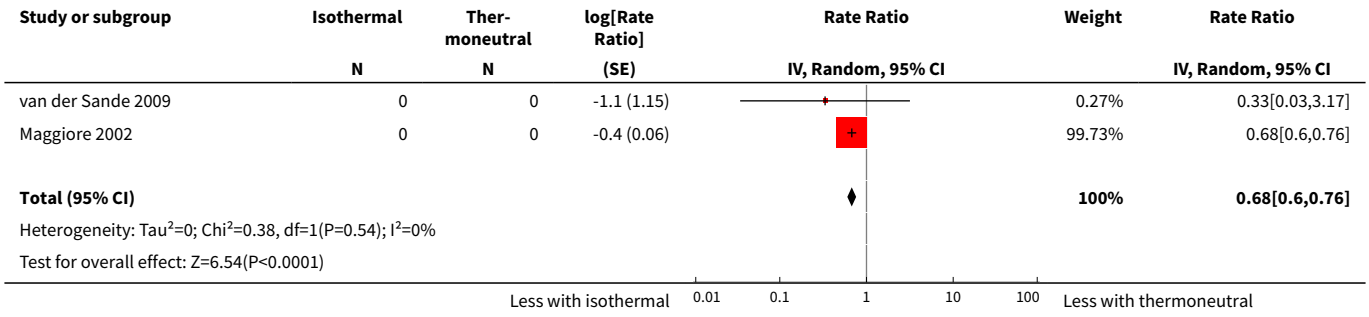
Analysis 1.4. Comparison 1 Fixed reduction of dialysate temperature versus standard dialysate temperature, Outcome 4 Change in body temperature during dialysis.



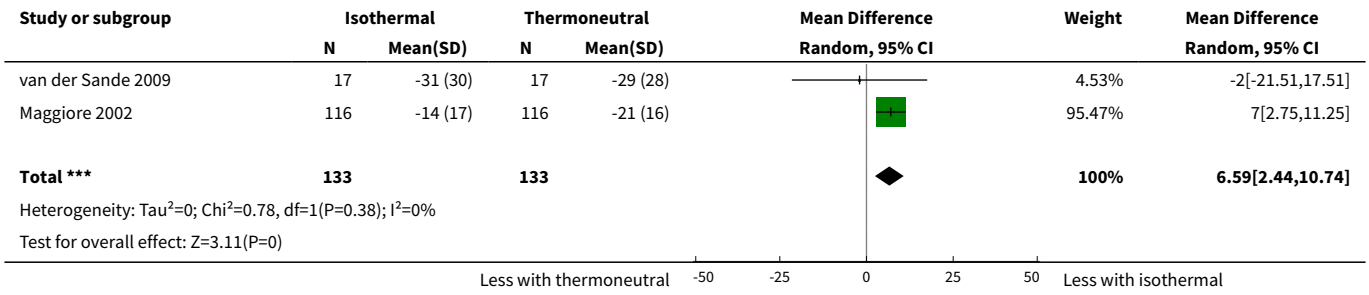
Comparison 2. Isothermal dialysate versus thermoneutral dialysate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Intradialytic hypotension	2		Rate Ratio (Random, 95% CI)	0.68 [0.60, 0.76]
2 Change in SBP during dialysis	2	266	Mean Difference (IV, Random, 95% CI)	6.59 [2.44, 10.74]
3 Change in body temperature during dialysis	2	266	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.60, -0.21]

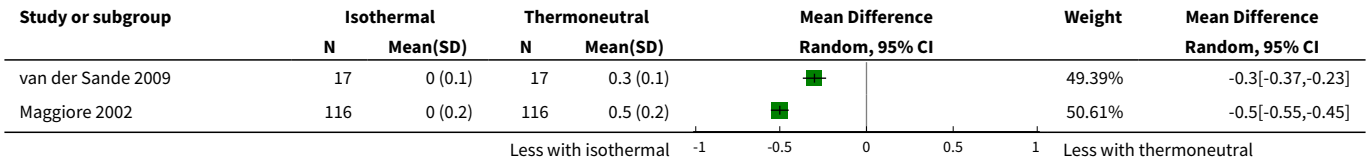
Analysis 2.1. Comparison 2 Isothermal dialysate versus thermoneutral dialysate, Outcome 1 Intradialytic hypotension.

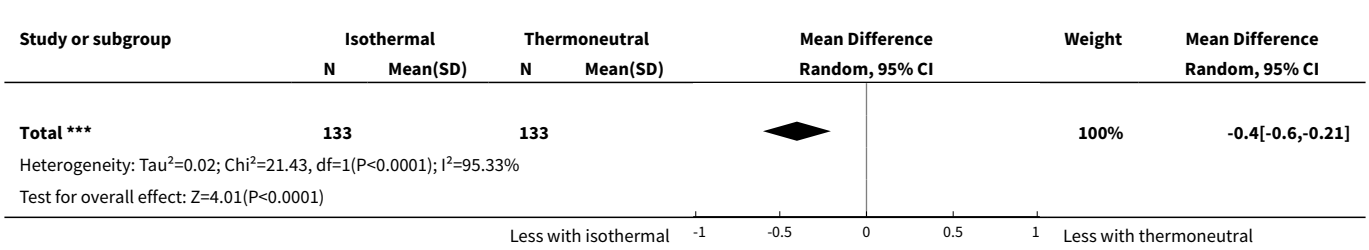


Analysis 2.2. Comparison 2 Isothermal dialysate versus thermoneutral dialysate, Outcome 2 Change in SBP during dialysis.



Analysis 2.3. Comparison 2 Isothermal dialysate versus thermoneutral dialysate, Outcome 3 Change in body temperature during dialysis.





APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. dialysis:ti,ab,kw 2. hemodialysis or haemodialysis):ti,ab,kw 3. hemodiafiltration or haemodiafiltration):ti,ab,kw 4. (hemofiltration or haemofiltration):ti,ab,kw 5. {or #1-#4} 6. (dialysis next solution*):ti,ab,kw 7. ((hemodialysis next solution*) or (haemodialysis next solution*)):ti,ab,kw 8. (dialysis next fluid*):ti,ab,kw 9. ((hemodialysis next fluid*) or (haemodialysis next fluid*)):ti,ab,kw 10.dialy*ate*:ti,ab,kw 11.{or #6-#10} 12.temperature:ti,ab,kw 13.heat*:ti,ab,kw 14.cold*:ti,ab,kw 15.cool*:ti,ab,kw 16.warm*:ti,ab,kw 17.tepid:ti,ab,kw 18.lukewarm:ti,ab,kw 19.{or #12-#18} 20.{and #5, #11, #19}
MEDLINE	1. Renal Replacement Therapy/ 2. Renal Dialysis/ 3. Hemodiafiltration/ 4. Hemodialysis, home/ 5. exp Hemofiltration/ 6. dialysis.tw. 7. (hemodialysis or haemodialysis).tw. 8. (hemofiltration or haemofiltration).tw. 9. (hemodiafiltration or haemodiafiltration).tw. 10.or/1-9 11.exp Dialysis Solutions/ 12.dialysis solution$.tw. 13.dialysis fluid$.tw.

(Continued)

	14.(hemodialysis solution$ or haemodialysis solution$).tw. 15.(hemodialysis fluid$ or haemodialysis fluid$).tw. 16.dialy#ate$.tw. 17.or/11-16 18.exp Temperature/ 19.temperature.tw. 20.reduc$.tw. 21.heat$.tw. 22.cool$.tw. 23.cold$.tw. 24.warm$.tw. 25.tepid.tw. 26.lukewarm.tw. 27.or/18-26 28.and/10,17,27
EMBASE	1. exp renal replacement therapy/ 2. extended daily dialysis/ 3. hemodialysis/ 4. home dialysis/ 5. hemofiltration/ 6. hemodiafiltration/ 7. dialysis.tw. 8. (hemodialysis or haemodialysis).tw. 9. (hemofiltration or haemofiltration).tw. 10.(hemodiafiltration or haemodiafiltration).tw. 11.renal replacement therapy-dependent renal disease/ 12.or/1-11 13.Hemodialysis Fluid/ 14.Dialysis Fluid/ 15.Dialysate/ 16.dialysis solution$.tw. 17.dialysis fluid$.tw. 18.(hemodialysis solution$ or haemodialysis solution$).tw. 19.(hemodialysis fluid$ or haemodialysis fluid$).tw. 20.dialy#ate$.tw. 21.or/13-20 22.Temperature/ 23.Heat/ 24.Cold/ 25.High Temperature/ 26.Low Temperature/ 27.temperature.tw. 28.heat$.tw. 29.cool$.tw. 30.cold$.tw. 31.warm$.tw. 32.tepid.tw. 33.lukewarm.tw. 34.or/22-33 35.and/12,21,34

Appendix 2. Risk of bias assessment tool

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

(Continued)

	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) 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.

CONTRIBUTIONS OF AUTHORS

1. Drafting the protocol: YT, HT, YN, YK, MK, SS, TI, S Fukuma, YY, S Fukuhara
2. Study selection: YT, HT
3. Extracting data from studies: YT, HT
4. Entering data into RevMan: YT
5. Carrying out the analysis: YT, YN, YK, MK, YY
6. Interpreting the analysis: YT, HT, YK, MK, SS, TI, S Fukuma, YY, S Fukuhara
7. Drafting the final review: YT
8. Disagreement resolution: YK
9. Updating the review: YT, HT, YN, YK, MK, SS, TI, S Fukuma, YY, S Fukuhara

DECLARATIONS OF INTEREST

All authors declare there are no conflicts of interest.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We attempted to contact study authors to ask for more detail, but they were unable to provide further information, or we were not able to make contact. Information on the outcomes reported was insufficient (e.g. lowest SBP or lowest BT). We therefore were not able to carry out the qualitative analysis as planned. Additionally, we performed quantitative syntheses based on paired data because of a lack of first phase data of cross-over studies.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dialysis Solutions [adverse effects]; *Temperature; Hypotension [*etiology] [prevention & control]; Randomized Controlled Trials as Topic; Renal Dialysis; Renal Insufficiency, Chronic [therapy]

MeSH check words

Humans