Effect of Lowering the Dialysate Temperature in Chronic Hemodialysis: A Systematic Review and Meta-Analysis

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Abstract

Background and objectives Lowering the dialysate temperature may improve outcomes for patients undergoing chronic hemodialysis. We reviewed the reported benefits and harms of lower temperature dialysis.

Design, setting, participants, & measurements We searched the Cochrane Central Register, OVID MEDLINE, EMBASE, and Pubmed until April 15, 2015. We reviewed the reference lists of relevant reviews, registered trials, and relevant conference proceedings. We included all randomized, controlled trials that evaluated the effect of reduced temperature dialysis versus standard temperature dialysis in adult patients receiving chronic hemodialysis. We followed the Grading of Recommendations Assessment, Development and Evaluation approach to assess confidence in the estimates of effect (*i.e.*, the quality of evidence). We conducted meta-analyses using random effects models.

Results Twenty-six trials were included, consisting of a total of 484 patients. Compared with standard temperature dialysis, reduced temperature dialysis significantly reduced the rate of intradialytic hypotension by 70% (95% confidence interval, 49% to 89%) and significantly increased intradialytic mean arterial pressure by 12 mmHg (95% confidence interval, 8 to 16 mmHg). Symptoms of discomfort occurred 2.95 (95% confidence interval, 0.88 to 9.82) times more often with reduced temperature compared with standard temperature dialysis. The effect on dialysis adequacy was not significantly different, with a Kt/V mean difference of −0.05 (95% confidence interval, −0.09 to 0.01). Small sample sizes, loss to follow-up, and a lack of appropriate blinding in some trials reduced confidence in the estimates of effect. None of the trials reported long-term outcomes.

Conclusions In patients receiving chronic hemodialysis, reduced temperature dialysis may reduce the rate of intradialytic hypotension and increase intradialytic mean arterial pressure. High–quality, large, multicenter, randomized trials are needed to determine whether reduced temperature dialysis affects patient mortality and major adverse cardiovascular events.

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Introduction

Approximately 2 million patients worldwide receive life–sustaining chronic hemodialysis treatments (1). Intradialytic hypotension occurs in ≤30% of hemodialysis treatments and is associated with substantial long–term mortality (2–4). Maggiore *et al.* (5) proposed cool dialysis to prevent intradialytic hypotension by increasing peripheral vascular resistance, improving cardiac output, and altering the levels of vasoactive peptides. Nephrologists, however, remain cautious about using this modality of hemodialysis because of limited evidence about its long-term effects and the assumed disadvantages. These disadvantages include the discomfort that patients may experience in association with cool dialysis and the concern that it may interfere with achieving adequate dialysis.

In 2006, Selby and McIntyre (6) conducted a systematic review to assess the effects of lowering dialysate temperature. The review was restricted to English language articles, and Selby and McIntyre (6) were unable to report the effects of lowering dialysate temperature on long–term patient–important outcomes because of lack of data. Since 2006, more trials have been published on this topic (7,8). We conducted this systematic review to evaluate the effect of cool dialysis compared with standard temperature dialysis on patient-important outcomes in adults undergoing maintenance chronic hemodialysis.

Materials and Methods

Data Sources and Searches

We conducted this systematic review in accordance with a prespecified registered protocol available at http://www.crd.york.ac.uk/PROSPERO (registration no. CRD42011001104). We reported the results

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according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (9).

We performed an electronic search of the Cochrane Central Register of Controlled Trials (until April of 2015), OVID MEDLINE (from 1946 to April of 2015), EMBASE (from 1947 to April of 2015), and Pubmed (from 1951 to April of 2015). A methodologic filter was applied to limit retrieval to clinical trials and the human population (detailed search strategy is provided in Supplemental Appendix 1) (10). We reviewed the reference lists of relevant articles and reviews as well as trials registered on the ClinicalTrials.gov website. We searched for conference proceedings from 2007 to 2014 using the Web of Science and abstracts presented at recent annual meetings of the American Society of Nephrology, the Canadian Society of Nephrology, the National Kidney Foundation, the European Renal Association-European Dialysis and Transplant Association, and the International Society of Nephrology.

Study Selection

We used the following eligibility criteria.

Studies. We included all randomized, controlled trials from January of 1946 to April of 2015. This included crossover, parallel arm, and cluster trials.

Participants. We included all adult patients (aged >18 years old) who received chronic hemodialysis in either an inpatient or outpatient setting, regardless of BP at baseline.

Intervention. We compared standard temperature dialysis with any method of cool dialysis. Different methods of cool dialysis include fixed reduction in dialysate temperature programmed patient cooling, isothermic dialysis, and negative energy balance using a biofeedback temperature monitoring device. We used the trials' definitions of standard and cool dialysis temperature. We only included bicarbonate-based dialysis and excluded acetate-based dialysis, because acetate-based dialysis is not used in common practice anymore. We did not include hemodiafiltration or acetate-free biofiltration in this review.

Outcomes Measures. We abstracted information on the following outcomes: mortality, hospitalization, quality of life (QOL), intradialytic hypotension, BP, cardiovascular events, access failure, system clotting, bleeding, dialysis adequacy, and symptoms, including discomfort caused by cold sensation and cramping. We did not assess the effect of cool dialysis on energy transfer, vasoactive peptides, or radiologic and diagnostic tests changes (*e.g.*, changes in magnetic resonance, echocardiogram, or computed tomography).

Language. We included trials published in any language.

Publication Status. We reviewed all published and unpublished studies. Abstracts with relevant information were also reviewed.

Two investigators independently screened the search results for articles on the basis of the title or the title and abstract. The full-text article was retrieved for any citation considered potentially relevant by any investigator. Each of the investigators then independently assessed the eligibility of each article by using a pilot–tested, standardized form with written instructions. Any disagreement was resolved by consensus. If at least one of the characteristics was not met, the article was excluded. We used Cohen κ-value to measure agreement beyond chance between reviewers (11).

Data Extraction and Quality Assessment

We extracted data using a pilot-tested and standardized form. Two investigators independently extracted all relevant data from included trials. Results of data extraction were then compared, and any discrepancy was resolved by discussion. When the same results were presented in more than one publication, we included the publication with the most complete results. If results were incomplete or unclear, we contacted study authors for additional information.

We collected the following information from each trial: trial characteristics (author name, year of publication, country, language, number of centers, number of countries, and inclusion and exclusion criteria), patient characteristics (number, patients completing follow-up, age, comorbidities, and baseline BP), intervention and comparison characteristics (type of dialysate cooling, duration of intervention, and temperature of dialysate in each group), cointerventions (concomitant BP medication use), and outcomes. Also, we collected information about funding sources, conflict of interest statements, consent, and ethics approval.

Two reviewers independently assessed the risk of bias of the selected trials. To assess any risk of bias, different domains were considered for each outcome. These domains were adequate random sequence generation, concealment of allocation, adherence to the intention-to-treat principle, stopping early for benefit, proportion of patients lost to follow-up, selective reporting of outcomes, freedom from other biases, and blinding of patients, investigators, dialysis nurses, clinical outcome assessors, data collectors, and data analyzers.

To assess the confidence in the estimates of effect (*i.e.*, quality of evidence) across studies, we followed the Grading of Recommendations Assessment, Development and Evaluation GRADE approach (12) by making judgments about the risk of bias, publication bias, indirectness, imprecision, and inconsistency among different trials. To assess publication bias, we used the funnel plot and Egger linear regression test (13).

Data Synthesis and Analyses

The intervention effect estimates for each outcome were combined quantitatively (pooled) from different trials when appropriate using RevMan, version 5. When quantitative synthesis of the data was not appropriate, the results were summarized qualitatively. The Breslow–Day test was used to measure the percentage of total variation across studies caused by heterogeneity (I^2). Trial data were considered worthy of exploration of heterogeneity when the I^2 statistic was >50%. Attempts were also made to explain heterogeneity on the basis of the patient clinical characteristics and interventions of the trials included.

Rates were expressed as rate ratios and compared using generic inverse variance. Continuous data were expressed as mean differences. Overall results were pooled using a random effects model (14,15).

Sensitivity analyses to assess robustness of results and subgroup analyses to determine whether the summary effects vary in relation to clinical characteristics of the population in the included trials were prespecified. The treatment effects were examined according to risk of bias. Two subgroup analyses were undertaken. The first compared the effect of fixed temperature reduction compared

with biofeedback devices on different outcomes. The second compared the effect of cooling dialysate in patients with stable and unstable BPs at baseline.

Results

Study Selection

Study selection is presented in Figure 1; 4019 citations were screened, and a total of 26 trials were included in the review. The chance-corrected agreement for full-text eligibility was good (κ=0.87). Details about the excluded studies are presented in Supplemental Appendix 2. The most important reasons for exclusion included the use of acetate dialysis, duplicate data, and a lack of primary data.

Study Characteristics

Table 1 presents the details about characteristics of included trials (16–40) (B. Jo *et al.*, unpublished data). All 26 trials selected for the final review were crossover, randomized trials published in English. Nineteen trials had no dropouts. The other seven trials had patient dropout of varying degrees (8%–42%) (16–22). One trial was an international multicenter study (20) (27 centers and nine countries), and the rest were conducted in single centers.

Participants. The included trials involved 484 participants; 24 of 26 trials were small, with <20 participants (6–19 participants). The remaining two trials involved 95 and 128 participants (19,20). The main inclusion criteria were adults (≥18 years old) with variability in baseline BP and duration on hemodialysis.

Intervention. Overall, the duration of each trial was short. Eighteen trials reported the effect of cool dialysis on the basis of two sessions of hemodialysis (one session in each arm of the trial) (16,17,21,23,27–39,41). Three trials evaluated the intervention in three to six hemodialysis sessions (22–24). Only three trials followed patients longer

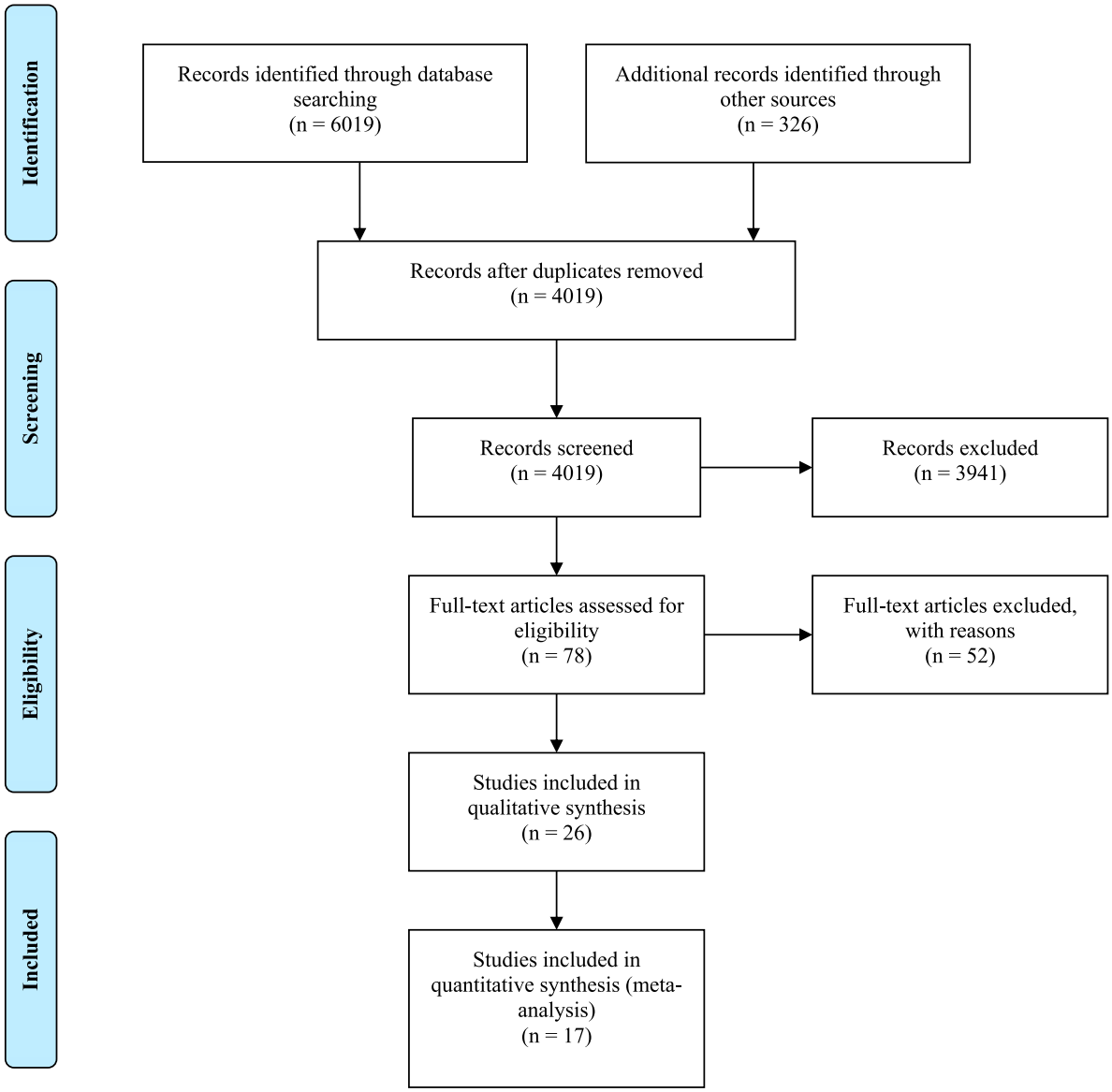

Figure 1. | **Flow chart of the article selection process based on preferred reporting items for systematic reviews and meta-analyses.**

Table 1. Characteristics of included trials

Study Country	Methods[a]	Participants	Intervention	Control	Outcomes	Exclusion Criteria
New Zealand (25)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: no; dropouts: 0	*n*=10; BP: five stable, five unstable; age 59.8±5.5 yr	Fixed temperature 35°C; duration: three sessions	Fixed temperature 36°C; duration: three sessions	Dialysis adequacy; BP; body temperature; symptoms; IDH	Circulation or vascular access problems, recent surgery, AKI, severe anemia, CAD
The Netherlands (16)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 1	*n*=12 (eight men, four women); BP: all stable; age 69±6 yr	Fixed temperature 35.5°C; duration: one session	Fixed temperature 36.5°C; duration: one session	BP; body temperature; hemodynamics	CHF (NYHA≥3), severe CAD, DM
The Netherlands (26)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 0	*n*=12 (seven men, five women); BP: all stable; age 64.7±2.6 yr	BTM (mean dialysate temperature 35.2°C); duration: one session	Fixed temperature 37.5°C; duration: one session	BP; body temperature; symptoms; IDH	CHF (EF≤25%), DM, CAD, NYHA≥3, using nitrates
United Kingdom (17)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: patients, not staff; dropouts: 1	*n*=10 (six men, four women); BP: not stable; age 67±2 yr	Fixed temperature 35°C; duration: one session	Fixed temperature 37°C; duration: one session	Dialysis adequacy; BP; body temperature; IDH; hemodynamics	Central venous catheter for access, severe CHF (NYHA≥3), heart transplant
United States (18)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 8	*n*=19 (six men, five women); BP: not stable; age 67.5 yr	Fixed temperature 35.5°C; duration: nine sessions	Fixed temperature 37°C; duration: nine sessions	Dialysis adequacy; BP; symptoms; IDH	Symptoms not reported
United States (23)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: staff, not patients; dropouts: 0	*n*=10 (three men, seven women); BP: not stable; age 61.1±12.5 yr	Fixed temperature 35°C; duration: three sessions	Standard fixed temperature; duration: three sessions	Dialysis adequacy; BP; symptoms; IDH	Uncontrolled HTN, DM, unstable angina, noncompliance, frequent hospitalizations, variable weight gain

Table 1. (Continued)

Study Country	Methods[a]	Participants	Intervention	Control	Outcomes	Exclusion Criteria
Canada (19)	Crossover design; allocation concealment: NR; sequence generation: block center randomization; blinding: patients and nurses; dropouts: yes but no clear details; some patients studied more than once	*n*=128; BP: all stable; age 58 yr	Fixed temperature 35°C; duration: 13 sessions on average	Fixed temperature 37°C; duration: seven sessions on average	IDH	Pre-HD body temperature 36°C–36.5°C
Sweden (27)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 0	*n*=10 (seven men, three women); BP: all stable; age 63 yr; time on HD: 3–49 mo	Fixed temperature 34.5°C; duration: one session	Fixed temperature 38.5°C; duration: one session	BP; body temperature	Not reported
United States (28)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 0	*n*=13 (eight men, four women); BP: not stable; age 67.6±13.8 yr	Fixed temperature 35.5°C; duration: one session	Fixed temperature 37°C; duration: one session	BP; hemodynamics; complications	Central venous catheter for access, vascular access dysfunction, active medical condition
Japan (29)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 0	*n*=7 (one men, six women); BP: not stable; age 53–75 yr	Fixed temperature 35.5°C; duration: one session	Fixed temperature 37°C; duration: one session	BP; symptoms	Not reported
United States (30)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: patients and investigators; dropouts: 0	*n*=12 (12 men); BP: not stable; age 62.5±3.6 yr; time on HD: 35.4±6.2 mo	Fixed temperature 35°C; duration: one session	Fixed temperature 37°C; duration: one session	BP; IDH; hemodynamics	Not reported
United States (31)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 0	*n*=15; BP: not reported	BTM negative energy (dialysate temperature 35.7°C); duration: one session	BTM thermoneutral (dialysate temperature 37.1°C); duration: one session	Dialysis adequacy; BP; body temperature; IDH; hemodynamics; symptoms	Not reported

Table 1. (Continued)

Study Country	Methods[a]	Participants	Intervention	Control	Outcomes	Exclusion Criteria
Japan (32)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 0	*n*=9; BP: not reported; age 43.5 yr	Fixed temperature 34°C; duration: one session	Fixed temperature 37°C; duration: one session	BP; hemodynamics	Not reported
Germany (33)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 0	*n*=9; BP: not reported	BTM (program cooling by 0.2°C); duration: one session	Fixed temperature 37°C; duration: one session	Dialysis adequacy; BP; body temperature; hemodynamics	Not reported
United States (34)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: patients and providers; dropouts: 0	*n*=6; BP: not reported; age 55±11 yr	Fixed temperature 35°C; duration: one session	Fixed temperature 37°C; duration: one session	BP; body temperature	Not reported
Nine countries (20)	Crossover design (27 centers); allocation concealment: NR; sequence generation: central; blinding: no; dropouts: 21	*n*=95; BP: not stable; age 66±12 yr	BTM isothermic; duration: 12 sessions on average	BTM thermoneutral; duration: 12 sessions on average	Dialysis adequacy; BP; symptoms; IDH; complications	Recent surgery, severe anemia, vascular access problems, malignancy, ascitis, CHF (NYHA class 4), use of any antihypertensive medications
United States (41)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: single blinded; dropouts: 0	*n*=7 (three men, four women); BP: all stable; age 46.1±4.2 yr	Fixed temperature 35°C; duration: one session	Fixed temperature 37°C; duration: one session	BP; body temperature; sleep measures	Chronic infection, CHF, chronic lung disease, arthritis, organic brain disease, drug/alcohol abuse or past psychiatric disorders requiring treatment; taking β-adrenergic blockers, clonidine,

Table 1. (Continued)

Study Country	Methods[a]	Participants	Intervention	Control	Outcomes	Exclusion Criteria
						methyldopa, antidepressants, sedatives, activating agents or pain medication, NSAIDs, and acetaminophen
Australia (35)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 0	*n*=8 (four men, four women); BP: not reported; age 54–79 yr	Fixed temperature 35.3°C±0.2°C; duration: one session	Fixed temperature 37.3°C±0.3°C; duration: one session	BP; body temperature	Not reported
United Kingdom (21)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: patients, not staff; dropouts: 1	*n*=10 (four men, six women); BP: not reported; age 65±11 yr	Fixed temperature 35°C; duration: one session	Fixed temperature 37°C; duration: one session	Dialysis adequacy; BP; body temperature; symptoms; IDH; QOL; hemodynamics	CHF (greater than NYHA class 3), cardiac transplant if it was not possible to obtain an echocardiogram
The Netherlands (36)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 0	*n*=9 (four men, five women); BP: three of nine not stable; age 68.7±10.4 yr	Fixed temperature 35.5°C; duration: one session	Fixed temperature 37°C; duration: one session	BP; body temperature; IDH	Not reported
The Netherlands (37)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 0	*n*=15 (seven men, eight women); BP: not reported; age 55 yr	Fixed temperature 35.5°C; duration: one session (1 h)	Fixed temperature 37.5°C; duration: one session (1 h)	BP; body temperature; symptoms; hemodynamics	Severe CAD, DM, CHF (LVEF<30%)
The Netherlands (38)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 0	*n*=12 (seven men, five women); BP: all stable; age 56.67±15.95 yr	Fixed temperature 35.5°C; duration: one session	Fixed temperature 37.5°C; duration: one session	BP; body temperature	Not reported

Table 1. (Continued)

Study Country	Methods[a]	Participants	Intervention	Control	Outcomes	Exclusion Criteria
The Netherlands (39)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 0	*n*=13; BP: all stable	BTM isothermic; duration: one session	BTM thermoneutral; duration: one session	Body temperature	Frequent IDH, severe CAD severe CHF, central venous catheter for access
The Netherlands (22)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 3	*n*=17; (eight men, six women); BP: not stable; age 60.9±10.4 yr	BTM isothermic; BTM cooling 0.5°C below body temperature; duration: 1.5 sessions on average	BTM thermoneutral; duration: 1.5 sessions on average	BP; body temperature; symptoms; hemodynamics; IDH	Age >85 yr, not able to read and understand English, using central venous catheter for access
China (24)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: patients; dropouts: 0	*n*=9; BP: not reported; age 63±2.2 yr	Fixed temperature 35°C; duration: two sessions	Fixed temperature 37.5°C; duration: two sessions	BP; body temperature; IDH; hemodynamics; dialysis adequacy	Not reported
Australia (40)	Crossover design; allocation concealment: NR; sequence generation: NR; blinding: NR; dropouts: 0	*n*=17 (nine men, eight women); BP: all stable; age 63.3±3.2 yr	Fixed temperature 35°C; duration: NC	Fixed temperature 37°C; duration: NC	BP; Hemodynamics	Arthritis, severe PAD, α- or β-adrenergic blockers

NR, not reported; IDH, intradialytic hypotension; CAD, coronary artery disease; CHF, congestive heart failure; NYHA, New York Heart Association classification; DM, diabetes mellitus; BTM, biofeedback temperature monitoring; EF, ejection fraction; HTN, hypertension; HD, hemodialysis; NSAIDs, nonsteroidal anti–inflammatory drugs; QOL, quality of life; LVEF, left ventricular ejection fraction; NC, not clear; PAD, peripheral arterial disease.

[a]None of the studies stopped early for benefit. It is not clear if the studies had selective reporting of outcomes.

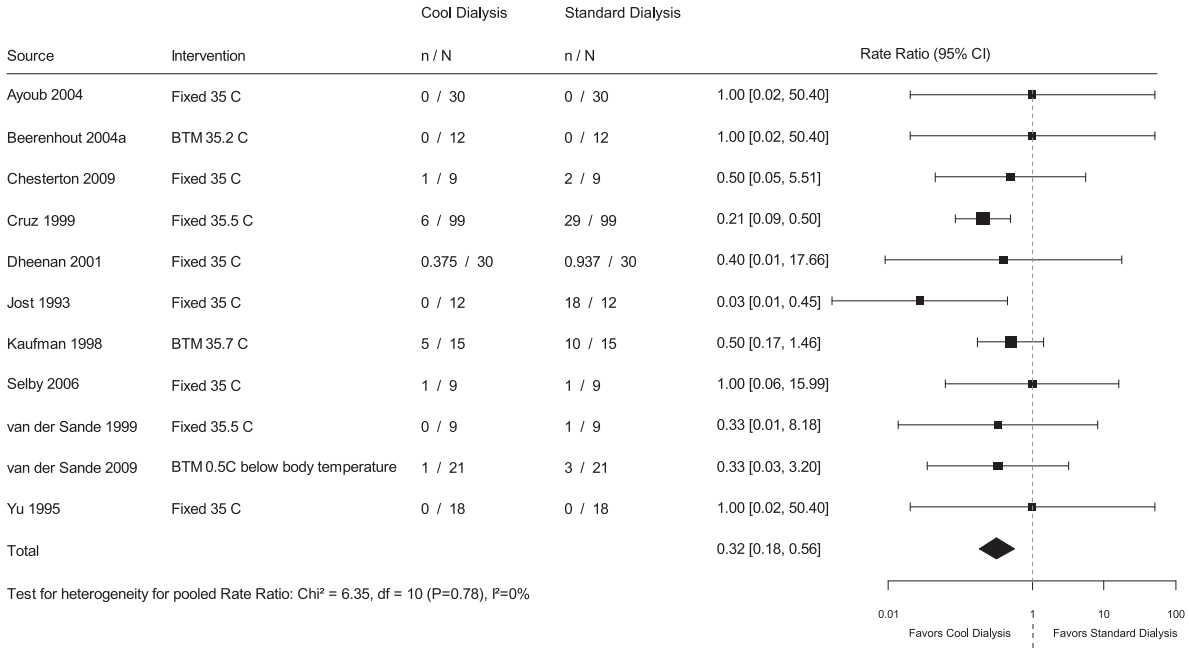

Figure 2. | **Effect of low temperature dialysis on intradialytic hypotension.** 95% CI, 95% confidence interval; BTM, biofeedback temperature monitoring.

than six sessions (18, 20, and 24 sessions on average, respectively) (18–20). Of note, trials with prolonged follow-up had a high dropout rate, and an intention-to-treat analysis was not followed. It is not clear if the dropouts were preferential in cool dialysis or not. Twenty trials used fixed temperature cooling of dialysate fluid (34°C–35.5°C). Six trials used a biofeedback temperature monitoring device (one negative energy, two cooling, and three isothermic devices). In the standard dialysis group, the dialysate temperature ranged from 36°C to 37.5°C, except for in one trial that used a temperature of 38.5°C. Including or excluding this trial did not affect our results, and we decided to include it, although a temperature >37.5°C is higher than the standard and an unusual practice.

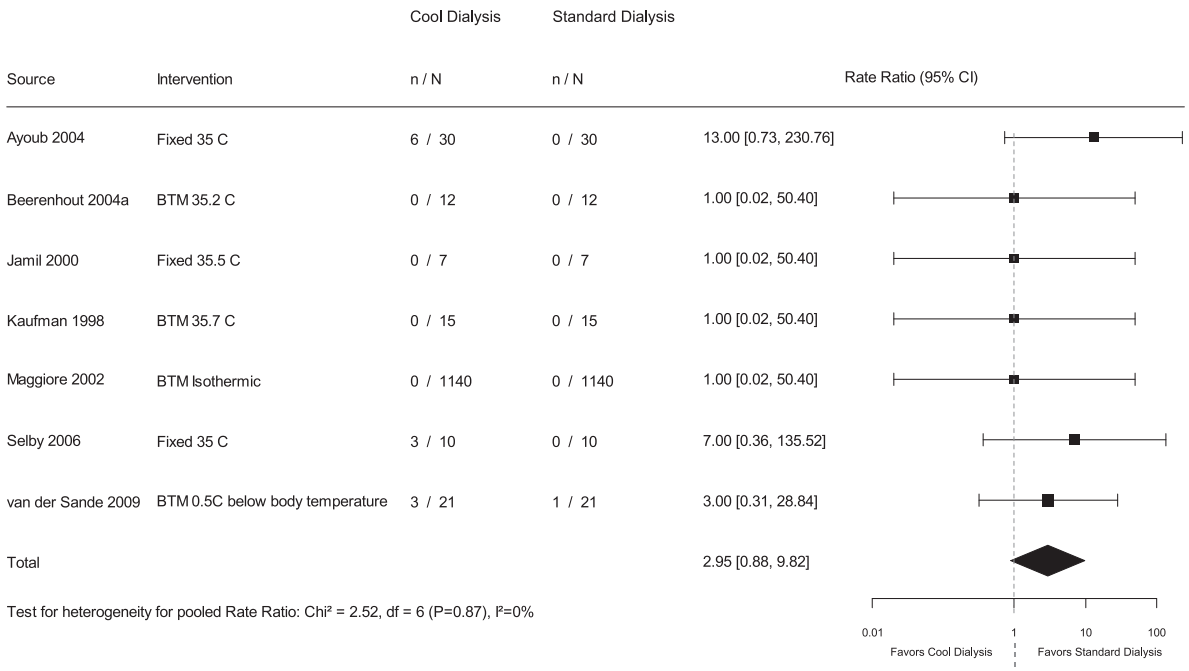

Figure 3. | **Effect of low temperature dialysis on symptoms of discomfort.** 95% CI, 95% confidence interval; BTM, biofeedback temperature monitoring.

Outcomes. No trial included mortality, hospitalization, cardiovascular events, access failure, bleeding, or system clotting as an outcome. One trial reported the effect of cooling dialysate on QOL; 12 trials reported intradialytic hypotension, 24 trials reported BP, nine trials reported dialysis adequacy, and ten trials reported symptoms of discomfort.

Risk of Bias within Studies

Seven trials described blinding of patients, four trials blinded health care providers or investigators, two trials reported no blinding, and blinding was unclear in the rest of the trials. Only one trial reported a central process for random sequence generation, and the rest did not report any methods for sequence generation or concealment of allocation. We encountered challenges when evaluating our criteria of selective reporting of outcomes, because published protocols for those trials were unavailable. None of the trials were stopped early for benefit or harm.

Intradialytic Hypotension

Thirteen trials reported intradialytic hypotension as an outcome. We summarize the definitions used by these trials to define intradialytic hypotension in Supplemental Appendix 3. Two trials (19,20) reported intradialytic hypotension as the proportion of sessions where it occurred. These studies (19,20) reported that 5.5%–25% of the dialysis sessions were complicated by intradialytic hypotension in the cool dialysis group compared with 11.2%–50% of the sessions in the usual dialysate group. The pooled effect on the basis of 11 trials (Figure 2), which included a total of 552 hemodialysis sessions in 120 patients (with an average of 4.6 sessions per patient), showed that the rate of intradialytic hypotension was reduced by 70% (95% confidence interval [95% CI], 49% to 89%) with cool dialysis compared with standard dialysis (I^2=0%).

Symptoms of Discomfort

The symptoms that were considered were discomfort on dialysis from feeling cold, shivering, or cramps. The reporting of symptoms of discomfort during dialysis was generally poor. Ten trials reported these symptoms, but they did not uniformly rate their severity. Cruz *et al.* (18) reported the proportion of sessions with symptoms on cold dialysate (13%). The pooled effect on the basis of nine trials (Figure 3), which included a total of 2548 hemodialysis sessions, showed that symptoms occur 2.95 (95% CI, 0.88 to 9.82) times more commonly with cool dialysis compared with standard dialysis (I^2=0%).

Dialysis Adequacy

Nine trials reported dialysis adequacy as an outcome. Dheenan and Henrich (23) reported urea reduction rate. Levin and colleagues (22) reported no difference in urea kinetics, but no clear estimates were presented. The other seven trials reported Kt/V. Our results show that cool

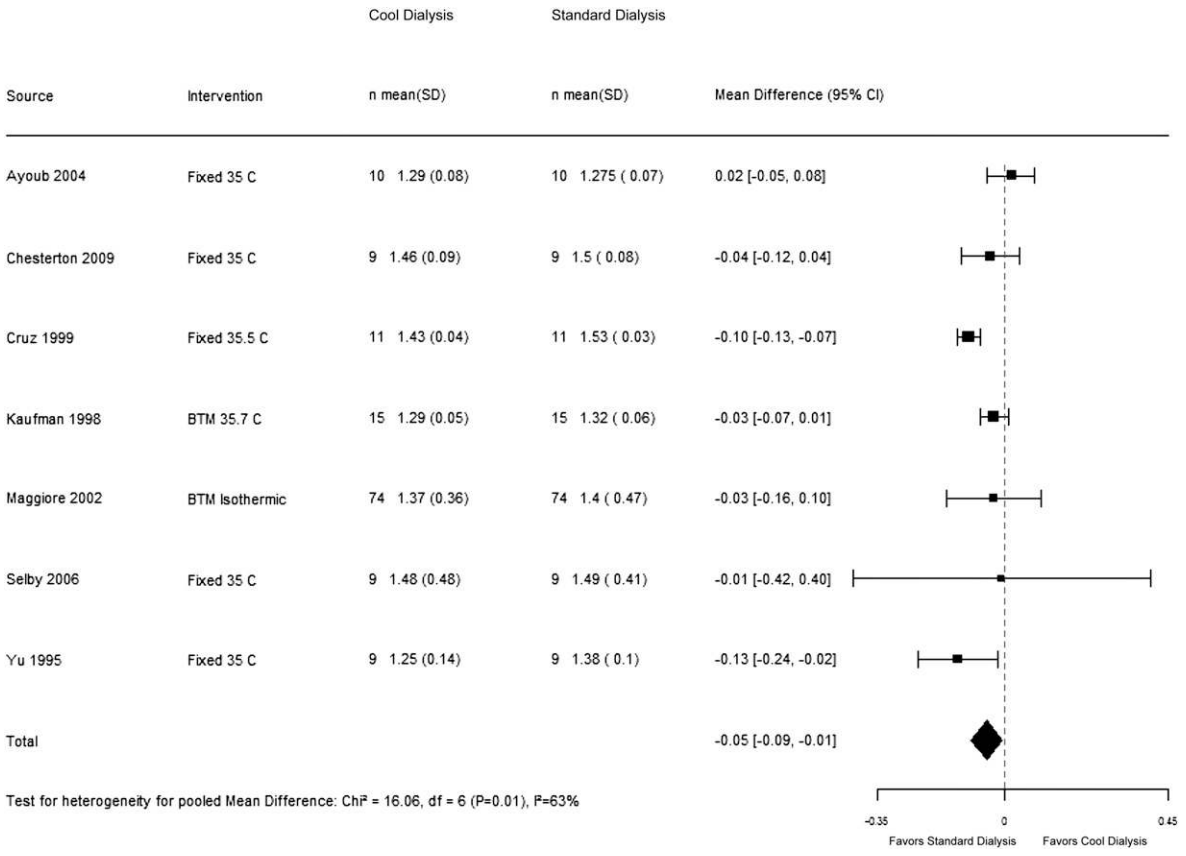

Figure 4. | **Effect of low temperature dialysis on dialysis adequacy.** 95% CI, 95% confidence interval; BTM, biofeedback temperature monitoring.

dialysis did not have a significant effect on dialysis adequacy compared with standard dialysis, with a pooled Kt/V mean difference of −0.05 (95% CI, −0.09 to 0.01). We observed some heterogeneity in the results on this outcome across the trials (I^2=63%) (Figure 4), which was partially explained (I^2=18%) when we conducted a predefined sensitivity analysis on the basis of risk of bias.

BP

Twenty-four trials reported BP. Some reported a change in mean arterial pressure (MAP), intradialytic MAP, MAP posthemodialysis, changes in systolic and diastolic BP, or systolic and diastolic BP posthemodialysis. We choose to pool change in MAP (before and after hemodialysis), because it is less affected by baseline BP before hemodialysis and was one of the most frequently reported BP measures in the included trials. We meta-analyzed the results of ten trials that reported change in MAP (Figure 5). Our results show that cool dialysis is associated with significantly higher MAP of 12 mmHg (95% CI, 8 to 16 mmHg) compared with standard dialysis (I^2=34%). Additionally, in Table 2, we summarize the effect on other measures of BP described in 14 trials that we were not able to mathematically pool.

QOL

The work by Selby *et al.* (21) was the only trial that reported the effect of cool dialysis on QOL. In this trial, there was no difference between cool and standard dialysis on QOL using the short form 36 health survey assessment tool. Ayoub and Finlayson (25), although not clearly assessing QOL, did indicate that 80% of the patients receiving cool dialysis self-reported a dramatic improvement in their general health.

Additional Analyses

According to our protocol for this systematic review, we explored the effects of cool dialysis on heterogeneous outcomes by subgroup analysis. We stratified by different interventions (fixed versus biofeedback temperature monitoring device cooling of dialysate) and patient characteristics (stability of baseline BP). The latter analysis was limited to the trials that reported baseline BP. The subgroup analyses did not explain heterogeneity and did not affect the overall pooled estimate of dialysis adequacy.

To assess the robustness of the pooled estimate, we conducted sensitivity analyses on the basis of risk of bias in studies. Excluding studies with significant loss to follow-up (18,20) resulted in partial explanation of heterogeneity (I^2=63%–18%) for dialysis adequacy without affecting the overall pooled estimates of the remaining trials.

Quality of Evidence for the Body of Evidence

Overall, the quality of evidence for the outcomes of interest across all studies was graded low or very low. Details about different domains assessing the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation approach are summarized in the evidence profile (Table 3). We did not find evidence for publication bias using funnel plots and Egger linear regression test (intradialytic hypotension [P=0.41], symptoms of discomfort [P=0.13], dialysis adequacy [P=0.49], and change in MAP [P=0.17]). We were not able to fit metaregression models to examine the association with loss to follow-up for dialysis adequacy because of insufficient data.

Discussion

Twenty-six crossover, randomized trials (including 484 patients) with varying degrees of methodologic rigor were

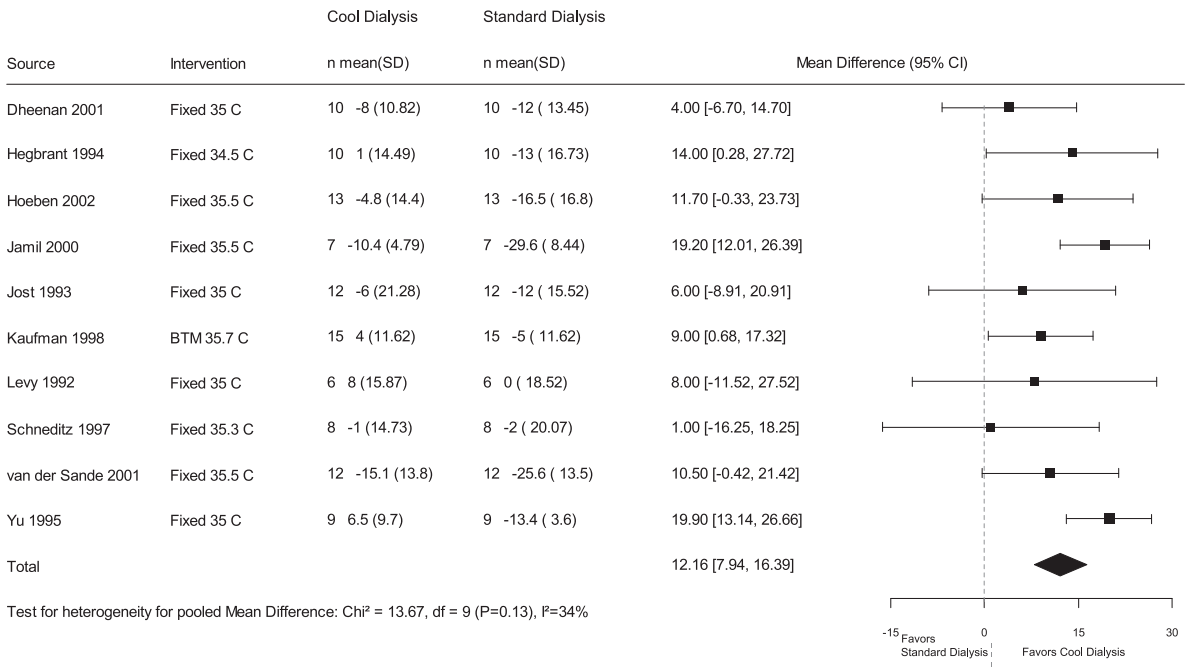

Figure 5. | Effect of low temperature dialysis on change in mean arterial pressure. 95% CI, 95% confidence interval; BTM, biofeedback temperature monitoring.

included in this systematic review. The results suggest that cool dialysis significantly reduces the rate of intradialytic hypotension. The available evidence suggests no negative effect on dialysis adequacy, with an increase in symptoms of discomfort of unclear severity.

This review has several strengths. This review extends the review by Selby and McIntyre (6) in many ways. We have identified and analyzed four more trials in this review. The comprehensive and up-to-date search makes it unlikely that relevant trials were missed. All steps, including initial screening, trials selection, and data abstraction, were performed independently in duplicate to minimize any potential biases arising from subjectivity in these tasks. Additionally, we translated non-English

Table 2. Summary of BP measures in trials that did not report change in mean arterial pressure

Reference no.	Cool HD	Standard HD
25	Low BP group: intradialytic MAP: 92±8.4 mmHg; postdialysis MAP: 95.9±10.9 mmHg; stable BP group: intradialytic MAP: 99±11.5 mmHg; postdialysis MAP: 102±13.5 mmHg	Low BP group: intradialytic MAP: 81±7.2 mmHg; $P<0.01$[a]; postdialysis MAP: 86.9±7.3 mmHg; $P=0.01$[a]; stable BP group: intradialytic MAP: 96.5±12.1 mmHg; postdialysis MAP: 100± 14.0 mmHg
16	Change in SBP: −6.0±2 mmHg[b]; change in DBP: −4.1±7.6 mmHg[b]	Change in SBP: −0.8±22.7 mmHg[b]; change in DBP: −3.8±12.4 mmHg[b]
26	SBP: 146±5 mmHg before dialysis; 140±6 mmHg after dialysis; DBP: 81±3 mmHg before dialysis; 79±4 mmHg after dialysis	SBP: 150±5 mmHg before dialysis; 132±4 mmHg after dialysis; DBP: 81±2 mmHg before dialysis; 76±3 mmHg after dialysis
17	SBP reduction: 2.71±0.97%; DBP reduction: 8.63± 1.19%; intradialytic MAP reduction: 3.01±0.98%	SBP reduction: −7.54±1.92%; $P<0.001$[a]; DBP reduction: −4.99±1.4%; $P<0.001$[a]; intradialytic MAP reduction: −8.99±1.71%; $P<0.001$
18	Mean lowest intradialytic SBP: 102.5±2.9 mmHg; mean lowest intradialytic DBP: 61.7±2.3 mmHg; intradialytic MAP: 75.0±2.3 mmHg; SBP: 132± 3.3 mmHg before dialysis; 118.1±3.5 mmHg after dialysis; DBP: 73.7±2.3 mmHg before dialysis; 69.2±2.6 mmHg after dialysis	Mean lowest intradialytic SBP: 90.6±2.5 mmHg; $P<0.001$[a]; mean lowest intradialytic DBP: 54.9± 2.2 mmHg; $P=0.02$[a]; intradialytic MAP: 66.8± 2.1 mmHg; $P=0.002$[a]; SBP: 132.7±3.4 mmHg before dialysis; 109.0±2.1 mmHg after dialysis; $P<0.01$[a]; DBP: 74.9±3.0 mmHg before dialysis; 63.6±1.9 mmHg after dialysis; $P=0.01$[a]
32	MAP did not change with time at the end of cool HD	MAP decreased by 10% at the end of normal HD; P= significant
33	MAP increased in six of nine sessions[b]	MAP increased in one of nine sessions[b]
20	SBP reduction: −14.2±16.5 mmHg; DBP reduction: −5.8±8.1 mmHg	SBP reduction: −20.5±15.7 mmHg; DBP reduction: −8.8±8.4 mmHg; $P<0.05$[a]
41	Mean intradialytic SBP: 136.9±11.4 mmHg; mean intradialytic DBP: 75.4±6.0 mmHg; mean intradialytic MAP: 95.7±7.5 mmHg	Mean intradialytic SBP: 130.7±10.5 mmHg; mean intradialytic DBP: 72.3±6.0 mmHg; average intradialytic MAP: 91.6±7.4 mmHg
21	Mean SBP: 158.8±14 mmHg; mean DBP: 78.6±4 mmHg; average intradialytic MAP: 110.9±7 mmHg	Mean SBP: 141.6±17 mmHg; $P<0.001$[a]; mean DBP: 69.4±5 mmHg; $P<0.001$[a]; average intradialytic MAP: 92.6±10 mmHg; $P<0.001$[a]
36	Maximum decrease in intradialytic SBP: 21.8± 26.1 mmHg; maximum decrease in intradialytic DBP: −0.1±19.2 mmHg; SBP: 130.3±21.7 mmHg before dialysis; 131.6±21.4 mmHg after dialysis; DBP: 72.2±10.2 mmHg before dialysis; 63.7± 9.0 mmHg after dialysis	Maximum decrease in intradialytic SBP: 43.2± 20.6 mmHg; maximum decrease in intradialytic DBP: 14.9±9.6 mmHg; SBP: 144.4±25.9 mmHg before dialysis; 117.3±26.1 mmHg after dialysis; DBP: 72.2±10.2 mmHg before dialysis; 67.0± 10.9 mmHg after dialysis
37	SBP: 144±24 mmHg before dialysis; 144±26 mmHg after dialysis; DBP: 68±14 mmHg before dialysis; 76±12 mmHg after dialysis	SBP: 152±22 mmHg before dialysis; 134±23 mmHg after dialysis; DBP: 75±9 mmHg before dialysis; 71±13 mmHg after dialysis
22	SBP: 159±35 mmHg before dialysis; 127±39 mmHg after dialysis; $P<0.05$[c]; DBP: 82±12 mmHg before dialysis; 70±17 mmHg after dialysis; $P<0.05$[c]; intradialytic lowest SBP: 113±30 mmHg	SBP: 151±27 mmHg before dialysis; 122±28 mmHg after dialysis; $P<0.05$[c]; DBP: 82±11 mmHg before dialysis; 65±12 mmHg after dialysis; $P<0.05$[c]; intradialytic lowest SBP: 104±27 mmHg; $P=0.08$
40	SBP: 127±6.4 mmHg before dialysis; 134± 3.9 mmHg after dialysis; DBP: 76±3.9 mmHg before dialysis; 81±3.5 mmHg after dialysis	SBP: 126±4.6 mmHg before dialysis; 127± 2.1 mmHg after dialysis; DBP: 74±2.8 mmHg before dialysis; 74±3.2 mmHg after dialysis

Effect estimates are presented as BP measure±SD. HD, hemodialysis; MAP, mean arterial pressure; NS, not significant; SBP, systolic BP; DBP, diastolic BP.

[a]P value comparing cool and standard HD.

[b]After HD compared with before HD.

[c]P value for end versus start of dialysis.

Table 3. Evidence profile

Quality Assessment	No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of Hemodialysis Sessions and Patients		Effect: Absolute	Quality	Importance
								Cool Dialysis	Standard Dialysis			
Mortality—not reported	0	—	—	—	—	—	—	—	—	—		Critical
Quality of life (measured with SF-36; better indicated by higher values)	1	Randomized trial	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	18 hemodialysis sessions in nine patients	18 hemodialysis sessions in nine patients	MD 1 higher (21.64 lower to 23.64 higher)	⊕○○○	Critical
Hospitalization—not reported	0	—	—	—	—	—	—	—	—	—		Critical
Intradialytic hypotension (measured with no. of events per dialysis session; rate ratio <1.0 implies that cool dialysis versus standard dialysis has a lower risk of the outcome)	11	Randomized trials	Very serious[c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	264 hemodialysis sessions in 120 patients	264 hemodialysis sessions in 120 patients	Rate ratio 0.3 higher (0.11–0.51 higher)	⊕⊕○○	Critical
Symptoms of discomfort (cold or cramping; measured with no. of events per dialysis session; rate ratio <1.0 implies that cool dialysis versus standard dialysis has a lower risk of the outcome)	9	Randomized trials	Very serious[d]	No serious inconsistency	No serious indirectness	Serious[e]	None	1234 hemodialysis sessions in 141 patients	1234 hemodialysis sessions in 141 patients	Rate ratio 2.95 (0.88–9.82)	⊕○○○	Critical
Dialysis adequacy (measured with Kt/V; better indicated by lower values)	7	Randomized trials	Very serious[f]	No serious inconsistency[g]	No serious indirectness	No serious imprecision	None	2100 hemodialysis sessions in 137 patients	2100 hemodialysis sessions in 137 patients	MD 0.05 lower (0.09 lower to 0.01 higher)	⊕⊕○○	Important
Change in mean arterial pressure (measured with millimeters of mercury; better indicated by lower values)	10	Randomized trials	Very serious[h]	No serious inconsistency	No serious indirectness	No serious imprecision	None	731 hemodialysis sessions in 102 patients	731 hemodialysis sessions in 102 patients	MD 12 higher (8–16 higher)	⊕⊕○○	Important

Question: what are the benefits and harms of cool versus standard dialysis for patients with ESRD? Settings: chronic hemodialysis (inpatient or outpatient). — denotes no data available. SF-36, short form 36 health survey; MD, mean difference; ⊕○○○ very low, ⊕⊕○○ low.

[a]Unclear method for sequence generation and concealment of allocation reported. Only patients were blinded; one of ten patients dropped out of the study (in the work by Selby *et al.* [21]).

[b]Only one trial reported quality of life. The 95% confidence interval of the results crossed zero, with a very wide 95% confidence interval ranging from considerable benefit to considerable harm.

[c]Unclear methods of sequence generation and concealment of allocation in any of 11 studies; two of 11 studies reported patient blinding, one of 11 studies reported staff blinding, one of 11 studies reported no blinding, and in seven of 11 studies, blinding was unclear.

[d]Unclear methods of sequence generation and concealment of allocation in eight of nine studies; only one of nine studies reported a central process of sequence generation. Two of nine studies reported no blinding, one of nine studies blinded staff but not patients, and blinding was not clear in six of nine studies. Three of nine studies report patients dropping out of the study; in one of them, 21 of 95 patients dropped out.

[e]Lower limit of the 95% confidence interval suggests no effect.

[f]Unclear methods of sequence generation or concealment of allocation in six of seven studies; only one of seven studies reported central sequence generation. Three of seven studies reported blinding of patients only, two of seven studies clearly reported no blinding, and blinding was not clear in two of seven studies. Four of seven studies had patients drop out of the studies; in one study, 21 of 95 patients dropped out, and in another study, eight of 19 patients dropped out.

[g]Substantial heterogeneity (I^2=63%) that was partially explained by excluding studies with loss to follow-up (I^2=18%).

[h]Unclear methods for sequence generation and concealment of allocation reported. Blinding: four of ten studies blinded patients, one of ten studies blinded staff, one of ten studies blinded providers, and one of ten studies blinded investigators.

articles. Finally, we analyzed sources of bias and explored reasons for diversity in the published literature.

This review has few limitations. The results of this review are inherently limited by the quality of the primary included studies. First, the majority of included studies are small with short follow-up times. Second, no studies reported long–term patient–important outcomes, which is a major limitation in this area. None of the included studies, except one, reported a central method of random sequence generation or allocation concealment. Also, none of the studies had appropriately blinded patients, investigators, dialysis nurses, clinical outcome assessors, data collectors, and data analyzers. Additionally, seven trials had significant patient dropout from 8% to 42%. One may assume that the high rates of dropouts in some studies may be because of intolerability. However, the lack of information about timing and reasons for the dropouts makes it difficult to know whether this assumption is true. Surprisingly, we did not observe any improvement in the methodologic quality of the trials in more recent reports compared with earlier ones. Also, we did not observe any progress in reporting long–term patient–important outcomes.

Despite our low confidence in the estimates of effect owing to imprecision and risk of bias, cool dialysis remains a promising therapy that, we believe, is not frequently used. This may be because of the lack of high-quality evidence to support its possible net benefit or physicians' beliefs about a negative side effect profile. Still, this intervention is quite simple and can be implemented in any dialysis center in the world without any additional cost other than training nursing staff on a new protocol.

Cool dialysis can be achieved by either a fixed reduction in the temperature of the dialysate fluid or use of a biofeedback device. It will be of interest to the nephrology community to have trials that directly compare the effect of fixed empirical reduction of dialysate temperature with isothermic or cool biofeedback temperature monitoring devices, because the former does not consider patients' variability in core temperature and access recirculation, but the latter does. This direct comparison may provide information about the optimal management for patients at high risk of intradialytic hypotension during hemodialysis without causing significant symptoms of discomfort.

Additionally, cool dialysis seems promising when evaluating other surrogate outcomes that we did not explore in this review. The study by Eldehni *et al.* (42) shows that hemodialysis results in a significant amount of magnetic resonance imaging changes signifying brain injury that could possibly be alleviated by the use of cold-temperature hemodialysis. Also, Parker *et al.* (41) have found that the use of cold-temperature hemodialysis may improve nocturnal sleep by decreasing sympathetic activation and sustaining the nocturnal skin temperature. The poor reporting of symptoms of discomfort and the lack of systematic evaluation of their severity continue to limit the ability to accurately assess the effect of cool dialysis on significant patient discomfort. This review highlights that high–quality, large, multicenter studies with long follow-up are needed to assess the effect of cool dialysis on long–term patient–important outcomes, like mortality, major adverse cardiovascular events, hospitalization, patients' functional and cognitive status, and discomfort.

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Disclosures

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