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[Intervention Review]

Low dialysate sodium levels for chronic haemodialysis

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ABSTRACT

Background

Cardiovascular (CV) disease is the leading cause of death in dialysis patients, and strongly associated with fluid overload and hypertension. It is plausible that low dialysate [Na+] may decrease total body sodium content, thereby reducing fluid overload and hypertension, and ultimately reducing CV morbidity and mortality.

Objectives

This review evaluated harms and benefits of using a low (< 138 mM) dialysate [Na+] for maintenance haemodialysis (HD) patients.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 7 August 2018 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

Randomised controlled trials (RCTs), both parallel and cross-over, of low (< 138 mM) versus neutral (138 to 140 mM) or high (> 140 mM) dialysate [Na+] for maintenance HD patients were included.

Data collection and analysis

Two investigators independently screened studies for inclusion and extracted data. Statistical analyses were performed using random effects models, and results expressed as risk ratios (RR) for dichotomous outcomes, and mean differences (MD) or standardised MD (SMD) for continuous outcomes, with 95% confidence intervals (CI). Confidence in the evidence was assessed using GRADE.

Main results

We included 12 studies randomising 310 patients, with data available for 266 patients after dropout. All but one study evaluated a fixed concentration of low dialysate [Na+], and one profiled dialysate [Na+]. Three studies were parallel group, and the remaining nine cross-over. Of the latter, only two used a washout between intervention and control periods. Most studies were short-term with a median (interquartile range) follow-up of 3 (3, 8.5) weeks. Two were of a single HD session, and two of a single week's HD. Half of the studies were conducted prior to 2000, and five reported use of obsolete HD practices. Risks of bias in the included studies were often high or unclear, lowering confidence in the results.

Compared to neutral or high dialysate [Na+], low dialysate [Na+] had the following effects on "efficacy" endpoints: reduced interdialytic weight gain (10 studies: MD -0.35 kg, 95% CI -0.18 to -0.51; high certainty evidence); probably reduced predialysis mean arterial blood pressure (BP) (4 studies: MD -3.58 mmHg, 95% CI -5.46 to -1.69; moderate certainty evidence); probably reduced postdialysis mean arterial BP (MAP) (4 studies: MD -3.26 mmHg, 95% CI -1.70 to -4.82; moderate certainty evidence); probably reduced predialysis serum [Na+] (7 studies: MD -1.69 mM, 95% CI -2.36 to -1.02; moderate certainty evidence); may have reduced antihypertensive medication (2 studies: SMD -0.67 SD, 95% CI -1.07 to -0.28; low certainty evidence). Compared to neutral or high dialysate [Na+], low dialysate [Na+] had the following effects on "safety" endpoints: probably increased intradialytic hypotension events (9 studies: RR 1.56, 95% 1.17 to 2.07; moderate certainty evidence); probably increased intradialytic cramps (6 studies: RR 1.77, 95% 1.15 to 2.73; moderate certainty evidence).

Compared to neutral or high dialysate [Na+], low dialysate [Na+] may make little or no difference to: intradialytic BP (2 studies: MD for systolic BP -3.99 mmHg, 95% CI -17.96 to 9.99; diastolic BP 1.33 mmHg, 95% CI -6.29 to 8.95; low certainty evidence); interdialytic BP (2 studies:, MD for systolic BP 0.17 mmHg, 95% CI -5.42 to 5.08; diastolic BP -2.00 mmHg, 95% CI -4.84 to 0.84; low certainty evidence); dietary salt intake (2 studies: MD -0.21g/d, 95% CI -0.48 to 0.06; low certainty evidence).

Due to very low quality of evidence, it is uncertain whether low dialysate [Na+] changed extracellular fluid status, venous tone, arterial vascular resistance, left ventricular mass or volumes, thirst or fatigue. Studies did not examine cardiovascular or all-cause mortality, cardiovascular events, or hospitalisation.

Authors' conclusions

It is likely that low dialysate [Na+] reduces intradialytic weight gain and BP, which are effects directionally associated with improved outcomes. However, the intervention probably also increases intradialytic hypotension and reduces serum [Na+], effects that are associated with increased mortality risk. The effect of the intervention on overall patient health and well-being is unknown. Further evidence is needed in the form of longer-term studies in contemporary settings, evaluating end-organ effects in small-scale mechanistic studies using optimal methods, and clinical outcomes in large-scale multicentre RCTs.

PLAIN LANGUAGE SUMMARY

Dialysate sodium levels for chronic haemodialysis

What is the issue?

Kidneys control salt and water balance in the body by the regulation of urine production. When kidneys no longer work, urine production ceases or becomes insufficient and salt and water balance must be managed using dialysis. Doctors looking after haemodialysis patients must select an appropriate amount of sodium to use in the dialysis fluids that are used to wash the patient's blood. If the sodium level in these fluids is too high, this can lead to the patient feeling thirsty after treatment, drinking too much more water and becoming fluid overloaded by the time the next treatment is due, which can cause heart damage. On the other hand, if the sodium level is too low in dialysis fluids, this will cause the patient to have cramps and drops in blood pressure, which is uncomfortable and potentially also a cause heart damage. The "right" sodium level for dialysis fluid is unknown.

What did we do?

We combined all studies of people treated with haemodialysis where outcomes were compared between people receiving low sodium in their dialysis fluid and those receiving higher levels.

What did we find?

We found 12 studies comparing low sodium levels in dialysis fluid with neutral or high sodium levels. Many studies were performed prior to 2000, studying technology and patients that are not always relevant today. Most were short-term studies, only lasting a few weeks. Our main findings in these studies were; that low sodium in dialysis fluid improves blood pressure and reduces gain of salt and water in between dialysis treatments, which are probably good things, but increases the number of cramps and low blood pressure events experienced by patients during dialysis, which are definitely bad things. The studies did not provide enough information about the participating patients for us to know which patients might benefit from low sodium dialysis fluid, and which patients might instead be harmed. The studies did not provide definitive information on the effect of low sodium dialysis fluids on heart structure and function, or patient quality of life and survival.

Conclusions

We are uncertain about whether low sodium in dialysis fluid improves overall health and well-being for people on haemodialysis, since there are a mixture of probably good and bad effects, and available research studies were not designed (or designed well-enough) to learn about effects of the intervention on the heart or on overall patient health and well-being. Larger and up-to-date definitive studies are needed to evaluate the medium to long-term effects of low sodium levels in dialysis fluid, and better inform clinical practice.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM) for chronic haemodialysis

Low dialysate [Na+]**(< 138 mM) versus neutral** dialysate [Na+]**(138 to 140 mM) or high** dialysate [Na+]**(> 140 mM) for chronic haemodialysis (HD)**

Patient or population: chronic HD
Setting: dialysis units
Intervention: Low dialysate [Na+] (< 138 mM)
Comparison: neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM)	Risk with Low dialysate [Na+] (< 138 mM)			
IDWG	The mean IDWG was 2.55 kg	MD 0.35 kg lower (0.51 lower to 0.18 lower)	-	352 (10)	⊕⊕⊕⊕ HIGH
Intradialytic hypotension	110 per 1,000	167 per 1,000 (125 to 222)	RR 1.52 (1.14 to 2.02)	12,570 (7)	⊕⊕⊕⊖ MODERATE [1]
Predialysis MAP	The mean predialysis MAP was 104.6 mmHg	MD 3.58 mmHg lower (5.46 lower to 1.69 lower)	-	156 (4)	⊕⊕⊕⊖ MODERATE [2]
Postdialysis MAP	The mean postdialysis MAP was 101.0 mmHg	MD 3.26 lower (4.82 lower to 1.7 lower)	-	150 (4)	⊕⊕⊕⊖ MODERATE [2]
Antihypertensive medication	The mean number of antihypertensive medications was 3.1	SMD 0.67 SD lower (1.07 lower to 0.28 lower)	-	103 (2)	⊕⊕⊖⊖ LOW [3]
Predialysis serum [Na+]	The mean predialysis serum [Na+] was 138.3 mM	MD 1.69 lower (2.36 lower to 1.02 lower)	-	258 (7)	⊕⊕⊕⊖ MODERATE [4]
Intradialytic cramps	74 per 1,000	130 per 1,000 (85 to 201)	RR 1.77 (1.15 to 2.73)	12,186 (6)	⊕⊕⊕⊖ MODERATE [5]

*__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; **RR:** Risk ratio; **MD**: mean difference; **SMD**: standardised mean difference

IDWG: interdialytic weigh gain; **MAP:** mean arterial pressure

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] Down-graded because of an era effect in some included studies (indirectness), affecting the applicability to modern settings - see section Overall completeness and applicability of evidence
[2] Down-graded because of only moderate number of studies and patients assessed (imprecision), and the lack of concurrent reporting on antihypertensive medication burden in any study in this analysis
[3] Down-graded because of low number of studies and patients assessed (imprecision)
[4] Down-graded because of heterogeneity of [Na+] measurements between studies
[5] Down-graded because of inconsistency between studies, albeit contributed by only one study (Liu 2016)

Summary of findings 2. Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) for chronic haemodialysis

Low dialysate [Na+] **(< 138 mM) versus neutral** dialysate [Na+]**(138 to 140 mM) for chronic haemodialysis (HD)**

Patient or population: chronic HD
Setting: dialysis units
Intervention: Low dialysate [Na+] (< 138 mM)
Comparison: neutral dialysate [Na+] (138 to 140 mM)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with neutral dialysate [Na+] (138 to 140 mM)	Risk with low dialysate [Na+] (< 138 mM)			
IDWG	The mean IDWG was 2.55 kg	MD 0.33 kg lower (0.51 lower to 0.14 lower)	-	263 (6 RCTs)	⊕⊕⊕⊕ HIGH
Intradialytic hypotension	111 per 1,000	165 per 1,000 (121 to 225)	RR 1.49 (1.09 to 2.03)	12084 (5 RCTs)	⊕⊕⊕⊖ MODERATE [1]
Predialysis MAP	The mean predialysis MAP was 107.1 mmHg	MD 3.52 mmHg lower (5.46 lower to 1.57 lower)	-	112 (2 RCTs)	⊕⊕⊖⊖ LOW [2]
Postdialysis MAP	The mean postdialysis MAP was 100.82 mmHg	MD 3.01 lower (4.69 lower to 1.34 lower)	-	112 (2 RCTs)	⊕⊕⊖⊖ LOW [2]

Antihypertensive medication	The mean number of antihypertensive medications was 3.1	SMD 0.67 SD lower (1.07 lower to 0.28 lower)	-	103 (2 RCTs)	⊕⊕⊖⊖ LOW [3]
Predialysis serum [Na+]	The mean predialysis serum [Na+] was 138.3 mM	MD 1.59 mM lower (2.4 lower to 0.78 lower)	-	169 (3 RCTs)	⊕⊕⊕⊖ MODERATE [4]
Intradialytic cramps	66 per 1,000	110 per 1,000 (61 to 197)	RR 1.66 (0.92 to 2.98)	11700 (4 RCTs)	⊕⊕⊖⊖ LOW [5]

*__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; **RR:** Risk ratio; **MD:** mean difference; **SMD:** standardised mean difference

IDWG: interdialytic weigh gain; **MAP:** mean arterial pressure

GRADE Working Group grades of evidence
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[1] Down-graded because of an era effect in some included studies (indirectness), affecting the applicability to modern settings - see section Overall completeness and applicability of evidence
[2] Down-graded because of low number of studies and patients assessed (imprecision), and the lack of concurrent reporting on antihypertensive medication burden in any study in this analysis
[3] Down-graded because of low number of studies and patients assessed (imprecision)
[4] Down-graded because of only moderate number of studies and patients assessed (imprecision)
[5] Down-graded because of inconsistency between studies, albeit contributed by only one study (Liu 2016), and overall imprecision of effect

Summary of findings 3. Low dialysate [Na+] (< 138 mM) versus high dialysate [Na+] (> 140 mM) for chronic haemodialysis

Low dialysate [Na+](< 138 mmol/L) versus high dialysate [Na+] (> 140 mmol/L) for chronic haemodialysis (HD)

Patient or population: chronic HD
Setting: dialysis units
Intervention: Low dialysate [Na+] (< 138 mmol/L)
Comparison: high dialysate [Na+] (> 140 mmol/L)

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with high dialysate [Na+] (> 140 mmol/L)	Risk with Low dialysate [Na+] (< 138 mmol/L)				
IDWG	The mean IDWG was 2.55 kg	MD 0.42 kg lower (0.8 lower to 0.05 lower)	-	89 (4 RCTs)	⊕⊕⊕⊖ MODERATE[1]	
Intradialytic hypotension	86 per 1,000	148 per 1,000 (49 to 438)	RR 1.71 (0.57 to 5.07)	486 (2 RCTs)	⊕⊕⊖⊖ LOW[2]	
Predialysis MAP	The mean predialysis MAP was 98.44 mmHg	MD 4.48 mmHg lower (12.07 lower to 3.1 higher)	-	44 (2 RCTs)	⊕⊕⊖⊖ LOW[3]	
Postdialysis MAP	The mean postdialysis MAP was 101 mmHg	MD 4.85 mmHg lower (9.1 lower to 0.6 lower)	-	38 (2 RCTs)	⊕⊕⊖⊖ LOW[3]	
Antihypertensive medication	see comment	see comment	-	-	-	Not reported
Predialysis serum [Na+]	The mean predialysis serum [Na+] was 138.3 mM	MD 1.92 mM lower (3.15 lower to 0.7 lower)	-	89 (4 RCTs)	⊕⊕⊕⊖ MODERATE[1]	
Intradialytic cramps	255 per 1,000	495 per 1,000 (393 to 623)	RR 1.94 (1.54 to 2.44)	486 (2 RCTs)	⊕⊕⊖⊖ LOW[4]	

*__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; **RR:** Risk ratio; **MD:** mean difference

IDWG: interdialytic weigh gain; **MAP:** mean arterial pressure

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
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[3] Down-graded because of low number of studies and patients assessed (imprecision), and the lack of concurrent reporting on antihypertensive medication burden in any study
[4] Down-graded because of low number of studies and patients assessed (imprecision)

BACKGROUND

Description of the condition

The kidneys control salt and water balance in the body principally by the regulation of urine production. When kidneys no longer function, urine production ceases or becomes insufficient and salt and water balance is managed through renal replacement therapy (RRT) with dialysis or kidney transplantation. Dialysis is the most common modality of RRT. At the end of 2013, there were approximately 3.2 million patients being treated for end-stage kidney disease (ESKD) worldwide. This number increases by approximately 6% each year, which is significantly higher than the population growth rate. Out of those 3.2 million patients, about 2.5 million were undergoing dialysis treatment (either haemodialysis (HD) or peritoneal dialysis), and about 678,000 were living with kidney transplants.

Patient survival is relatively poor on dialysis, with a prognosis that is similar to or worse than many common cancers. Cardiovascular (CV) disease accounts for the majority of deaths in dialysis patients, and develops de-novo in most patients who start dialysis without it (Marshall 2017). The precise causal pathways responsible for this accelerated CV disease are not known. However, elevated blood pressure (BP) and salt and water overload are common conditions in dialysis patients and moreover two of the strongest risk factors for CV death, and thought to originate from excessive body sodium content driving increased thirst and water intake (Charra 2004; Davenport 2008; Fischbach 1988; Kimura 1984; Matsuoka 1990; Shepherd 1987; Stiller 2001; Van Stone 1982). In addition, elevation in serum sodium concentration ([Na+]) (above 135 mM) has been observed to directly increase BP by stiffening blood vessel walls (Oberleithner 2007). Ultimately, this combination of features is thought to culminate in left ventricular (LV) hypertrophy, congestive heart failure and premature CV death (Charra 2004).

Excessive body sodium content in dialysis patients derives from either excessive dietary consumption or via the treatment itself. For those on HD, sodium loading during treatment can arise from two main sources: from higher fixed or profiled concentrations of [Na+] in dialysate, and from the saline used to treat intradialytic hypotension and to prime or wash-back the extracorporeal blood circuit (Dunlop 2012). Of these two sources, the most important one is the dialysate. Dialysate [Na+] that is higher than the patient's will result in transfer of sodium to the patient, and [Na+] that is lower will result in transfer out of the patient. The most common dialysate [Na+] is 140 mM (Hecking 2011; Mc Causland 2012; Peixoto 2011), which is generally higher than that in patients' plasma. This is likely to be contributing factor to the fact that most people on conventional HD regimens (~four hours, three times/week) have chronic salt and water overload, and hypertension that is inadequately controlled by antihypertensives (Agarwal 2003; Rahman 1999; Zazgornik 1997).

Improving CV morbidity and death is a leading priority in the care of dialysis patients, and a prime opportunity for doing so is through control of excess body sodium content.

Description of the intervention

HD removes fluid and solutes through convection and diffusion. Convective losses of sodium during HD are dependent on ultrafiltration, and are brought about by solvent drag. Diffusive transfer of sodium depends on the direction and extent of the concentration gradient between the dialysate and the patient's plasma, and is brought about by Brownian motion. Plasma contains negatively charged proteins that may complex with sodium ions, reducing their availability to move across the dialyser membrane. The difference between total and diffusable sodium in plasma arises from the Gibbs-Donan effect (Locatelli 1984). Dialysate contains no proteins; therefore all ionised sodium is ionically active and able to move across the membrane. The difference in available diffusible sodium (the sodium ionic activity) between dialysate and plasma thus drives diffusive transfer (Flanigan 1998). In practical terms, without measuring sodium ionic activity and approximating the Gibbs-Donan effect, the sodium gradient can be considered neutral if the dialysate [Na+] is set approximately 2 mM below the plasma sodium concentration (Flanigan 2008; Lomonte 2011).

The intervention under consideration in this review is low dialysate [Na+]. Dialysate [Na+] is considered to be low when it is below neutral. There are very few studies of sodium balance in dialysis patients characterising the ionic activity of sodium in plasma water, or calculating the gradient with respect to dialysate. Therefore, for this review, we will consider dialysate [Na+] levels below 138 mM to be "low"; 138 mM to 140 mM as "neutral"; and more than 140 mM as "high". Dialysate [Na+] can be estimated in three ways: 1) from dialysate conductivity multiplied by 10 (Gotch 1990; Ragon 1985); 2) from [Na+] measurements in dialysate using flame photometry or potentiometry with ion specific electrodes (calibrated against aqueous solutions as opposed to plasma); and 3) from the HD machine itself, which uses conductivity measurement in conjunction with proprietary models (specific to the manufacturer) that account for the presence of other ions in the dialysis fluid (Polaschegg 1985). In the routine clinical practice of the approximately 300 million HD treatments performed per year, all are prescribed and monitored by the latter method. The former methods are only performed in research or audit settings.

How the intervention might work

HD patients do not exist in a steady state. They accumulate exogenous and endogenous solutes and water between dialysis treatments, which are then removed by the dialysis procedure to return the patient to a baseline state. For sodium, accumulation between treatments is from dietary intake and removal during HD most obviously by convection: the patient is ultrafiltrated from their observed weight to a target weight, with removal of a proportion of excess sodium body content that is contained in the ultrafiltrated volume.

It has been shown that low dialysate [Na+] leads to greater diffusive sodium removal during dialysis (Manlucu 2010) and therefore lower total body sodium content by the end of treatment, which might therefore lessen thirst and subsequent water intake in the interdialytic period. This in turn might reduce extracellular fluid overload, hypertension, and ultimately, left ventricular hypertrophy and CV death. The clinical value proposition of dialysate [Na+] therefore pertains to a lower risk of excessive body sodium content through both greater sodium diffusion on dialysis, with reduced water intake in the interdialytic period.

Why it is important to do this review

From the above arguments, it may seem self-evident that a lower rather than higher dialysate [Na+] would be more commonly applied during HD. Currently, however, the most common dialysate [Na+] setting around the world is approximately 140 mM, which is not low (Hecking 2012; Mc Causland 2012). This customary practice has been adopted by practitioners to make dialysis more comfortable for patients, guided by cumulative clinical experience over half a century of less intradialytic hypotension and associated symptoms with higher, as opposed to lower, dialysate [Na+] (Cybulsky 1985; Port 1973; Stewart 1972; Wilkinson 1977). The dialysate [Na+] of 140 mM provides these benefits by enhancing salt and water transfer from the interstitial compartment into the blood during HD, thereby maintaining blood volume during ultrafiltration, and reducing the drops in BP during the procedure. Although this is helpful to patients, the relatively high dialysate [Na+] of 140 mM also provides a considerable sodium load to patients (Munoz Mendoza 2011; Peixoto 2011; Raimann 2009; Thein 2007), with potential to drive or at least exacerbate the excess CV morbidity and death in this population. Lower dialysate [Na+] has therefore been suggested as an intervention to avoid this situation, thereby improving CV outcomes. Prima facie, the intervention of low dialysate [Na+] seems attractive, since it addresses an important gap in outcomes, and is simple, universally accessible, and cost-free to apply. However, at this time there is no definitive study of the intervention, and a review is needed to synthesise evidence of efficacy from existing studies.

Another issue concerns the safety of lower dialysate [Na+], which has been associated with higher death rates in some HD populations (Hecking 2012; Mc Causland 2012). Importantly, these data are not experimental, and a causal pathway has not been proven. Nonetheless, there is a suggestion that low dialysate [Na+] might not be harmless. The first and foremost source of risk arises from the potential loss of increased intradialytic haemodynamic stability afforded by higher dialysate [Na+], especially when large ultrafiltration rates/volumes are required (Peixoto 2011; Santos 2008): lower dialysate [Na+] may increase the occurrence of intradialytic hypotension. The assessment of this endpoint is made difficult by the lack of an agreed definition for the syndrome. The original definition was a decrease in systolic BP by ≥ 20 mmHg, or mean arterial BP (MAP) by ≥ 10 mmHg, as well as associated symptoms (K/DOQI Workgroup 2005). Since, others have defined intradialytic hypotension as fall in BP requiring an intervention such as saline bolus, UF reduction, or blood flow reduction (Eknoyan 2002). Yet others use a definition based on a fall in BP alone, since symptoms and intervention data are often unavailable in large databases (Dheenan 2001; Dubin 2011; Kyriazis 2002; Oliver 2001b; Zhou 2014). Irrespective of definition, the syndrome of intradialytic hypotension is not harmless. Many case and cohort studies have reported end-organ damage with intradialytic hypotension, such as retinal ischaemia, brain ischaemia, gut ischaemia, loss of residual kidney function, and vascular access thrombosis (Basri 2002; Chang 2011; Eldehni 2012; Eldehni 2015; McIntyre 2011; Taratufolo 2001; Wells 2004). Intradialytic hypotension also reduces patient satisfaction with care (Amro 2014; Caplin 2011; Schipper 2011; Davies 2016 [pers comm]), leading to additional sodium loading through the use of saline boluses to alleviate symptoms, or to early abandonment of HD or even overt non-adherence lessening treatment effectiveness (Schreiber 2001). Perhaps most importantly, intradialytic hypotension is associated with temporary reduction in heart contractility during HD itself (Boon 2004; Bos 2000; McIntyre 2008), and repeated episodes are associated with the development of regional wall motion abnormalities and evolution of congestive cardiac failure (Burton 2009; Selby 2007a; Sherman 2011). In epidemiological studies, intradialytic hypotension is associated with increased hospitalisation, major CV events, and death (Flythe 2015; Sands 2014; Shoji 2004; Stefansson 2014; Tisler 2003). A review is needed to synthesise evidence of safety of low dialysate [Na+] from existing studies, with particular reference to the important adverse event of intradialytic hypotension and associated symptoms.

The second and more controversial source of risk with low dialysate [Na+] arises from a potential effect on serum [Na+]. There is a well-established inverse association between serum [Na+] and death in HD patients (Hecking 2012; Mc Causland 2012; Waikar 2011), which predicts an increase in death even when serum [Na+] is at the lower end of the normal range (as it does for the general population (Waikar 2009)). Once again, these data are not experimental, and a causal pathway has not been proven. A variety of causal pathways have been proposed, including; increased inflammation and/or cachexia (Poulikakos 2014; Sukhanov 2011; Swart 2011; Rodrigues Telini 2013), lower resistance to infection (Mandai 2013); changes in vascular responsiveness and therefore resistance to intradialytic hypotension (Grassi 2002); and direct toxicity from osmolar fluctuations on HD (Waikar 2011). However, low serum [Na+] in these studies may also be simply a marker for the severity of co-morbid disease in HD patients, especially those co-morbidities that predispose to thirst (Hoorn 2013). In support of this contention are data from Hecking 2012, who identified a frail phenotype who was more likely to have low serum [Na+] in their studies, with diseases such as diabetes mellitus, coronary artery disease, congestive heart failure, lung disease and/or cancer. Concerningly however, a reduction in serum [Na+] has been associated with use of lower dialysate [Na+] in several non-randomised interventional studies, presumably reflecting a progressive reduction in sodium loading and total body sodium content (Song 2002; Song 2005; Thein 2007). Notwithstanding the controversies in this area, these data must be considered a signal of potential harm. A review of the safety of low dialysate [Na+] should also synthesise data on the outcome of serum [Na+].

At present, there is no agreement as to what [Na+] should be in dialysate, with equipoise arising from a lack of definitive evidence around safety and efficacy. In the Dialysis Outcomes and Practice Patterns Study (DOPPS), the mean dialysate [Na+] across countries varied from 138.3 mM in the UK to 140.8 mM in Italy, with no correlation between dialysate [Na+] and patient characteristics such as serum [Na+] (Hecking 2012; Mc Causland 2012). In the absence of any evidence-based guidance to clinicians, this review quantifies the relative benefits and harms of low dialysate [Na+] from existing literature, to inform further research in the area and enable appropriate shared decisions between consumers and health care providers / professionals.

OBJECTIVES

This review evaluated harms and benefits of using a low (< 138 mM) dialysate [Na+] for maintenance HD patients.

METHODS

Criteria for considering studies for this review

Types of studies

We reviewed all randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) that evaluated the effects of using low dialysate [Na+] in maintenance HD patients. We included both parallel group and cross-over studies.

Types of participants

All patients undergoing HD for ESKD. No age, sex or comorbid inclusion or exclusion criteria were applied.

Types of interventions

We included comparisons between low and higher dialysate [Na+]. For sodium profiled dialysis, we analysed dialysate [Na+] as the *time-averaged* concentration. We made the following comparisons:

1. Low (< 138 mM) dialysate [Na+] versus high (> 140 mM) OR neutral (138 to 140 mM) dialysate [Na+]
2. Low (< 138 mM) dialysate [Na+] versus neutral (138 to 140 mM) dialysate [Na+]
3. Low (< 138 mM) dialysate [Na+] versus high (> 140 mM) dialysate [Na+].

We excluded the following interventions.

1. Low dialysate [Na+] interventions that were combined with other dialysis co-interventions not present identically in the intervention and comparison groups
2. Low dialysate [Na+] interventions that were < 3 mM different from the comparison dialysate [Na+]
3. Sodium profiled dialysis where the profile was not sufficiently described to calculate a time-averaged dialysate [Na+]
4. Patients undergoing HD for acute kidney injury
5. Patient on HD schedules of greater or less than three times/week.

Types of outcome measures

We evaluated the effects of the intervention on the following outcome measures:

Primary outcomes

1. Interdialytic weight gain (IDWG) (efficacy)
2. Intradialytic hypotension, as defined by study investigators (safety)

Secondary outcomes

1. BP: predialysis, postdialysis, intradialytic and interdialytic time points; systolic, diastolic, MAP
2. Antihypertensive medication burden, as defined by study investigators
3. Fluid overload (extracellular fluid volume by bioimpedance analysis)
4. Serum [Na+]: predialysis, postdialysis, intradialytic and interdialytic time points
5. Thirst
6. Dietary sodium intake, as defined by study investigators
7. Cramp during HD treatment sessions
8. Left ventricular volume (magnetic resonance imaging, echocardiography)
9. Left ventricular mass (magnetic resonance imaging, echocardiography)
10. Arterial stiffness (carotid-femoral pulse wave velocity measurement)
11. Hospitalisation
12. Myocardial infarction
13. Stroke
14. CV death
15. Death (all causes)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register up to 7 August 2018 through contact with the Information Specialists using search terms relevant to this review. The Cochrane Kidney and Transplant 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 journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

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

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

Searching other resources

1. Handsearching 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

We used the search strategy as described to obtain titles and abstracts of studies that might have been relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were clearly inapplicable or ineligible. However, studies and reviews that might have included

relevant data or information were retained in the initial stages. The two authors then independently assessed the retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfy the inclusion criteria.

Data extraction and management

Two authors independently assessed retrieved abstracts and, if necessary the full text of these studies to determine which studies satisfied the inclusion criteria. Any uncertainties about study eligibility were discussed between authors. Data extraction was carried out independently by the two authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data used in the analyses. Where relevant outcomes were only published in earlier publications of the study, these data were used. Any discrepancy between published versions were evaluated and highlighted.

Assessment of risk of bias in included studies

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

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - 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? These were pre-specified as: baseline imbalance, interim reporting, deviation from study protocol in a way that does not reflect clinical practice, pre-randomisation administration of an intervention that could enhance or diminish the effects of a subsequent randomised intervention, contamination, occurrence of 'null bias' due to interventions being insufficiently well delivered or overly wide inclusion criteria, selective reporting of subgroups, reporting of trial registration, reporting of funding source(s), publication as full journal report, and fraud.

Measures of treatment effect

Extraction of data measurements was performed in adherence of standard operating procedures in the *Cochrane Handbook for Interventions in Systematic Reviews* (Higgins 2011). For dichotomous outcomes such as death, results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (e.g. BP, thirst scores, IDWG, left ventricular hypertrophy), the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales were used. A SMD of 0.2 indicates a small difference, 0.5 a moderate difference and 0.8 a large difference. We evaluated mean end of treatment values for continuous outcomes together with the reported standard deviation. Studies that did not report change from baseline (or raw treatment data to calculate change from baseline) were excluded from the meta-analyses. If subgroups within each outcomes were not independent, with participants that contributed to more than one subgroup, we did not perform meta-analysis for the entire group, or formally compare effect estimates between sub-groups.

We compared effect size estimates between the following groups of studies to determine if there was a "dose effect" with respect to the intervention.

1. Low (< 138 mM) dialysate [Na+] versus neutral (138 to 140 mM) dialysate [Na+]
2. Low (< 138 mM) dialysate [Na+] versus high (> 140 mM) dialysate [Na+]

To explore any "dose effect", we compared effect size of the intervention on a few key outcomes between the two comparison groups above.

1. IDWG
2. Predialysis MAP
3. Postdialysis MAP
4. Predialysis serum [Na+]
5. Postdialysis serum [Na+]
6. Intradialytic cramps
7. Intradialytic hypotension

To quantify differences in MD and SMD between subgroups and between comparisons, standard deviation (SD) of effect size point estimates were calculated from 95% CI, and comparisons made using the Student t-test, in adherence of standard operating procedures in the *Cochrane Handbook for Interventions in Systematic Reviews* (Higgins 2011), with the addition of a Bonferroni correction. Comparisons were not performed with samples that were not independent, if participants contributed to both subgroups or comparisons.

To quantify corresponding differences in RR between comparisons, we computed standard error (SE) of the log from confidence intervals [95% CI = exp(log(RR)±1.96xSE(log(RR))], and performing a z-test on the difference of the logs, defining the z-statistic being their ratio [(log(RR1-hat)-log(RR2-hat)) in the numerator, and sqrt(SE(log(RR1-hat))^2+SE(log(RR2-hat))^2) in the denominator], with a null hypothesis that it has mean of zero (Altman 2003). Similarly to above, comparisons were not performed with samples that were not independent, and therefore omitted if participants contributed to both subgroups or comparisons.

Unit of analysis issues

Studies with more than two interventions were evaluated in this review. We used recommended methods for data extraction and analysis described in the *Cochrane Handbook for Interventions in Systematic Reviews* (Higgins 2011). In these cases, provided there were adequate data from the study, then treatment arms relevant to the treatment comparisons of interest were included in applicable meta-analyses.

For cross-over studies, data from the end of the first phase of cross-over studies was included in applicable meta-analysis if possible, using an approximation of a paired analysis.

There were no cluster randomised studies included in this meta-analysis.

Dealing with missing data

Any further information was requested from the original authors by email when appropriate, and any relevant information obtained in this manner included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population were carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) was critically appraised (Higgins 2011).

Assessment of heterogeneity

Statistical heterogeneity in treatment effects among studies was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

There were insufficient data to generate funnel plots to assess for the potential existence of small study bias for the primary outcomes.

Data synthesis

Treatment estimates were summarised using random-effects meta-analysis.

Subgroup analysis and investigation of heterogeneity

There were insufficient extractable data to conduct subgroup and univariate meta-regression analysis to explore the following variables as possible sources of heterogeneity: age, time on dialysis, era in which they were receiving dialysis, residual kidney function, whether they were on conventional or extended hours dialysis regimes, predialysis serum [Na+], presence of diabetes or ischaemic heart disease or other co morbidities, duration of intervention, magnitude of difference between dialysate and serum [Na+], whether [Na+] were individualised or changed on a group level, sample size, whether participants were randomised or crossed over, and how BP outcomes were measured.

Sensitivity analysis

There were insufficient extractable data to perform the following sensitivity analyses in order to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country
- Repeating the analysis excluding any cross-over studies with a washout period of less than one week
- Repeating the analysis excluding any studies with single treatment interventions
- Repeating the analysis excluding any studies with interventions using sodium profiled dialysis.

'Summary of findings' tables

We presented the main results of the review in 'Summary of findings' tables. These tables present 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 selected outcomes (Schünemann 2011a). The 'Summary of findings' tables also include 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 (Schünemann 2011b). The outcomes presented in the 'Summary of findings' tables include (in order of importance).

- IDWG
- Intradialytic hypotension
- Predialysis MAP
- Postdialysis MAP
- Antihypertensive medication burden, as defined by study investigators
- Predialysis serum [Na+]
- Intradialytic cramps

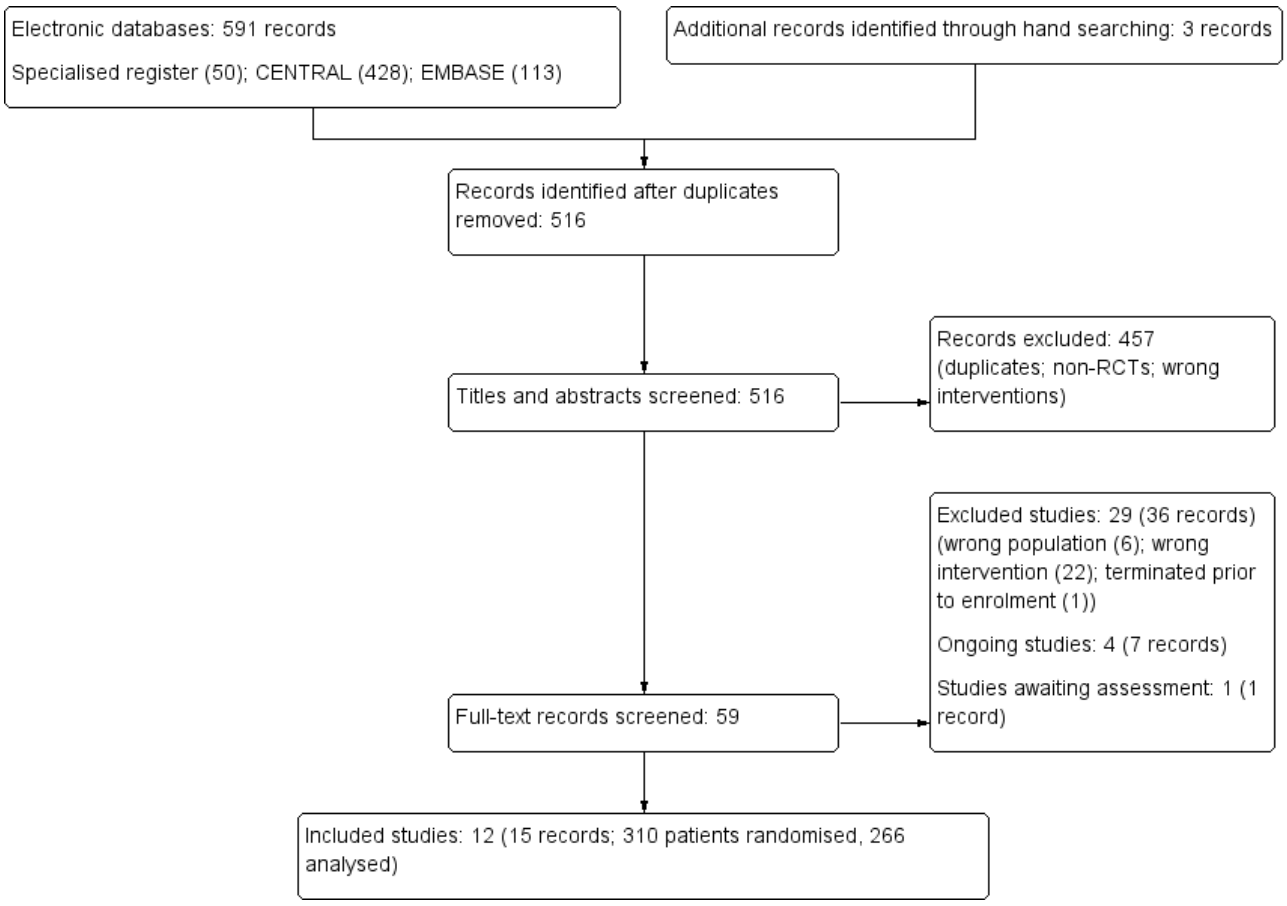
RESULTS

Description of studies

Results of the search

The electronic search strategy identified 516 unique records (Figure 1). After duplicates were removed and titles and abstracts screened we retrieved 59 full-text articles for further assessment.. Of these, 12 studies (15 records) were included and 29 studies (36 records) were excluded. Four ongoing studies were identified (7 records), and one study is awaiting assessment (1), these will be assessed in a future update of this review (Figure 1).

Figure 1. Flow chart illustrating the process of literature searching up to the identification of studies to be included in the systematic review.



Included studies

See: Characteristics of included studies and Table 1 and Table 2.

The 12 studies included randomised 310 patients, but only 266 patients could be analysed after attrition due to dropout. Most studies were cross-over studies with only three being parallel group studies (Akdag 2015; Beduschi 2013; Liu 2016). Given the predominance of studies with cross-over designs, of these 266 patients 194 contributed to low dialysate [Na+] arm, and 196 to the higher dialysate [Na+] arm.

The median (interquartile range) for follow-up was low at 4 (3, 8.5) weeks. Two studies were of only one HD session per intervention (Suckling 2013; Van Kuijk 1996), and three others were of only one week's HD per intervention (Chambers 2002; MATCH-NA 2015; Ogden 1978).

Studies were conducted in Brazil (Beduschi 2013), China (Liu 2016), the Netherlands (Van Kuijk 1996), Spain (Quereda 1988), Turkey (Akdag 2015), UK (Chambers 2002; Suckling 2013), and the USA (Boquin 1977; Daugirdas 1985; Henrich 1982; MATCH-NA 2015; Ogden 1978),

Six studies that reported funding received funding from government or healthcare organisations, one from industry, and five studies did not report their funding source.

The intervention was profiled dialysate [Na+] in only one study (Chambers 2002), with the remainder using fixed concentrations of dialysate [Na+] in the intervention and control arms. In the 12 studies, the mean dialysate [Na+] in the intervention arms was 134 mM, and in the control arms 144 mM.

Excluded studies

See: Characteristics of excluded studies

We excluded 29 studies (36 reports). The most common reasons for exclusion were: the study did not evaluate low dialysate [Na+] as an intervention; the population was in haemodiafiltration rather than HD; or the study evaluated more than one intervention at the same time.

Risk of bias in included studies

Risk of bias in the included studies is described in Characteristics of included studies, Figure 2; Figure 3.

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

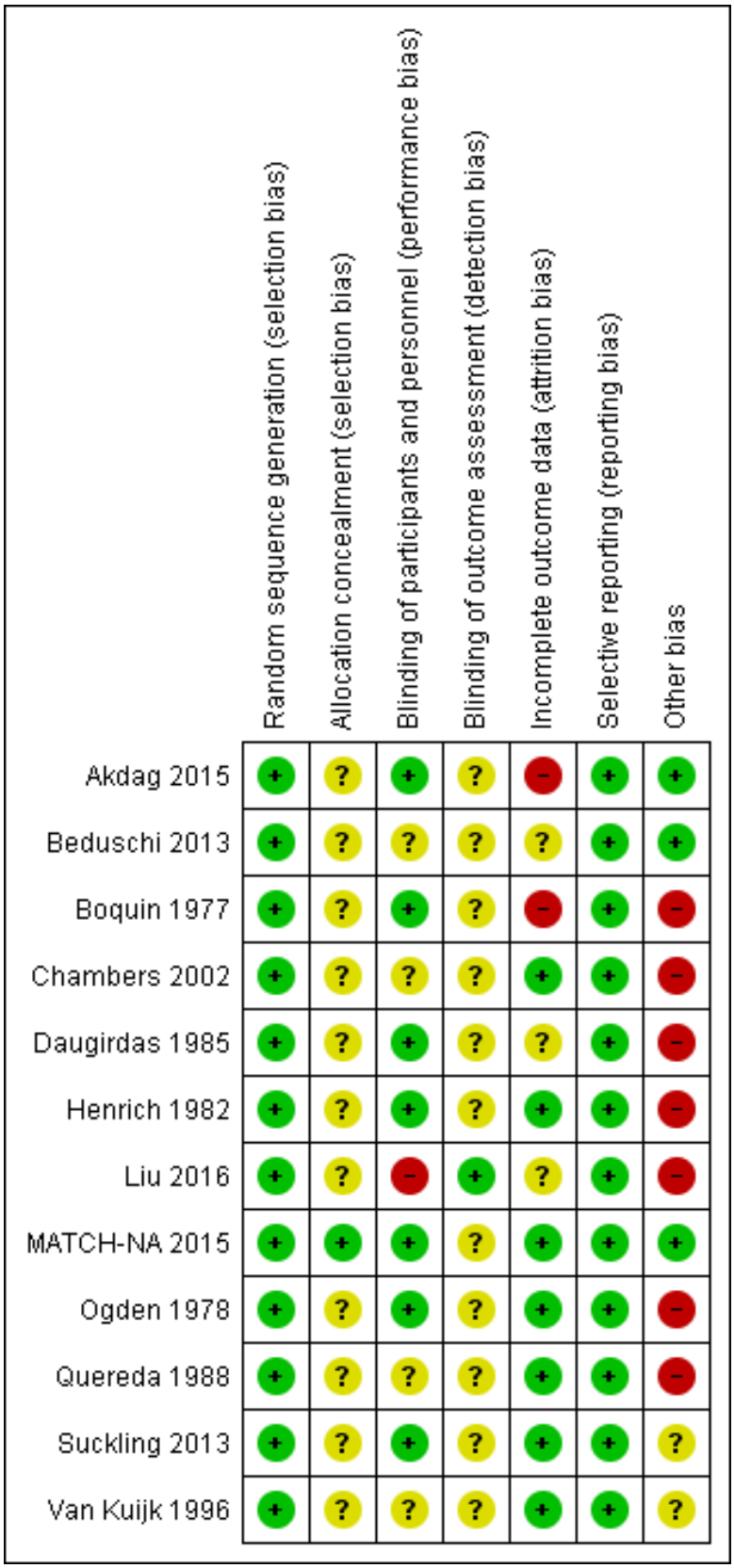
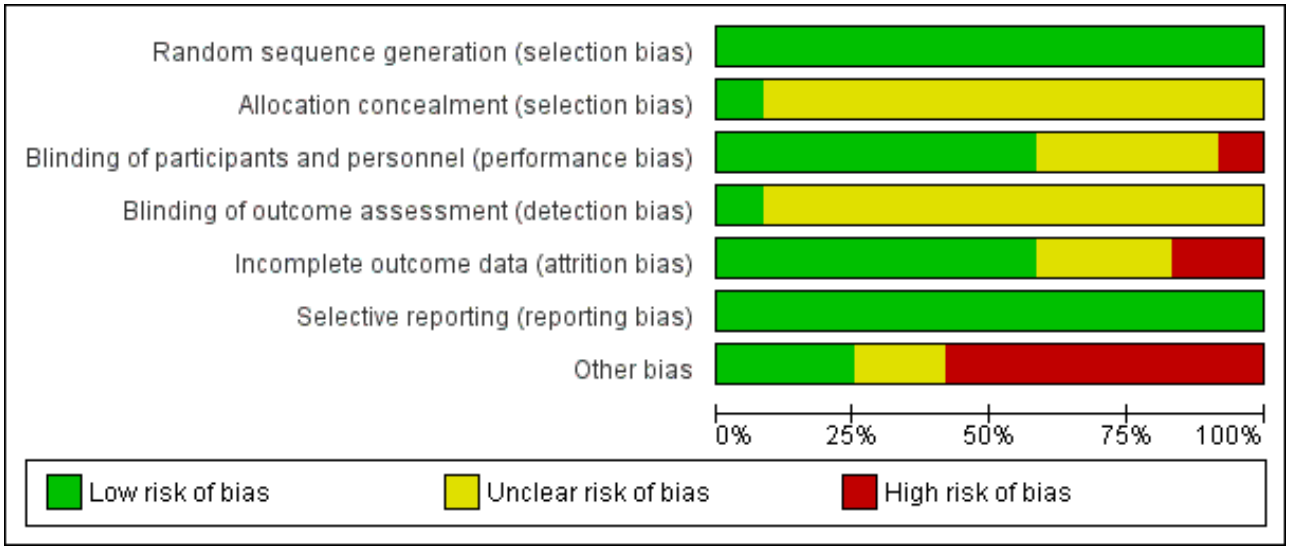


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



In most studies, conduct and reporting of most studies were not guided by the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) initiative (CONSORT home page) because of their era. Of the four studies published since 2010, only one (MATCH-NA 2015) was reported in a manner compliant with CONSORT standards), and only two were registered with a Clinical Trials Registry (Akdag 2015; MATCH-NA 2015). Where reporting of methodology was incomplete, authors were contacted directly to seek clarification, particularly about whether the intervention allocation was randomised or not.

Allocation

Random sequence generation

Following updated information from authors, we felt that all the included studies had adequate (low risk) random sequence generation.

Allocation concealment

Only MATCH-NA 2015 reported allocation concealment. Risks from allocation concealment were unclear in the remaining studies.

Blinding

Performance bias

Only Liu 2016 was open-label and at high risk of performance bias, while most studies were blinded.

- Double-blind: Akdag 2015, Daugirdas 1985, Henrich 1982, Ogden 1978
- Single-blind: Boquin 1977, MATCH-NA 2015, Suckling 2013

Risks from blinding were unclear in the remaining four studies (Beduschi 2013; Chambers 2002; Quereda 1988; Van Kuijk 1996

Detection bias

Only Liu 2016 reported assessor blinding and was at low risk of detection bias. Risks from detection bias were unclear in the remaining studies. Of note, most of the outcomes reported in the studies were automated and objective, and not easily amenable observer bias.

Incomplete outcome data

In all studies, there has not been any imputation of missing data, or analyse data using the intention to treat framework rather than a complete/as treated/safety set framework. Risk from attrition bias was low in most studies (Chambers 2002; Henrich 1982; MATCH-NA 2015; Ogden 1978; Quereda 1988; Suckling 2013; Van Kuijk 1996), either because they had no dropouts, or minimal dropouts that were clearly for reasons unrelated to the intervention. Risk was unclear in three studies (Beduschi 2013; Daugirdas 1985; Liu 2016) because of considerable dropout, albeit for reasons that were reportedly unlikely to be related to the intervention. In this setting the risk of attrition bias in related only to the development of unmeasured confounder imbalance between arms post-randomisation, and could not be assessed. The risk of attrition bias was assessed as high in two others (Akdag 2015; Boquin 1977). Where risk was high, there had been considerable dropout, for reasons including cramp or intradialytic hypotension in the intervention arm (3 out of 20 in Akdag 2015, and 7 out of 51 in Boquin 1977) and without any attempt to impute missing data in that arm.

Selective reporting

Within the limitations of what was reported in the included study articles, no obvious errors of omission were detected.

Other potential sources of bias

Indirectness was judged to be present in two studies (Suckling 2013; Van Kuijk 1996) due to these being studies of single dialysis treatments, performed with fixed ultrafiltration rates and with interventions being truncated at two hours. Although these studies met the requirements for inclusion, the intervention that was studied was likely to be less effective given the way it was applied, compared to how the intervention would be applied in most routine clinical settings.

Indirectness was also assessed as being present in a number of older studies, since the studies report now-obsolete HD practices such as the use of cellulosic dialysers (Boquin 1977; Henrich 1982; Ogden 1978; Quereda 1988), acetate-buffered dialysate (Boquin 1977; Daugirdas 1985; Henrich 1982; Ogden 1978; Quereda 1988), and parallel plate dialysers (Daugirdas 1985; Quereda 1988; Ogden 1978). The age of these studies means that the studies were undertaken in an era of non-computerised HD monitors and manual ultrafiltration systems. As such, the intervention that was studied may have had a different effect given the way it was applied, compared to the intervention as it would be applied in most modern clinical settings.

Most studies were cross-over studies, with only three being parallel group studies (Akdag 2015; Beduschi 2013; Liu 2016). Cross-over studies frequently have a carry-over effect, and very few studies that we reviewed reported a "washout" period to separate the two treatment periods that would minimise such "carry-over" effects. Only MATCH-NA 2015) and Suckling 2013 specified a washout period (one week), with Van Kuijk 1996 being unclear, and the remaining having no washout between intervention and control treatments (Boquin 1977; Chambers 2002; Henrich 1982; Ogden 1978; Quereda 1988). For these studies, the effect of lower dialysate [Na+] may have been under-estimated.

Effects of interventions

See: **Summary of findings for the main comparison** Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM) for chronic haemodialysis; **Summary of findings 2** Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) for chronic haemodialysis; **Summary of findings 3** Low dialysate [Na+] (< 138 mM) versus high dialysate [Na+] (> 140 mM) for chronic haemodialysis

The following treatment comparisons were made.

1. Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM)
2. Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM)
3. Low dialysate [Na+] (< 138 mM) versus high dialysate [Na+] (> 140 mM).

Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM)

See Summary of findings for the main comparison.

Interdialytic weight gain

Low dialysate [Na+] reduced IDWG compared to neutral or high dialysate [Na+] (Analysis 1.1 (10 studies, 352 participants): MD -0.35 kg, 95% CI -0.51 to -0.18; I^2 = 0%; high certainty evidence), reflecting an effect that can be regarded as being clinically small in size (Wong 2017). Of note, Suckling 2013) and Van Kuijk 1996 performed single HD session studies, and IDWG data from these studies were not included in this analysis as they were not subject to the study intervention.

Predialysis blood pressure

Low dialysate [Na+] probably reduced predialysis MAP compared to neutral or high dialysate [Na+] (Analysis 1.2.1 (4 studies, 156 participants): MD of -3.58 mmHg, 95% CI -5.46 to -1.69; I^2 = 0%; moderate certainty evidence), reflecting an effect that can be regarded as being clinically moderate in size (Heerspink 2009).

Low dialysate [Na+] may have reduced predialysis systolic BP (Analysis 1.2.2 (3 studies, 83 participants): MD -7.56 mmHg, 95% CI -15.92 to 0.80; I^2 = 0%; low certainty evidence). Low dialysate [Na+] may have made little or no difference to predialysis diastolic BP (Analysis 1.2.3 (2 studies, 52 participants): MD -3.13 mmHg, 95% CI -11.79 to 5.54); I^2 = 0% low certainty evidence).

Of note, Boquin 1977 presented mean predialysis systolic and diastolic BP for the intervention and control, but no measures of distribution or P values relating to them - this study was therefore excluded from the analyses of systolic and diastolic BP. Suckling 2013 and Van Kuijk 1996 performed single HD session studies, and predialysis BP data from these studies were not included in this analysis as they were not subject to the study intervention.

Intradialytic blood pressure

It is uncertain whether low dialysate [Na+] changed intradialytic MAP because the certainty of this evidence is very low (Analysis 1.3.1 (1 study, 20 participants):MD -4.00 mmHg, 95% CI -18.52 to 10.52; low certainty evidence). Low dialysate [Na+] may have made little or no difference to intradialytic systolic BP (Analysis 1.3.2 (2 studies, 34 participants): MD -3.99 mmHg, 95% CI -17.96 to 9.99); I^2 = 0%; low certainty evidence). Low dialysate [Na+] also may have made little or no difference to intradialytic diastolic BP (Analysis 1.3.3 (2 studies, 34 participants): MD 1.33 mmHg; 95% CI -6.29 to 8.95; I^2 = 0%; low certainty evidence).

Postdialysis blood pressure

Low dialysate [Na+] probably reduced postdialysis MAP compared to neutral or high dialysate [Na+] (Analysis 1.4,1 (4 studies, 150 participants): -3.26 mmHg; 95% CI -4.82 to -1.70; I^2 = 0%; moderated certainty evidence), reflecting an effect that can be regarded as being clinically moderate in size (Heerspink 2009). It is uncertain whether low dialysate [Na+] changes postdialysis systolic BP (Analysis 1.4.2 (1 study, 18 participants): MD -5.00 mmHg, 95% CI -31.86 to 21.86; very low certainty evidence). It is also uncertain whether low dialysate [Na+] changes postdialysis diastolic BP (Analysis 1.4.3 (1 study, 18 participants): MD 0.00 mmHg, 95% CI -13.98 to 13.98; very low certainty evidence).

Of note, Boquin 1977 presented mean postdialysis systolic and diastolic BP, but no measures of distribution or P values relating to them, and this study was therefore excluded from the analyses of systolic and diastolic BP. Henrich 1982 and Beduschi 2013 did not present systolic and diastolic BP, only MAP.

Interdialytic blood pressure

Low dialysate [Na+] may have made little or no difference to Interdialytic systolic BP compared to neutral or high dialysate [Na+] (Analysis 1.5.2 (2 studies, 103 participants): MD -0.17 mmHg, 95% CI -5.42 to 5.08; I^2 = 0%; low certainty evidence). Compared to neutral or high dialysate [Na+], low dialysate [Na+] may have reduced Interdialytic diastolic BP (Analysis 1.5.3 (2 studies, 103 participants):MD -2.00 mmHg, 95% CI -4.88 to 0.84; I^2 = 0%; low certainty evidence).

Of note, both Akdag 2015 and Liu 2016 presented postdialysis systolic and diastolic BP from which measures of central tendency for MAP might be calculated, but not corresponding measures of distribution - these studies were therefore excluded from the analysis of MAP.

Serum [Na+]

Low dialysate [Na+] probably reduced serum predialysis serum [Na+] compared to neutral or high dialysate [Na+] (Analysis 1.6.1 (7 studies, 258 participants):MD -1.69 mM, 95% CI -2.36 to -1.02; I^2 = 0%; moderate certainty evidence), reflecting an effect that can be regarded as being clinically small in size (Hecking 2012; Hecking 2015; Mc Causland 2012). It is uncertain whether low dialysate [Na+] changed Intradialytic serum [Na+] (Analysis 1.6.2 (1 study, 20 participants): MD -4.37 mM, 95% CI -6.24 to -2.40; very low certainty evidence).

Low dialysate [Na+] probably reduced postdialysis serum [Na+] compared to neutral or high dialysate [Na+] (Analysis 1.6.3 (3 studies, 99 participants): MD -4.74 mM, 95% CI -8.30 to 1.77; I^2= 86% moderate certainty evidence), reflecting an effect that can be regarded as being moderate in size (Hecking 2012; Hecking 2015; Mc Causland 2012). Heterogeneity was high almost certainly as a result of the different "doses" of dialysate [Na+] between the three studies, and corresponding "dose effect" for interventions on the outcome. For instance, the difference in dialysate [Na+] between the intervention and control arms was ˜15 mM in Ogden 1978, ˜10 mM in Van Kuijk 1996 and only ˜2 mM in Liu 2016, as expected leading to the sub-physiologic low postdialysis serum [Na+] in Ogden 1978 and relatively normal one in Liu 2016, with Van Kuijk 1996 being in between.

Intradialytic cramps

Low dialysate [Na+] probably increased intradialytic cramp compared to neutral or high dialysate [Na+] (Analysis 1.8 (6 studies, 12,186 HD sessions): RR 1.77, 95% CI 1.15 to 2.73; I^2= 89%; moderate certainty evidence). Of note, Akdag 2015 did not quantify this outcome (i.e. over how many sessions), but merely stated it as a reason for withdrawal from the study and exclusion from their analysis; this study was not included in our analysis. There was high heterogeneity between the studies, contributed by the inconsistency of a single study (Liu 2016), again almost certainly due to the relatively smaller "dose effect" for the intervention of only ˜2 mM difference in dialysate [Na+] between arms in that that study.

Intradialytic hypotension

Low dialysate [Na+] probably increased intradialytic hypotension compared to neutral or high dialysate [Na+] (Analysis 1.8 (9 studies, 12,681 HD sessions): RR 1.56, 95% CI 1.17 to 2.07; I^2= 81%; moderate certainty evidence) reflecting an effect that can be regarded as being large in size. Of note, Akdag 2015 did not quantify this outcome (i.e. over how many sessions), but merely stated it as a reason for withdrawal from the study and exclusion from their analysis; this study was not included in our analysis.

Of note, there was considerable variability between studies around how intradialytic hypotension was assessed that might have contributed to the observed high heterogeneity between studies, and a summary is tabulated in additional Table 3 ("Definition of intradialytic hypotension in included studies"). Although these different definitions can give different results, it is likely that this feature did not reduce the internal validity the studies, nor hamper consistent interpretation of the literature - in each study, the patients' responses to therapy in both the intervention and control groups were assessed in the same manner, and are therefore directly comparable. The differences between arms in each of the studies can be synthesised without issue.

Postdialysis extracellular fluid status

It is uncertain whether low dialysate [Na+] changed postdialysis extracellular fluid status (Analysis 1.9 (1 study, 38 participants): MD -0.30 L, 95% CI -2.07 to 1.47); very low certainty evidence). The extracellular fluid status was as assessed by bioimpedance analysis (Beduschi 2013).

Dietary salt intake

Low dialysate [Na+] may have decreased dietary salt intake compared to neutral or high dialysate [Na+] (Analysis 1.10 (2 studies, 95 participants): MD 0.21 g/d, 95% CI -0.48 to 0.06; I^2= 0%; low certainty evidence. In these two studies intake was assessed from three-day food diaries, and reported as salt intake in g/d (note: Beduschi 2013 reported intake as sodium/day, but it is in fact salt/day as confirmed with the authors - the corrected data were used in this analysis).

Left ventricular structure

It is uncertain whether low dialysate [Na+] changed left ventricular mass index compared to neutral or high dialysate [Na+] (Analysis 1.11.1 (1 study, 57 participants): MD -8.00 g/m^2, 95% CI -17.11 to 1.11; very low certainty evidence) . It is also uncertain whether low dialysate [Na+] changed either end-diastolic dimension (Analysis 1.11.2 (1 study, 57 participants): MD 0.40 cm, 95% CI -3.18 to 3.98; very low certainty evidence) or end-systolic dimension, with a and Analysis 1.11.3 (1 study, 57 participants): 0.4 cm, 95% CI -2.59 to 3.39; very low certainty evidence). Of note, the single study in this analysis (Liu 2016) was subject to high risk ascertainment bias, since the outcome was determined by single operator, albeit blinded to allocation, at two points separated at 12 months with no control for potential observer drift, using echocardiography as opposed to the research standard of cardiac magnetic resonance imaging.

Antihypertensive medication

Low dialysate [Na+] may have reduced antihypertensive medication burden compared to neutral or high dialysate [Na+] (Analysis 1.12 (2 studies, 103 participants): SMD -0.67, 95% CI -1.07 to -0.28; I^2= 0%; low certainty evidence). Of note, SMD was used for this analysis rather than MD - antihypertensive medication burden was quantified as number of antihypertensive drugs in Akdag 2015, and as aggregated equivalent dose units in Liu 2016.

Fatigue

It is uncertain whether low dialysate [Na+] changed fatigue compared to neutral or high dialysate [Na+] (Analysis 1.13 (1 study, 32 participants): MD 6.52, 95% CI -18.57 to 31.60; very low certainty evidence) on a 100-point fatigue scale (100 most fatigued).

Thirst

It is uncertain whether low dialysate [Na+] changed thirst compared to neutral or high dialysate [Na+] (Analysis 1.14 (1 study, 14

participants): MD -0.60, 95% CI -2.07 to 0.87; very low certainty evidence), on a 9-point thirst scale (9 most thirsty).

Pulse wave velocity

It is uncertain whether low dialysate [Na+] changed pulse wave velocity compared to neutral or high dialysate [Na+] (Analysis 1.15 (1 study, 57 participants): MD -0.20 m/s, 95% CI -1.45 to 1.05; very low certainty evidence),

Vascular resistance

It is uncertain whether low dialysate [Na+] changed vascular resistance compared to neutral or high dialysate [Na+] (Analysis 1.16 (1 study, 18 participants): MD -17 mmHg/mL/100mL/s, 95% CI -867.03 to 901.03; very low certainty evidence).

Venous tone

It is uncertain whether low dialysate [Na+] changed venous tone compared to neutral or high dialysate [Na+] (Analysis 1.17 (1 study, 18 participants): MD 0.40 mmHg/mL/100mL, 95% CI -2.28 to 3.08; very low certainty evidence).

Outcomes not reported

Predialysis extracellular fluid status, hospitalisation, myocardial infarction, stroke, CV death, and death (all causes) were not reported.

Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM)

See Summary of findings 2.

Data synthesis for the available outcomes is presented in additional Table 4 ("Outcomes reported for low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM)"). The following text summarises the data synthesis only briefly, listing only the outcomes and where there are no available data, and highlighting differences between this comparison and the main one.

Data were available for IDWG, predialysis BP, postdialysis BP, interdialytic BP, serum [Na+], intradialytic cramps, intradialytic hypotension, postdialysis ECF status, dietary salt intake, left ventricular structure, antihypertensive medication, fatigue, and pulse wave velocity. For all of these outcomes, the effect of the intervention was directionally similar to that identified in the main comparison, and the size of the effect also similar.

Data were not available for intradialytic BP, predialysis, thirst, vascular resistance, venous tone, hospitalisation, myocardial infarction, stroke, CV death, and death (all causes).

Low dialysate [Na+] (<138 mM) versus high dialysate [Na+] (>140 mM)

See Summary of findings 3.

Data synthesis for the available outcomes is presented in additional Table 5 ("Outcomes reported for low dialysate [Na+] (< 138 mM) versus high dialysate [Na+] (> 140 mM)"). The following text summarises the data synthesis only briefly, listing only the outcomes and where there are no available data, and highlighting differences between this comparison and the main one.

Data were available for IDWG, predialysis BP, intradialytic BP, postdialysis BP, predialysis serum [Na+], intradialytic cramps, intradialytic hypotension, thirst, vascular resistance, and venous tone. For all of these outcomes, the effect of the intervention was directionally similar to that identified in the main comparison, and the size of the effect was also similar.

Data were not available for interdialytic BP, predialysis extracellular fluid status, postdialysis extracellular fluid status, dietary salt intake, left ventricular structure, antihypertensive medication, fatigue, pulse wave velocity, hospitalisation, myocardial infarction, stroke, CV death, death (all causes).

Additional Table 6 ("Dose effect" for intervention of lower versus higher dialysate [Na+]) examines 7 key outcomes and compares:

- the effect of the intervention in comparison to neutral dialysate [Na+] (138 to 140 mM), versus,
- the corresponding effect of the intervention in comparison to high dialysate [Na+] (> 140 mM).

As can be seen in additional Table 6, the point estimates in each comparison directionally show a greater effect size with the intervention in the latter comparison compared to the former one, although formal hypothesis testing identifies that the difference is only certain for postdialysis serum [Na+].

DISCUSSION

Summary of main results

This review has synthesised data from 12 studies randomising 310 patients, with 266 analysed after attrition due to dropout. The key findings from our meta-analysis relevant to clinical practice are as follows.

- Low dialysate [Na+] compared to higher dialysate [Na+] reduces IDWG
- Low dialysate [Na+] compared to higher dialysate [Na+] probably reduces BP
- Low dialysate [Na+] compared to higher dialysate [Na+] probably reduces serum [Na+] concentration
- Low dialysate [Na+] compared to higher dialysate [Na+] probably increases intradialytic hypotension
- Low dialysate [Na+] compared to higher dialysate [Na+] probably increases intradialytic cramp
- Point estimates suggest that the effect of low dialysate [Na+] may be smaller relative to neutral dialysate [Na+], and greater in comparison to high dialysate [Na+]
- There are insufficient data to inform on other patient-centred outcomes and dietary sodium intake.
- There are insufficient data to inform on cardiac structure and function.
- There are no data to inform on hospitalisation and death.
- Only one study reported health related quality of life, and they did not report the results by arm but for the cohort as a whole (Chambers 2002).

In the included studies, lower dialysate [Na+] led to lower IDWG and probably BP. These outcomes are both key clinical indicators in the routine care of HD patients, and a reduction in IDWG is associated with improvements in long-term morbidity and death (Charra 2004;

Cabrera 2015; Kalantar-Zadeh 2009; Kimura 1984; London 2001; Matsuoka 1990; Movilli 2013; Ozkahya 2002; Shepherd 1987; Van Stone 1982), and reduction in BP lowers the risk of death in clinical trials (Heerspink 2009). In the studies we reviewed, it can be concluded that lower dialysate [Na+] has some effects that are very likely to be beneficial ones.

On the other hand, lower dialysate [Na+] also probably led to increased intradialytic hypotension. This is also a key clinical indicator in routine care, and an increase is associated with reduced patient satisfaction with care (Amro 2014; Caplin 2011; Schipper 2011), development of cardiac end-organ disease (Boon 2004; Bos 2000; Burton 2009; McIntyre 2008; Selby 2007a; Sherman 2011), and increased hospitalisation, major CV events and death (Flythe 2015; Sands 2014; Shoji 2004; Stefansson 2014; Tisler 2003; McIntyre 2014). In addition, lower dialysate [Na+] probably led to a decrease in serum [Na+], albeit a modest one that remained within the normal reference range (135 to 145 mM) in the majority of studies. The only exception was Ogden 1978, where the low dialysate [Na +] was amongst the lowest in the review, and sub-physiologic at 131 mM. Excluding all the studies with sub-physiologic dialysate [Na+] from the analysis (Boquin 1977; Ogden 1978; Quereda 1988) did not meaningfully change the direction or size of the effect of low dialysate [Na+] on predialysis serum [Na+] (MD -1.49 mM, 95% CI -2.35 to -0.63]). In the studies we reviewed, it can be concluded that lower dialysate [Na+] also has some effects that are likely to be harmful ones.

The only patient-centred outcome that we could evaluate was intradialytic cramps. In the included studies, lower dialysate [Na +] probably led to more cramps. In addition to cramps being painful and distressing to patients, cramps can also reduce the effectiveness of HD in a similar way to intradialytic hypotension, through the use of saline boluses to alleviate symptoms, or through early abandonment of HD sessions before therapeutic targets are met. As such, this often-trivialised adverse event must be considered an important harmful effect.

In the studies we reviewed, there was a suggestion of a "dose-effect" relating to the intervention, insofar as the point estimates of the effect size of the intervention tended to be larger when the comparator was high dialysate [Na+], and relatively more modest when the comparator was neutral dialysate [Na+] (see additional Table 6 ""Dose effect" for intervention of lower versus higher dialysate [Na+]"). When rudimentary hypothesis testing is applied, however, these effect size estimates do not appear to be significantly different between comparisons other than for postdialysis serum [Na+], where a greater difference in dialysate [Na +] between the intervention and control arms resulted in a greater difference in postdialysis serum [Na+]. Our hypothesis of a "dose-effect" is consistent with biological models of sodium kinetics, whereby the [Na+] gradient between dialysate and blood defines mass transport, therefore determining body Na+ content, and from there the physiological effect of sodium loading on physiological function and outcomes (Dunlop 2012; Gotch 1990; Keen 2007).

Only single studies were available for the outcomes of thirst and measures of CV structure and function; only two studies were available for dietary sodium intake. No data were available on the "hard" clinical outcomes of hospitalisation and death. Data are therefore insufficient or absent to allow a robust evaluation of these outcomes.

Overall completeness and applicability of evidence

In terms of external validity, many of the studies were old, with half being from last century. This raises the potential for an era effect, since the studies report now-obsolete HD practices such as the use of cellulosic dialysers (Boquin 1977; Henrich 1982; Ogden 1978; Quereda 1988), acetate-buffered dialysate (Boquin 1977; Daugirdas 1985; Henrich 1982; Ogden 1978), and parallel plate dialysers (Daugirdas 1985; Ogden 1978; Quereda 1988). The age of these studies means that the studies were undertaken in an era of non-computerised HD monitors and manual ultrafiltration systems. These characteristics all lead to a greater risk of HD-induced haemodynamic instability during treatment in the reviewed studies compared to the contemporary setting. The analysis of older studies therefore overestimates of risks related to intradialytic hypotension in modern practice. Patient characteristics in the reviewed study also reflect an era effect, since the study populations (and likely source populations) were younger and healthier than those of today. For instance, the weighted mean age of patients included in this meta-analysis is 57.9 years, with a weighted mean average vintage on dialysis of 51.5 months, indicating that many started dialysis with an age in their early 50's, between 10 and 20 years earlier than the typical patient these days (see Table 2). Moreover, the percentage of those with end-stage diabetic kidney disease was 27.6%, which is much lower than that in most parts of the world (United States Renal Data System Report 2015 - International Comparisons). Compared to the participants in the reviewed studies, contemporary HD patients with relatively higher co-morbid burden are likely to have less robust compensatory mechanisms in the face of ultrafiltration, as well as less tolerance to end-organ ischaemia.

Another important factor was that the median (interquartile range) for follow-up in the studies was low at 3 (3, 8.5) weeks. Two studies were of only one HD session per intervention (Suckling 2013; Van Kuijk 1996), and two others were of only one week's HD per intervention (Chambers 2002; MATCH-NA 2015; Ogden 1978). This is important since a pre- post-study by Thein 2007 demonstrated that BP was still falling four months after a low dialysate [Na +] intervention was made, presumably on the basis of ongoing depletion of participants' non-osmotic sodium stores (Titze 2008; Titze 2009). Therefore, the short-term follow-up of the studies we reviewed may have underestimated the treatment effect of low dialysate [Na+] on outcomes, especially those pertaining to fluid volume status and BP.

Finally, the effect of the intervention might be dependent on the baseline serum [Na+] and co-morbidities of individual patients. No study reported enough data to perform subgroup analyses according to patient characteristics, which is an important gap in the synthesis.

A comment is warranted about the safety outcomes in this review, and the ascertainment or measurement of both intradialytic hypotension and serum [Na+] in the included studies. With respect to intradialytic hypotension, the various definitions in the literature are tabulated in additional Table 7 ("A priori definitions of intradialytic hypotension in the literature"), although the weight of evidence shows that either the Nadir90/Nadir100 definition or the KDOQI definition are the most appropriate ones with which to assess intradialytic hypotension, with the strongest associations with poorer outcomes (Flythe 2015; Sands 2014; Shoji 2004; Stefansson 2014; Tisler 2003). The various definitions of

intradialytic hypotension in the included studies are tabulated in in additional Table 3 ("Definitions of intradialytic hypotension in included studies") . It should be noted that all of them include key aspects Nadir90/Nadir100 and KDOQI definitions, and as such the assessment of intradialytic hypotension in this synthesis is likely to be robust. With respect to serum [Na+], there was considerable variability between studies around how measurements were made, and a summary is tabulated in additional Table 8 ("Methods for measuring [Na+] in included studies"). Although these methods can give slightly different results (Ekbal 2016), it is likely that this feature did not reduce the internal validity the studies, nor hamper consistent interpretation of the literature - in each study, the patients' responses to therapy in both the intervention and control groups were assessed in the same manner, and are therefore directly comparable. The differences between arms in each of the studies can be synthesised without issue, since these values were determined "within-(calibrated)-assay", not "between-(calibrated)-assay".

In terms of completeness, only two of the reviewed studies evaluated antihypertensive usage, and this may have clouded the size of the treatment effect with respect to the outcome of BP. It is plausible that improvement in BP control will manifest as a reduction in antihypertensive requirement, rather than as an overall lowering of BP. For instance, in the Frequent Hemodialysis Network trials of frequent in-centre and home dialysis, there was a 6.8% and 5.4% lowering of predialysis systolic BP with intensive HD, respectively (Chertow 2010; Rocco 2011). However, a less well reported finding is that there was a 40.8% and 32.3% concurrent reduction in the number of antihypertensive's used by participants (Kotanko 2015) . The lack of reporting of antihypertensive usage may have under-estimated the treatment effect of low dialysate [Na+] on BP. There were few studies that reported dialysate temperature, which would also influence intradialytic hypotension event rates.

Quality of the evidence

We assessed the quality of study evidence using standard risks of bias domains within the Cochrane tool together with GRADE methodology. Confidence in IDWG results was high, BP and sodium intake results was moderate, but confidence in intradialytic cramps and hypotension as low. We downgraded for the possibility of publication bias due to the very low numbers of data observations for each outcome, precluding formal testing. Data summary was also difficult due to the variable methods of reporting in the individual studies, especially the heterogeneous manner of reporting intradialytic cramps and hypotension. Some studies did not report an estimate of variance (SE or SD) and some provided data in descriptive or figure format only. For the cross-over studies, we had to combine data from both arms, despite the general recommendation to use just the first part, since these latter data were not available. This increases the chances of a carry-over effect, especially if there was not washout clear period to separate the two treatment periods (Boquin 1977; Chambers 2002; Henrich 1982; Ogden 1978; Quereda 1988; Van Kuijk 1996). For these studies, the intervention of higher dialysate [Na+] was similar if not identical to their usual HD prescription, and the effect of lower dialysate [Na+] on outcomes may have been under-estimated.

A comment is warranted about the issue of dialysate [Na+] settings on HD machines. There are only a few studies that compare the accuracy of dialysate [Na+] settings on HD machines with direct measurements using other methods (Ekbal 2016; Hecking 2011; Gul 2016; Descombes 2014). However, these studies themselves are contradictory. In one such study, the difference between prescribed and measured dialysate [Na+] concentrations was on average very close to zero, and its distribution was not skewed (Hecking 2011). In the other studies, the measured dialysate [Na+] was either much higher than the prescribed dialysate [Na+] (Ekbal 2016), or slightly higher (Gul 2016; Descombes 2014). To complicate things further, these comparisons differed markedly according to the brand of machinery. There are many reasons for this variation in prescribed versus delivered dialysate [Na+]. The majority appears to be due to variation in operating characteristics for HD treatments: irrespective of the type of machine, facilities that use a wide variation is dialysis prescription and temperature or those that mix their concentrates themselves will test the limits of calibration for their machines, with a sacrifice in accuracy. Another source of variation is the machines themselves. Machines automatically convert the user prescription of sodium and bicarbonate concentration in dialysate to conductivity. These algorithms vary between machines, and are proprietary and not published. In addition, different machines proportion dialysate differently, some with volumetric and some with conductometric systems. The International Standard on concentrate for HD (ISO 13958) limits the concentration variation to 5% for all components, except for sodium, for which it is only 2.5%. Notwithstanding, a variation in 2% in a volumetric systems is an error in dialysate [Na+] of ± 5 mM. When well calibrated, the errors of both of these systems are low (< 1%) but careful dialysis machine maintenance is essential to preserve reliability and precision of systems (Stragier 2018). This may not always happen in "real world" settings. While these differences might seem small, there are potentially different associations between dialysate [Na+] and various outcomes according to different machines (Stragier 2018) and different regions of the world (Hecking 2017). These issues raise concerns about the applicability of the entire body of literature on prescribed dialysate [Na+] as a whole.

Of the included studies, about half measured dialysate [Na+] and delivered the intervention and control treatment according to these measurements as shown in Table 8 ("Methods for measuring [Na+] in included studies"). This will paradoxically decrease the applicability of these studies in "real-world" settings, where without exception prescribed dialysate [Na+] is performed using the machine settings. The internal validity of included studies is not affected, however - in each study, the patients' responses to therapy in both the intervention and control groups were tested in the same manner, and are therefore directly comparable. The differences between arms in each of the studies can therefore be synthesised without issue. The only caution that is required is around interpretation of the dialysate [Na+] itself - although we have separated the studies in sensitivity analyses into neutral dialysate [Na+] (138 to 140 mM) versus high dialysate [Na+] (> 140 mM), this categorisation is of course according to how the study investigators assessed dialysate [Na+], and may not translate to machine settings in "real world" settings.

Potential biases in the review process

Potential biases in this review relate to the data availability in the individual studies. First, there was heterogeneity in treatment interventions and comparisons; due to the small number of data observations, robust statistical estimates of heterogeneity could

not be estimated. Second, we could not assess for potential reporting bias due to the small number of studies in the review. Third, studies were frequently at high risk of bias, but poorer quality studies could not be excluded from sensitivity analyses due to the limited number of data observations. Fourth, the treatment endpoints were principally surrogate markers of health (IDWG, BP, serum [Na+]) and the effects of low dialysate [Na+] on cardiac structure and function and "hard" clinical outcomes remains uncertain. Fifth, most follow-up was short, and the longer term effects of low dialysate [Na+] on outcomes remains uncertain. Sixth, adverse event reporting in the available studies was infrequent and incomplete. Finally, there is dearth of reporting on patient-centred outcomes such as quality of life and treatment satisfaction. Notwithstanding, we have attempted to avoid any bias in our review process. Wherever there was any uncertainty regarding methodology of RCT conduct we contacted the study authors directly to seek further clarification before deciding on whether to a study should be included or not.

Agreements and disagreements with other studies or reviews

A narrative review of 23 studies evaluating high versus low dialysate [Na+] has been published (Basile 2015). In contrast to this review, it included observational studies and non-randomised interventional studies. Overall, their conclusions were similar to ours regarding high heterogeneity between studies and a lack of data about antihypertensive use and "hard" clinical outcomes.

Many narrative reviews or editorials have been written on the subject of low versus high dialysate [Na+] over the years (Hecking 2015; Marshall 2012; Weiner 2014). Most are opinion-based, and do not include meta-analysis methodology. Nonetheless most draw the conclusion that the intervention is a promising one, and that definitive clinical trial-based evidence is required to inform practice. Of note, some opinion leaders advocate utilising a universally individualised dialysate [Na+], calculated around patients' current or recent predialysis serum [Na+] measurements (Lomonte 2011; Penne 2011; Santos 2008). However, the practicality or necessity of such a specific intervention is uncertain, and it is likely that considerations other than just serum [Na +] should determine optimal sodium balance for patients, and therefore the required dialysis [Na+].

AUTHORS' CONCLUSIONS

Implications for practice

On the basis of this review, lower dialysate [Na+] reduces IDWG and BP, but probably decreases serum [Na+] and increases intradialytic adverse events. The combined effect of these factors on overall patient experience and clinical outcome is unknown. The implications of this treatment effect need careful consideration. On the one hand it may be beneficial, as these changes may represent a reduction in total body sodium content and thus an improvement in CV structure and function, and reduction in CV morbidity and death. However, the alternative consideration is that a lowering of serum [Na+] may represent a signal of harm, and that an increase in intradialytic hypotension is a cause of decreasing effectiveness of HD, cardiac damage, and ultimately increasing CV morbidity and death. Moreover, there are few data to provide insights into patient-centred outcomes other than cramps and intradialytic hypotension, and what low-quality evidence exists is in favour of higher rather than lower dialysate [Na+].

A question might be asked about a third approach to dialysate [Na+]: "In practice, why not avoid high or low dialysate [Na+] altogether, and simply match dialysate [Na+] to serum [Na+] to avoid any disruption on HD?" (Keen 2007; Raimann 2018; Santos 2010). This so-called "isonatraemic HD" requires individualisation of dialysate [Na+] so that it is close to the patient's predialysis serum [Na+], and is based upon the sodium "set-point" paradigm: people maintain themselves in optimal sodium balance above and below which health is compromised. Indeed, serum [Na+] is observed to be very stable across time in both healthy and HD patients (Peixoto 2010; Zhang 2014). There are two issue with this approach, one philosophical, and the other logistic. The philosophical issue arises from assuming that an individual's observed sodium balance is optimal. In fact, sodium intake in modern society is largely dictated by conditions other than metabolic need, and determined largely by palatability and custom. Moreover, an individual's sodium "set point" can be easily "re-set" (Braunwald 1965; Hollenberg 1972; Hollenberg 1980; Strauss 1958): normal people who are established on low sodium diets will promptly excrete any administered sodium. For this reason, attempts to define a "healthy" sodium balance from an observed state of balance is meaningless. In an analogous argument, isocaloric nutrition is not automatically ideal for HD patients, despite a stable weight over time, unless they are in nutritionally optimal to start with. The second objection to isonatraemic HD is logistic. As described above, there is wide variation in the accuracy by which HD machines measure and manage sodium, and there are at present no reliable technical means which would automatically ensure isonatremic HD.

No strong recommendation for practice can be made on the basis of these data. These preliminary findings represent potential mechanisms for both benefit and harm from lower dialysate [Na +], but the net effect of these physiological processes on patient experiences and outcomes at a population level remains unknown. Until the results of a definitive study are available, a decision on what dialysate [Na+] to use will have to be made between every patient and doctor, without definite knowledge of whether lower or higher dialysate [Na+] is better for the average patient. If the patient has a high BP, fluid overload, or high IDWG, then it is probably helpful to consider a lower dialysate [Na+] - the evidence from this review suggests that this strategy will improve those problems. If these problems are not an issue, then perhaps it is better to place priority on avoiding intradialytic hypotension, and advise a higher dialysate [Na+] - the evidence from this review suggests that this strategy will reduce the likelihood of that problem. Even when the results of a definitive study are known, this individualised approach should probably still continue, except that at that time will know for sure whether the starting point for shared decision making should be a lower dialysate [Na+] at a population)i.e. dialysis unit) level, or a higher one.

Implications for research

Further research is needed to define longer-term outcomes with lower dialysate [Na+], using modern HD machinery and customary practices, in participants who are reflective of modern patients, examining both mechanistic and clinical outcomes including:

- cardiac structure and function as assessed by optimal methods such as magnetic resonance imaging,
- fluid status as assessed by optimal methods such as bioimpedence analysis,
- hospitalisation,
- CV morbidity and death,
- patient symptoms scores, satisfaction with care, and quality of life.

Sufficiently powered and well-designed clinical studies are necessary to provide definitive results. There is an ongoing medium-sized but short-term clinical study exploring the effect of low dialysate [Na+] on BP, IDWG and intradialytic hypotension (NCT00724633), a medium-sized and medium-term study exploring the effect of low dialysate [Na+] on these outcomes as well as cardiac structure and function and patient-centred outcomes SoLID 2013, and a large pragmatic study of dialysate [Na+] of 137mM versus 140 mM on clinical outcomes (NCT02823821). A large gap in research is the absence of studies to provide definitive results around the net effect of low dialysate [Na+] on CV morbidity and death, and this gap must be filled before clear recommendations can be made for clinical practice. It would be important for this research to include appropriate predefined subgroup analysis by predialysis serum [Na+] and comorbidity, and economic analyses since this is one of few interventions that may be able to provide benefit at no cost.

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CHARACTERISTICS OF STUDIES

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

Akdag 2015

Methods	• Study design: parallel RCT • Duration of study (recruitment): March 2013 to December 2013 • Duration of follow-up: 6 months
Participants	• Country: Turkey • Setting: single centred • Outpatients on HD (age criteria not reported) with a vintage of ≥ 1 year at enrolment, treated previously with standard dialysate [Na+] of 140 mM • Number (randomised/analysed): treatment group (25/22); control group (25/24) • Mean age ± SD (years): treatment group (45.2 ± 2.8); control group (43.6 ± 2.5) • Sex (M/F): treatment group (13/9); control group (14/10) • Mean time on dialysis ± SD (months): treatment group (52.1 ± 37.9), control group (55.6 ± 32.3) • Measured characteristics and comorbidities otherwise balanced • Exclusion criteria: CrCl ≥ 10 mL/min/1.73 m^2; masking or white coat hypertension (not otherwise defined); heart failure; cardiomyopathies; acute coronary syndromes; chronic Ischaemic heart disease; acute or chronic liver disease; endocrine or pulmonary diseases; valvular heart diseases; malignancies; active UTI; Hb < 8 g/dL; hypotension tendency (not otherwise defined)
Interventions	HD regimen • 3 times/week, 4 hours/session • Low-flux polysulfone dialyser • Bicarbonate-buffered dialysate • QB: 300 to 350 mL/min Treatment group • Dialysate [Na+]: 137 mM for 6 months Control group • Dialysate [Na+]: 140 mM for 6 months
Outcomes	• Outcomes were assessed at baseline and 6 months * 24 hour ambulatory BP monitoring on a mid-week non-dialysis day (a variety of analyses within this pertaining to SBP, DBP, daytime, night-time and nocturnal dipping) * IDWG * Numbers of antihypertensives * Neither intradialytic hypotension or cramp was quantified as an outcome, merely a reason for withdrawal from the study and exclusion from analysis ☐ Intradialytic hypotension: defined as a drop in SBP of 20 mmHg or greater accompanied by symptoms requiring active treatment such as saline infusion, unclear as to how frequency was measured (i.e. over how many sessions) ☐ Cramp: defined as that requiring active medical treatment such as saline infusion, unclear as to how frequency was measured (i.e. over how many sessions)
Notes	• Funding source: not reported • NCT0262145

Risk of bias

Bias	Authors' judgement	Support for judgement

Akdag 2015 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation clearly stated in published article, along with mechanism of randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Clearly stated to be double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	3 dropouts in the intervention group due to intradialytic hypotension and cramps, which are likely to be related to the intervention. The study is not analysed as intention to treat, and data from those who dropped out are excluded from analysis. There is a high risk of attrition bias
Selective reporting (reporting bias)	Low risk	The study appears to be free of reporting bias
Other bias	Low risk	The study appears to be free of other sources of bias

Beduschi 2013

Methods	• Study design: parallel RCT • Duration of study (recruitment): April 2007 to February 2009 • Duration of follow-up: 16 weeks
Participants	• Country: Brazil • Setting: single centre • Adults ≥18 years on HD with a vintage of ≥ 90 days at enrolment, treated previously with standard dialysate [Na+] of 138 mM • Number (randomised/analysed): treatment group (29/20); control group (23/18) • Mean age ± SD (years): treatment group (64.95 ± 14.02); control group (60.22 ± 13.96) • Sex (M/F): treatment group 14/6; control group (10/8) • Mean time on dialysis; IQR (months): treatment group (30.9; 19.5, 75.0); control group (49.5; 26.0, 58.0) • Measured characteristics and comorbidities otherwise balanced • Exclusion criteria: acute inflammatory processes; chronic inflammatory diseases; antibiotic use within the past 2 months; malignancies; central venous catheter use
Interventions	HD regimen • 3 times/week, 3.5 to 4 hours/session • Low-flux polysulfone dialyser • Bicarbonate-buffered dialysate • Prescribed Kt/V at least 1.4 Treatment group • Dialysate [Na+]: 135 mM Control group

Beduschi 2013 *(Continued)*

- Dialysate [Na+]: 138 mM

Duration

- 16 weeks (864 HD sessions in control group, 960 in treatment group)

Outcomes	• Outcomes were assessed at 8 and 16 weeks, with BP and IDWG being assessed as the mean of the last 10 preceding sessions * Predialysis SBP * Predialysis DBP * Predialysis MAP * Postdialysis MAP * Intradialytic hypotension: "defined as the presence of BP levels lower than 90 x 60 mmHg" * Intradialytic cramps * IDWG * Predialysis serum [Na+] * Postdialysis extracellular fluid volume status: multipolar bioimpedance analysis * Dietary salt intake: 3-day food diary * Other biochemical measurements
Notes	• Funding source: FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo). • Extra information was requested and supplied in full from authors (all emails on file) * SD for IDWG instead of IQR * Pre- and postdialysis MAP (mean and SD) * % of treatments (rather than of patients as reported) with intradialytic cramps or hypotension. * Presence and extent of blinding * An error in the paper with respect to the reporting of dietary sodium intake between groups, where the daily sodium intake (g/d) was at the end of these study was 8.71 (0.8) in group A and 9.24 (1.28) in group B. This was confirmed with the authors and should have been reported as salt intake per day, and equates to a sodium intake (g/d) of 3.43 (0.3) in group A and 3.64 (0.5) in group B.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation clearly stated in published article, along with mechanism of randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Patients not blinded, although outcomes are unlikely to be biased by their nature
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	14/52 (27%) participants were withdrawn because of acute infections during the study period, 9 from the treatment group and 5 from the control group. The study is not analysed as intention to treat, and data from those who dropped out are omitted from analysis. Although the reasons for dropout do not appear to be related to the treatment, there is still a possibility of attrition bias. In addition, this large number of dropouts may have affected balance of patient characteristics by arm. The groups appeared balanced on measured

Beduschi 2013 *(Continued)*

		confounders in Table 1, but an effect of these dropouts on unmeasured confounders is unknown
Selective reporting (reporting bias)	Low risk	The study appears to be free of reporting bias
Other bias	Low risk	The study appears to be free of other sources of bias

Boquin 1977

Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 4 weeks
Participants	• Country: USA • Setting: single centre • Prevalent (undefined except for the term maintenance) HD patients from a "satellite" HD unit (no clinical characteristics reported) • Number: 51 patients allocated to control and then treatment, or treatment and then control, attrition of 14 patients (4 for hospitalisation (reasons not reported), 3 for transplantation, and 7 because they could not titrate down to 130 mM, leaving 37 patients analysed in the final report • Mean age ± SD (years): not reported • Mean time on dialysis: not reported • Sex (M/F): not reported • Exclusion criteria: not specified, the only comment about sampling frame is the term "unselected"
Interventions	HD regimen • 3 times/week, 4 hours/session • Low-flux CDAK 2.5 M^2 dialyser • Acetate-buffered dialysate • QB 200 to 250 ml/min and QD 480 to 520 mL/min Treatment group • Dialysate [Na+]: 130 mM Control group • Dialysate [Na+]: 140 mM Duration • 1 month (444 HD sessions in control group, 444 in treatment group)
Outcomes	• Outcomes were assessed over the entire period of treatment/observation: * Predialysis SBP (measures of central tendency only) * Predialysis DBP (measures of central tendency only) * Postdialysis SBP (measures of central tendency only) * Postdialysis DBP (measures of central tendency only) * Intradialytic hypotension: "hypotension requiring treatment" * Intradialytic cramps * IDWG * Predialysis serum [Na+]

Boquin 1977 *(Continued)*

Notes	• Funding source: not reported • Raw data extracted from graphs using Ploy Digitizer as able • Extra information was requested from the authors, and the senior author Dr Levine confirmed the following (all emails on file) * Randomisation was most likely by drawing lots * Information was not reported for the excluded patients, and data presented on per protocol basis relating only to the patients completing the study. On the basis of this information, n was analysed as 37 * The P values in Fig. 5 were very likely related to calculated MAP, although the he could not categorically exclude them relating to SBP only. On the basis of this information, BP was analysed as MAP calculated from the reported data, excluding systolic and DBPs from meta-analysis, with distribution of MAP calculated from the P values relating to them

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation clearly stated in published article, but not the mechanism of randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Single (patient) blinding clearly stated in published article
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	14/51 patients were removed from the study, 4 because of hospitalisation not otherwise specified, 3 because of transplantation, and 7 because they could not clinically tolerate the treatment. The study is not analysed as intention to treat, and data from those who dropped out are omitted from analysis. There is a high risk of attrition bias.
Selective reporting (reporting bias)	Low risk	The study appears to be free of reporting bias
Other bias	High risk	• Obsolete dialysis practice patterns (cellulosic dialysers, acetate buffered dialysate), with a patient sample that is not reflective of modern populations. Risk of poor external validity (indirectness) • No washout

Chambers 2002

Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 1 week
Participants	• Country: UK • Setting: single centre • Adults ("elderly") on HD

Chambers 2002 *(Continued)*

- Number: 16 patients allocated to control and then treatment, or treatment and then control, no attrition
- Mean age (range): 75.8 years (65.5 to 88.6)
- Sex (M/F): not reported
- Mean time on dialysis: not reported
- Exclusion criteria: not reported

Interventions	HD regimen • 3 times/week, 3.5 h/session • Dialyser, buffer, and dialysis dose not reported Treatment group 1 (called B in abstract) • UF profiling and dialysate [Na+] 136 mM (data not used) Treatment group 2 (called C in abstract) • Sodium profiling with a time averaged dialysate [Na+] of 140 mM Treatment group 3 (called D in abstract) • UF and sodium profiling with a time averaged dialysate [Na+] of 140 mM (data not used) Control group • Dialysate [Na+]: 136 mM Duration • 1 week (48 HD sessions in control group, 48 in treatment group)
Outcomes	• Outcomes were assessed over the entire period of treatment/observation * Intradialytic hypotension: "drop in systolic BP by 30mmHg or decrease to an absolute level of <90 mmHg" * Intradialytic cramps * IDWG * HRQoL: SF 36 * Fatigue: Fisk Fatigue Impact Scale instrument
Notes	• Funding source: not reported • Extra information was requested from the authors (all emails on file). However, the original data could not be retrieved (has been lost or destroyed), although a PowerPoint file from the oral presentation of the abstract at the conference (ASN) was provided to us as additional information • Some of the study data were reported in graphical form, with individual marker points for the mean and a whisker for the SEM. We digitised the graphs on slide 9 from the oral presentation of the abstract at the ASN using Plot Digitizer, and calculated SD from SEM x SQRT(N) • HRQoL could not be used since it was not reported for each arm

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation stated in published article, but not mechanism of randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Chambers 2002 *(Continued)*

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	Low risk	The study appears to be free of attrition bias
Selective reporting (reporting bias)	Low risk	The study appears to be free of reporting bias
Other bias	High risk	• Abstract study only, with sparse reporting of procedural details - potential for information bias • No washout

Daugirdas 1985

Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 4 weeks
Participants	• Country: USA • Setting: single centre • Prevalent (on HD for > 1 year) HD patients (clinical characteristics not reported other than being prone to intradialytic hypotension and cramps and not clinically fluid overloaded) • Number: 10 patients allocated to control and then treatment, or treatment and then control, attrition of 3 patients for hospitalisation due to treatment-unrelated illness, resulting in 7 for final analysis • Mean age ± SD (years): not reported • Sex (M/F): not reported • Mean time of dialysis: not reported • Exclusion criteria: not reported
Interventions	HD regimen • 3 times/week, 4 hours/session • Low-flux 1.0 m^2 PAN plate dialysers • Acetate-buffered dialysate • QB 250 mL/min, QD 500 mL/min, URR and Kt/V not reported Treatment group 1 • Dialysate [Na+]: 135 mM Treatment group 2 • Dialysate [Na+]: 143 mM Treatment group 3 • Profiled dialysate [Na+] from 160 to 133 mM (average dialysate [Na+] for session = ??, data not used)

Daugirdas 1985 *(Continued)*

	Duration • 4 weeks for each (only the last 3 weeks of any given 4-week block was analysed) (63 HD sessions in control group, 63 in treatment group)
Outcomes	• Outcomes were assessed over the entire period of treatment/observation * Intradialytic hypotension - "15% fall in mean arterial BP" * Predialysis SBP and DBP * Intradialytic SBP and DBP * Intradialytic cramps * IDWG * Thirst (VAS) * Predialysis serum [Na+] * Weakness score
Notes	• Funding source: not reported • Extra information was requested from the authors but the original study data have been lost • Weakness scores were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation clearly stated in published article, but not mechanism of randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinding clearly stated in published article and confirmed by the lead author
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 patient dropouts "were judged to be treatment-unrelated, and accordingly, their data were excluded from analysis". The study is not analysed as intention to treat, and data from those who dropped out is omitted from analysis. Although the reasons for dropout do not appear to be related to the treatment, there is still risk of attrition bias. In addition, this large number of dropouts may have affected balance of patient characteristics by arm. The groups appeared balanced on measured confounders in table 1, but an effect of these dropouts on unmeasured confounders is unknown
Selective reporting (reporting bias)	Low risk	The study appears to be free of reporting bias
Other bias	High risk	Obsolete dialysis practice patterns (acetate buffered dialysate, parallel plate dialysers), with a patient sample that is not reflective of modern populations. Risk of poor external validity (indirectness)

Henrich 1982

Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 6 weeks
Participants	• Country: USA • Setting: single centre • Prevalent (undefined except for the term "chronic") on HD (age criteria not reported), "stable" (undefined), treated previously with standard dialysate [Na+] 135 to 140 mM • Number: 10 patients allocated to control and then treatment, or treatment and then control, no attrition • Mean age ± SD: 57.2 ± 24.7 years • Sex (M/F): not reported • Mean time on dialysis ± SD: 31.5 ± 25.3 months • Exclusion criteria: not reported
Interventions	HD regimen • 3 times/week, 5 hours/session • Low-flux 1.3 m^2 cellulosic dialyser • Acetate-buffered dialysate • QB between 238 and 242 mL/min, QD not reported • URR and Kt/V not reported Treatment group • Dialysate [Na+]: 144 mM Control group • Dialysate [Na+]: 132 mM Duration • 6 weeks (180 sessions in control group, 180 in treatment group)
Outcomes	• Outcomes were assessed over the entire period of treatment/observation: * Predialysis MAP * Postdialysis MAP * Intradialytic hypotension - "arbitrarily defined prior to the beginning of the study as a recumbent systolic blood pressure of <=90 mmHg." * Episodes of discomfort during dialysis * IDWG * Predialysis serum [Na+]
Notes	• Funding source: Texas Chapter of the National Kidney Foundation, the Educational Research Foundation, and the William Bragg Kidney Research Fund. • Extra information was requested from the authors, and all information was provided as much as could be, although the lead author confirmed that the original data were lost (all emails on file). The following information was obtained: * Randomisation was employed * % of treatments with intradialytic cramps or hypotension not available * SBP and DBP not available

Risk of bias

Bias	Authors' judgement	Support for judgement

Henrich 1982 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation was not reported in published article, but confirmed by the lead author upon direct contact. The mechanism of randomisation is unknown / unrecalled
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinding clearly stated in published article and confirmed by the lead author
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study appears to be free of attrition bias
Selective reporting (reporting bias)	Low risk	The study appears to be free of reporting bias
Other bias	High risk	• Obsolete dialysis practice patterns (cellulosic dialysers, acetate buffered dialysate), with a risk of poor external validity (indirectness) • No washout

Liu 2016

Methods	• Study design: parallel, open-label RCT • Duration of study: not reported • Duration of follow-up: 12 months
Participants	• Country: China • Setting: single centre • Prevalent patients on HD (age criteria not reported) with a time on dialysis of > 6 months at enrolment, treated previously with standard dialysate [Na+] 138 mM, hypertensive (defined as a mean ambulatory BP of > 135/85 and < 160/100), on stable antihypertensive medication (no adjustments in the month prior to enrolment), left ventricular ejection fraction > 40%, serum albumin > 30 g/L, average predialysis serum [Na+] over the last 12 months > 138 mM • Number (randomised/analysed): treatment group (32/28); control group (32/29) • Mean age ± SD (years): treatment group (59 ± 10); control group (57 ± 11) • Sex (M/F): treatment group (16/12); control group (15/14) • Mean time on dialysis; IQR (months): treatment group (61; 8 to 91); control group (68; 13 to 108) • Measured characteristics and comorbidities otherwise balanced • Exclusion criteria: stroke, MI, or limb ischaemia in the previous 6 months; residual daily urine output > 200 mL/d; hypotension-prone (not otherwise defined)
Interventions	HD regimen • 3 times/week, 4 hours/session • Low-flux polysulfone dialyser • Bicarbonate buffer • QB 200 to 300 mL/min, QD 500 mL/min

Liu 2016 *(Continued)*

	Treatment group • Dialysate [Na+]: 136 mM Control group • Dialysate [Na+] 138 mM Duration • 12 months (4524 sessions in control group, 4368 in treatment group)
Outcomes	• Outcomes were assessed at baseline and 12 months, with the exception of predialysis BP, IDWG, cramps and intradialytic hypotension which were assessed over the entire period of observation: * Interdialytic ambulatory SBP (midweek, 44 hours) * Interdialytic ambulatory DBP (midweek, 44 hour) * Home SBP (3 times/day, 7 days/week, one week/month) * Home DBP (3 times/day, 7 days/week, one week/month) * Intradialytic hypotension - "decrease in systolic BP by 20 mm Hg or a decrease in mean arterial pressure by 10 mm Hg associated with clinical events and need for nursing interventions" * Intradialytic cramps - "symptoms that required emergency medical attention or saline infusion without a reduction in BP" * IDWG * Predialysis serum [Na+] (monthly) * Postdialysis serum [Na+] (monthly) * Types and numbers and doses of antihypertensives * Postdialysis extracellular fluid volume status: multipolar bioimpedance analysis (monthly) * Dietary salt intake - 3 day food diary (monthly) * Pulse wave velocity (single operator, blinded to allocation) * Pulse wave velocity (single operator, blinded to allocation) * LVMI, EDD, ESD, SWT, PWT by echocardiography (single operator, blinded to allocation) * Other biochemical measurements
Notes	• Funding source: Beijing High-Level Talents in Health Care System Funding 2014-3-021. • Postdialysis extracellular fluid volume status not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation clearly stated in published article, along with mechanism of randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding included outcomes assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7/64 patients were removed from the study, 5 because of death, 2 because of transplantation, and 1 because of loss to follow-up. These serious adverse events are not otherwise reported. The study is not analysed as intention to

Liu 2016 *(Continued)*

		treat, and data from those who dropped out is omitted from analysis. The reasons for dropout might be related to the treatment, and there is a risk of attrition bias. In addition, dropouts may have affected balance of patient characteristics by arm, although they are only a small number
Selective reporting (reporting bias)	Low risk	The study appears to be free of reporting bias
Other bias	High risk	PWV and echocardiography performed by a single, albeit blinded assessor. There is potential for ascertainment bias, and also potential for drift with respect to the echocardiography, which was assessed 12 months apart

MATCH-NA 2015

Methods	• Study design: cross-over RCT • Duration of study (recruitment): June 2012 to July 2012 • Duration of follow-up: 1 week
Participants	• Country: USA • Setting: single centre • Adults (18 to 85 years) on HD from 3 facilities, with a time on dialysis of > 30 days at enrolment, dialysate [Na+] 139.5 mM prior to study, ability to provide informed consent, nephrologist deemed patient was at target dry weight, hypertension (predialysis BP > 140/90 mmHg or postdialysis BP > 130/80 mmHg), and SBP increases ≥ 10 mmHg pre- to postdialysis for at least 4 of the last 6 HD sessions • Number: 7 patients allocated to high to low group, 9 to low to high group, attrition of 3 patients • Mean age ± SD: 58.8 ± 9.5 years • sex (M/F): 15/1 • Time on dialysis: > 1 year (12/16) • Measured characteristics and comorbidities otherwise balanced • Exclusion criteria: active cancer or active wounds; inability to measure BP in the upper extremity; current antibiotic treatment or intravenous antibiotics within the past month; life expectancy less than 6 months; inability to provide informed consent
Interventions	HD regimen • 3 times a week, 233 minutes/session • QD 725 mL/min, QB 456 mL/min • bicarbonate buffer • URR and Kt/V not reported Treatment group 1 • Dialysate [Na+] 134.3 mM Treatment group 2 • Dialysate [Na+]: 142.9 mM Duration • 1 week with 1 week washout

MATCH-NA 2015 *(Continued)*

Outcomes	• Outcomes were assessed over the entire period of treatment/observation * Predialysis BP * Postdialysis BP * Intradialytic hypotension * IDWG * Predialysis serum [Na+]
Notes	• Funding source: the University of Texas Southwestern O'Brien Kidney Research Core (National Institutes of Health [NIH] grant P30DK079328), NIH University of Texas Southwestern Clinical Translational Science Award (NIH UL1RR024982), American Heart Association grant CRP11680033 (Dr Inrig), and NIH grants F32DK085965 (Dr Van Buren) and 5K24DK002818 (Dr Toto) • Extra information was requested from the authors about (all emails on file): * Rates of intradialytic hypotension (provided) * Mean and SD of SBP, DBP and MAP (only SBP provided) * Blinding (patients blinded, assessors not blinded)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation clearly stated in published article, but not mechanism of randomisation
Allocation concealment (selection bias)	Low risk	Allocation concealment clearly stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Single (patient) blinding clearly stated in published article
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All available data included including those from dropouts, analysed as intention to treat
Selective reporting (reporting bias)	Low risk	The study appears to be free of reporting bias
Other bias	Low risk	The study appears to be free of other sources of bias

Ogden 1978

Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 1 week
Participants	• Country: USA • Setting: single centre • Prevalent (undefined except for the term "chronic") HD patients with time on dialysis > 3 months at enrolment, HCT ≥ 20%

Ogden 1978 *(Continued)*

- Number: 12 patients allocated to control and then treatment, or treatment and then control, no attrition
- Mean age ± SD (years); not reported
- Sex (M/F): not reported
- Time on dialysis: not reported
- Exclusion criteria: transfusion requirement (not defined)

Interventions	HD regimen • Frequency not reported (although a frequency of 3 times a week can be inferred from the description of "Patients were studied twice at 1 week intervals" and "over the 9 days of study" and the "42 hour inter-dialytic interval"), ≥4 hours/session • Low-flux cellulosic dialyser • Acetate-buffered dialysate • URR reported as 55.5% Treatment group • Dialysate [Na+]: 146 mM Control group • Dialysate [Na+] 131 mM (NB, article has contradictory low dialysate [Na+] reports in the body of the text and table 1) Duration • 1 week
Outcomes	• Outcomes were assessed over a single HD session, although the treatment was applied for a week: * IDWG * Predialysis serum [Na+] * Postdialysis serum [Na+] * Predialysis MAP * Composite score of intradialytic hypotension and cramps and other discomfort
Notes	• Funding source: not reported • This study was subsequently extended and 2 additional patients added to the study population. The resulting study was published as an abstract (see Ogden & Cohen 1979). We chose to use the full paper rather than the abstract due to the level of detail reported and available for meta-analysis • Although Dr Ogden died in the 1980s, his co-author on the abstract (Dr Irvin M Cohen) was able to confirm that the study was randomised, although he could not remember how (all emails on file). • Some of the study data were reported in the Results section as mean ± 2 x SEM, and much of the study data were reported in graphical form. Graphs were either scatter plots with individual marker points for each participant's measurements, or marker (mean) and whisker (2 x SEM) plots for the entire study population. We digitised the graphs (Fig. 2, 7 and 8) using Plot Digitzer, and determined a high level of agreement between values derived from these digitised plots, and the corresponding values from reported study data (see below) • Study data were meta-analysed as follows * IDWG: mean as reported in the article. Note: the mean as reported in the article was 2. 23 kg and 2. 68 kg for the low and high dialysate [Na+] arms, versus 2.236299 and 2.66571 kg from the digitised graph of Fig. 8, respectively. * IDWG: SD from digitised graph of Fig. 7 * Predialysis serum [Na+]: mean as reported in the article * Predialysis serum [Na+]: SD calculated from 2 x SEM as reported in the article, according to the formula SEM x SQRT(N) * Postdialysis serum [Na+]: mean as reported in the article for high dialysate [Na+] comparison, and from digitised graph for low dialysate [Na+] treatment. Note: the mean serum [Na+] reported in the

Ogden 1978 *(Continued)*

article for high dialysate [Na+] comparison was 142 mM, versus 141.9489533 mM from the digitised graph of Fig. 2

* Postdialysis serum [Na+]: SD from digitised graph of Fig. 2
* Predialysis MAP: mean as reported in the article. Note: the mean as reported in the article was 91 mmHg and 96 mmHg for the low and high dialysate [Na+] arms, versus 90.6293545 mmHg and 95.54645117 mmHg from the digitised graph of Fig. 8
* Predialysis MAP: SD from digitised graph of Fig. 8
* Separate estimates of intradialytic hypotension and crams could not be estimated because of composite nature of the score reported and graphed in the article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation has been confirmed by the authors, although the mechanism of randomisation is unclear
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding (participants and investigators) clearly stated in the published article
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study appears to be free of attrition bias
Selective reporting (reporting bias)	Low risk	The study appears to be free of reporting bias
Other bias	High risk	• Obsolete dialysis practice patterns (cellulosic dialysers, acetate buffered dialysate, parallel plate dialysers), with a risk of poor external validity (indirectness) • No washout

Quereda 1988

Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 2 weeks
Participants	• Country: Spain • Setting: single centre • Prevalent patients on HD (age criteria not reported) • Number: 8 patients allocated to control and then treatment, or treatment and then control, no attrition • Mean age ± SD: 58 ± 9 years • Sex (M/F): 2/6

Quereda 1988 *(Continued)*

- Mean time on dialysis ± SD: 27 ± 22 months
- None had diabetes mellitus
- Exclusion criteria: not reported

Interventions	HD regimen • Frequency not reported • Low-flux cellulosic dialyser (PAN or CU) • Acetate buffer • QB and QD not reported • Kt/V and URR not reported Treatment (performed in 8 phases) • CU dialyser + dialysate [Na+] 133 mM + temp 37 • CU dialyser + dialysate [Na+] 139 mM + temp 37 • PAN dialyser + dialysate [Na+] 133 mM + temp 37 • PAN dialyser + dialysate [Na+] 139 mM + temp 37 • CU dialyser + dialysate [Na+] 133 mM + temp 35 • CU dialyser + dialysate [Na+] 139 mM + temp 35 • PAN dialyser + dialysate [Na+] 133 mM + temp 35 • PAN dialyser + dialysate [Na+] 139 mM + temp 35 Duration • 6 dialysis sessions for each patient on each phase (192 HD session with dialysate [Na+] 133 mM, 192 HD session with dialysate [Na+] 139 mM)

Outcomes	• Outcomes were pooled by dialysate [Na+], since other interventions were identical across groups
	• Outcomes were assessed over the entire period of treatment/observation:
	  * Predialysis SBP
	  * Intradialytic hypotension: "defined as a fall of systolic BP below 90 mm Hg."
	  * IDWG

Notes	• Funding source: not reported • This research was presented as 2 separate abstracts at EDTA and a local congress, and then published in Int Journal of Artificial Organs • SBP values were not reported in a format that could be analysed • Extra information was requested from the authors, but none was provided • Treatment groups were collapsed by dialysate [Na+], and given the identical sample sizes, the point estimates for each outcomes were calculated as the weighted mean from table 1, and the standard deviations as the square root of the weighted variances from table 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation clearly stated in published article, but not mechanism of randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information to permit judgement

Quereda 1988 *(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	Low risk	The study appears to be free of attrition bias
Selective reporting (reporting bias)	Low risk	The study appears to be free of reporting bias
Other bias	High risk	• Obsolete dialysis practice patterns (cellulosic dialysers, parallel plate dialysers), with a risk of poor external validity (indirectness) • No washout

Suckling 2013

Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 1 HD session analysed
Participants	• Country: UK • Setting: single centre • Prevalent outpatients on HD (age criteria not reported), "stable", with time on dialysis > 3 months • Number: 10 patients allocated to control and then treatment, or treatment and then control, no attrition • Mean age ± SD: 60.9 ± 5.1 years • Sex (M/F): 5/5 • Mean time on dialysis: not reported • Exclusion criteria: not reported
Interventions	HD regimen • 2 hours/session of treatment/control • High-flux polysulfone dialyser • Bicarbonate buffer • QB 250 to 350 mL/min, QD 500 mL/min • mean URR ± SD: 75.9% ± 1.5% Treatment group • Dialysate [Na+]: 135 mM over a single HD session Control group • Dialysate [Na+]: 145 mM over a single HD session Duration • A single HD treatment, assessed over the first 2 hours of HD under the condition of zero UF, treatment and control sessions separated by washout of a week

Suckling 2013 *(Continued)*

Outcomes	• Outcomes assessed over one HD session * Predialysis SBP * Predialysis DBP * Predialysis MAP * Intradialytic (120 minutes) SBP * Intradialytic (120 minutes) DBP * Intradialytic (120 minutes) MAP * Predialysis serum [Na+] * Intradialytic (120 minutes) serum [Na+] * Cardiac index using transthoracic bioimpedance
Notes	• Funding source: Hypertension Trust • Because UF volume was controlled, IDWG was not included in the SR • Because the study treatment was a single session separated by a week, predialysis study data were not included in meta-analyses (they were not subject to the study treatment) • Although a measure of cardiac function was described in the paper, this was reported as a cardiac index and was not interpretable directly • Extra information was requested from the authors, and the following was provided (although only 120 minute data were used): * Mean and SD of predialysis [Na+] * Mean and SD of 120 minute [Na+] * Mean and SD of predialysis SBP DBP, and MAP * Mean and SD of 120 minute SBP, DBP, and MAP

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation stated in published article, but not mechanism of randomisation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Single-blinding (participant) clearly stated in the published article
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study appears to be free of attrition bias
Selective reporting (reporting bias)	Low risk	The study appears to be free of reporting bias
Other bias	Unclear risk	Is a study of treatment over a single dialysis session, and the effect size attributable to the treatment is likely to be attenuated - risk of ascertainment bias

Van Kuijk 1996

Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 1 HD session analysed
Participants	• Country: the Netherlands • Setting: single centre • Prevalent outpatients on HD (age criteria not reported), "haemodynamically stable patients • who rarely suffered from intradialytic hypotension" • Number: 9 patients allocated to control and then treatment, or treatment and then control, no attrition • Mean age (range): 46 years (23 to 71) • sex (M/F): 8/1 • Mean time on dialysis (range): 46 months (12 to 53) • Exclusion criteria: severe coronary (NYHA II or more) or valvular heart disease; compromised left ventricular function (ejection fraction 30% or less); diabetes mellitus
Interventions	HD regimen • 2 hours/session of treatment/control • Low-flux hemophan dialyser • Bicarbonate buffer • QB 250 mL/min, QD 500 mL/min • URR not reported Treatment group • Dialysate [Na+]: 134 mM over a single HD session Control group • Dialysate [Na+]: 144 mM over a single HD session Duration • A single HD treatment, assessed over the first 2 hours of HD under the condition of 1 L/hour UF, treatment and control sessions separated by an unreported length of time

Outcomes	• Outcomes assessed over one HD session
	  * Forearm venous tone
	  * Forearm vascular resistance
	  * Relative blood volume
	  * Predialysis SBP
	  * Predialysis DBP
	  * Postdialysis MAP
	  * Postdialysis SBP
	  * Postdialysis DBP
	  * Postdialysis MAP
	  * Predialysis serum [Na+]
	  * Postdialysis serum [Na+]
	  * PGE2
	  * Intradialytic hypotension

Notes	• Funding source: Gambro AB • Because the study treatment was a single session separated by a week, predialysis study data were not included in meta-analyses (they were not subject to the study treatment)

Van Kuijk 1996 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation clearly stated in published article, but not mechanism of randomisation
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	Low risk	The study appears to be free of attrition bias
Selective reporting (reporting bias)	Low risk	The study appears to be free of reporting bias
Other bias	Unclear risk	• Is a study of treatment over a single truncated dialysis session with fixed UF, and the effect size attributable to the treatment is likely to be attenuated • Uncertain washout

BP - blood pressure; CrCl - creatinine clearance; CU - cuprammonium cellulose; DBP - diastolic BP; EDD - end-diastolic diameter; ESD - end-systolic diameter; Hb - haemoglobin; HCT - haematocrit; HD - haemodialysis; HRQoL - health-related quality of life; IDWG - interdialytic weight gain; IQR - interquartile range; Kt/V - dialyser clearance adequacy; LVMI - left ventricular mass index; M/F - male female; MAP - mean arterial pressure; MI - myocardial infarction; NYHA - New York Heart Association; PAN - polyacrylonitrile membrane; PWT - posterior wall thickness; PWV - pulse wave velocity; QB - blood (pump) flow rate; QD - dialysate flow rate; RCT - randomised controlled trial; SBP - systolic BP; SD - standard deviation; SEM - standard error of the mean; SQRT - square root; SWT - septal wall thickness; UF - ultrafiltration; URR - urea reduction ratio; UTI - urinary tract infection; VAS - visual analogue scale

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

Study	Reason for exclusion
Acchiardo 1975	Wrong intervention: study of what solution to infuse for treatment of cramps
AIMS 2011	Wrong population: HDF rather than HD
Bachtiar 2005	Wrong intervention: tested low dialysate [Na+] versus BIS-guided target weight adjustment on BP. The dialysate [Na+] in the latter group was not specified. The authors were emailed for clarification but never replied
Barre 1988	Wrong intervention: high dialysate [Na+] versus higher dialysate [Na+]
CARNIDIAL 2012	Wrong intervention: carnitine supplementation
Coli 2000	Wrong intervention: dialysate [Na+] with a co-intervention of UF profiling

Study	Reason for exclusion
De Nicola 2000	Wrong intervention: neutral dialysate [Na+] versus high dialysate [Na+]
de Vries 1990	Wrong intervention: dialysate [Na+] with a co-intervention of UF profiling
Ebrahimi 2017	Wrong intervention: dialysate [Na+] not < 138 mM
Ekart 2015	Wrong population: HDF rather than HD
Enia 1998	Wrong population: CAPD patients
Ficociello 2012	Wrong intervention: specific alignment of dialysate [Na+] to serum [Na+]
HEMATOL 2013	Wrong population: critically ill rather than maintenance HD patients
Henrich 1983	Wrong intervention: high sodium bicarbonate and acetate HD
Lambie 2005	Wrong intervention: on-line conductivity monitoring; did not compare low dialysate [Na+] to medium or high dialysate [Na+]
Levin 1996	Wrong intervention: did not test low dialysate [Na+]
Macon 1995	Wrong intervention: slow HD versus dialysate [Na+] modelling
Mahiout 1987	Wrong intervention: high dialysate [Na+] versus higher dialysate [Na+]
Meira 2010	Wrong intervention: high dialysate [Na+] versus profiled dialysate [Na+] with an average dialysate [Na+] that was also high
Moret 2006	Wrong intervention: neutral dialysate [Na+] versus high dialysate [Na+]
NCT01015313	This study has been withdrawn prior to enrolment
NCT01168947	Wrong intervention: saline versus 5% dextrose as priming and rinsing fluids
NCT01766882	Wrong intervention: goal weight challenging versus dietary sodium restriction in the setting of a fixed dialysate [Na+] of 137 mM
Oliver 2001	Wrong population: effect of low dialysate [Na+] on patients with high or low baseline IDWG
Oliver 2001a	Wrong intervention: dialysate [Na+] with a co-intervention of UF profiling
Robberechts 2013	Wrong intervention: the authors did not define low dialysate [Na+], although the study meets the other criteria to be included in the review. The authors were emailed for clarification but never replied
Sandy 1996	Wrong population: critically ill rather than maintenance HD patients
Sang 1997	Wrong intervention: high dialysate [Na+] to higher dialysate [Na+]
Selby 2007	Wrong intervention: low dialysate [Na+] to lower dialysate [Na+]

BP - blood pressure; CAPD - continuous ambulatory peritoneal dialysis; HDF - haemodiafiltration; HD - haemodialysis; IDWG - interdialytic weigh gain; UF - ultrafiltration

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

ISRCTN71215609

Methods	RCT The two groups will both undergo a 1-week period of initial data collection while being maintained on routine dialysis.
Participants	HD patients
Interventions	Dialysis will be performed using a default dialysate [Na+] of 140 mmol/L. The first group will then continue to dialyse against a standard dialysate [Na+] of 140 mmol/l, while the second group undergoes a period of 1 month of sequential reduction of dialysate [Na+] according to online conductivity monitoring, aiming for isonatric dialysis (i.e. Ionic mass balance of 0-100 mmol of sodium). This will then be maintained for a period of one month. After that time, there will be a crossover period of adjustment, during which the first group will have their dialysate [Na+] tailored to their requirements, and the second group will revert in a gradual manner to a dialysate [Na+] of 140 mmol/L. Again the two groups will be maintained for a further month, before both groups revert to a standard dialysate [Na+] at the end of the study.
Outcomes	Primary outcome measure Neutral sodium balance as assessed by ionic mass balance reduction in IDWG. Secondary outcome measures Pre- and postdialysis BP, number of antihypertensive agents stability on dialysis, thirst score.
Notes	Primary contact Dr Chris W McIntyre Derby Hospitals NHS Foundation Trust Department of Nephrology Derby City General Hospital Uttoxeter Road Derby DE22 3NE United Kingdom

HD - haemodialysis; RCT - randomised controlled trial

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

NCT00724633

Trial name or title	Effect of lowering the dialysate sodium on blood pressure in haemodialysis patients: a randomized controlled trial
Methods	Randomised, parallel-assignment, double-blind clinical trial
Participants	Canada Sample size 150 patients

NCT00724633 *(Continued)*

	Eligibility criteria: aged 18 years and older; on 3 times weekly HD of at least 3 months; elevated average ambulatory BP; current dialysate [Na+] prescription 140 mEq/L; average predialysis serum [Na+] < 140 mEq/L Exclusion criteria: frequent intradialytic hypotension; estimated life expectancy < 1 year; non-adherence to dialysis prescription pregnancy; inability or unwillingness to complete study measures
Interventions	HD regimen: not reported Control: dialysate [Na+] 140 mM Intervention 1: dialysate [Na+] = patient predialysis serum [Na+] Intervention 2: dialysate [Na+] < patient predialysis serum [Na+] Duration: 3 months
Outcomes	Primary outcome is ambulatory BP Secondary outcomes Thirst HRQoL scores by KDQoL IDWG Intradialytic hypotension EFV Sodium ionic mass
Starting date	November 2011
Contact information	rita.suri@lhsc.on.ca
Notes	The recruitment status of this study is unknown because the information has not been verified recently. Was due for completion November 2014.

NCT02145260

Trial name or title	Trial of dialysate sodium in chronic hospitalized haemodialysis patients
Methods	Single-centre, prospective, randomised, double-blind, controlled parallel assignment 4-year clinical study
Participants	USA Sample size 200 Eligibility criteria: chronic HD (> 90 days), age ≥ 18 years, informed consent, first admission during study period. Exclusion criteria: use of pressors, predialysis serum sodium ≤ 128 mmol/L or > 145 mmol/L, predialysis SBP >180 mmHg, intensive care stay earlier in admission, expected length of stay < 24 hours (e.g. admission for HD access procedure), acute coronary syndrome within seven days, acute stroke, institutionalised individuals, pregnancy
Interventions	HD regimen: not reported

NCT02145260 *(Continued)*

	Control: dialysate [Na+] 138 mM Intervention: dialysate [Na+] 142 mM Duration: 6 treatments
Outcomes	Primary outcome is magnitude of intradialytic decline in SBP Secondary outcome is change in predialysis high-sensitivity troponin I
Starting date	July 2014
Contact information	fmccausland@partners.org
Notes	Due for completion July 2018

RESOLVE 2016

Trial name or title	Randomised Evaluation of SOdium dialysate Levels on Vascular Events (RESOLVE)
Methods	Pragmatic, cluster-randomized, prospective, open label, controlled parallel arm 7 years clinical study
Participants	Australia, New Zealand, UK, India, China, Canada, Germany Sample size 51,520 Inclusion criteria • Predominantly dialyses adults (≥ 18 years old) receiving maintenance HD • Rates of withdrawal within the first two years of commencing dialysis for social reasons have been less than 15% for the 2 years prior to recruitment and are not expected to increase above 15% • Has a minimum of 10 dialysis recipients at time of randomisation • Utilises a default dialysate [Na+] at the time of recruitment (a substantial majority of dialysis sessions are conducted with the default dialysate [Na+]) • Is a self-contained unit (i.e. unit patients do not regularly rotate through another unit. Brief trips by patients to a parent or other unit do not exclude a site) • Willing to accept randomisation to either intervention (as determined by nominated Director of Unit) • Is not a home dialysis training or support unit (sites that include both in-centre/satellite dialysis patients and home patients may participate but the study procedures and assessments will only be conducted in the in-centre/satellite component of the site) Exclusion criteria • Not able to comply with data collection methods
Interventions	Participating dialysis sites will be randomised to a default dialysate [Na+] of 137 mM versus 140 mM
Outcomes	Time to first occurrence of an event in the primary composite outcome, Time frame: through to study completion (estimated to occur after an average of 5 years follow up) Primary outcome is a composite of major CV events (hospitalised acute myocardial infarction, hospitalised stroke) and all-cause death. Study completion is endpoint driven, but is expected to be when the average follow up is around 5 years
Starting date	June 2016

RESOLVE 2016 *(Continued)*

Contact information	mjardine@georgeinstitute.org.au
Notes	Due for completion 2023

SoLID 2013

Trial name or title	A randomised, controlled trial of low sodium dialysate versus conventional sodium dialysate to reduce left ventricular mass index in patients receiving home haemodialysis: The Sodium Lowering In Dialysate (SOLID) Trial
Methods	Multicentre, prospective, randomised (permuted randomly sized blocks), single-blind (outcomes assessor), controlled parallel assignment 3-year clinical study
Participants	NZ Sample size 96 patients Eligibility criteria: incident or prevalent patients treated with maintenance home or self-care HD; aged 18 years or older; suitable for both low and standard dialysate [Na+] in the view of their treating physician; predialysis plasma [Na+] ≥ 135 mM; willing to participate and able to provide consent Exclusion criteria will include HD treatments at a frequency greater than 3.5 times per week; treatment with maintenance HDF; life expectancy of less than 12 months; scheduled for live donor kidney trans-plantation within 12 months of entry to the study; considered by the treating nephrologist to have concomitant illnesses or conditions that limit or contraindicate study procedures and follow-up (e.g. frequent intradialytic hypotension requiring fluid resuscitation); considered by the treating nephrologist to have a high chance of non-adherence to study treatments and non-attendance for procedures and follow up; current enrolment in clinical studies involving antihypertensive medications, change sin HD operating parameters, or any other intervention that is likely to confound the outcome of the study; currently using sodium profiling during HD treatments; documented infiltrative cardiomyopathies
Interventions	HD regimen: no limits on session length or dialyser flux, bicarbonate buffer, not to increase HD session frequency to greater than 3.5 times a week Intervention: dialysate [Na+] 135 mM Control: dialysate [Na+] 140 mM Duration: 12 months
Outcomes	Primary outcome is left ventricular mass index, as measured by cardiac magnetic resonance imaging Secondary outcomes LV volumes, geometry, and regional wall motion score IDWG Intradialytic hypotension NT-pro-BNP levels Troponin-T levels ECF volume by BIA Intra- and interdialytic ambulatory BP

SoLID 2013 *(Continued)*	Number and dose of antihypertensives PWV and PWA HRQoL by EQ5D and KDQOL Xerostomia and thirst inventory scores Predialysis plasma γNa Dietary sodium intake via 3 day food diary Safety and tolerability
Starting date	March 2012, completed recruitment
Contact information	joanna.dunlop@middlemore.co.nz; mrmmarsh@inspire.net.nz
Notes	Full results will be available in late 2017

ECF - extracellular fluid; HD - haemodialysis; HRQoL - health-related quality of life; IDWG - interdialytic weigh gain; LV - left ventricular; PWA - pulse wave amplitude; PWV - pulse wave velocity; SBP - systolic blood pressure

DATA AND ANALYSES

Comparison 1. Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM)

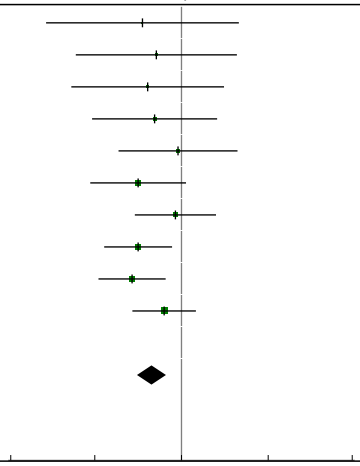
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Interdialytic weight gain	10	352	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.51, -0.18]
2 Predialysis BP	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Mean arterial pressure	4	156	Mean Difference (IV, Random, 95% CI)	-3.58 [-5.46, -1.69]
2.2 Systolic BP	3	83	Mean Difference (IV, Random, 95% CI)	-7.56 [-15.92, 0.80]
2.3 Diastolic BP	2	52	Mean Difference (IV, Random, 95% CI)	-3.13 [-11.79, 5.54]
3 Intradialytic BP	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Mean arterial pressure	1	20	Mean Difference (IV, Random, 95% CI)	-4.0 [-18.52, 10.52]
3.2 Systolic BP	2	34	Mean Difference (IV, Random, 95% CI)	-3.99 [-17.96, 9.99]
3.3 Diastolic BP	2	34	Mean Difference (IV, Random, 95% CI)	1.33 [-6.29, 8.95]
4 Postdialysis BP	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Mean arterial pressure	4	150	Mean Difference (IV, Random, 95% CI)	-3.26 [-4.82, -1.70]
4.2 Systolic BP	1	18	Mean Difference (IV, Random, 95% CI)	-5.0 [-31.86, 21.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 Diastolic BP	1	18	Mean Difference (IV, Random, 95% CI)	0.0 [-13.98, 13.98]
5 Interdialytic BP	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Mean arterial pressure	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Systolic BP	2	103	Mean Difference (IV, Random, 95% CI)	-0.17 [-5.42, 5.08]
5.3 Diastolic BP	2	103	Mean Difference (IV, Random, 95% CI)	-2.0 [-4.84, 0.84]
6 Serum [Na+]	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Predialysis	7	258	Mean Difference (IV, Random, 95% CI)	-1.69 [-2.36, -1.02]
6.2 Intradialytic	1	20	Mean Difference (IV, Random, 95% CI)	-4.37 [-6.24, -2.50]
6.3 Postdialysis	3	99	Mean Difference (IV, Random, 95% CI)	-4.74 [-8.30, -1.17]
7 HD sessions complicated by intradialytic cramps	6	12186	Risk Ratio (M-H, Random, 95% CI)	1.77 [1.15, 2.73]
8 HD sessions complicated by intradialytic hypotension	9	12681	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.17, 2.07]
9 Postdialysis extracellular fluid status	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10 Dietary salt intake	2	95	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.48, 0.06]
11 Left ventricular structure	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 Mass index [g/m^2]	1	57	Mean Difference (IV, Random, 95% CI)	-8.0 [-17.11, 1.11]
11.2 End-diastolic dimension [mm]	1	57	Mean Difference (IV, Random, 95% CI)	0.40 [-3.18, 3.98]
11.3 End-systolic dimension [mm]	1	57	Mean Difference (IV, Random, 95% CI)	0.40 [-2.59, 3.39]
12 Antihypertensive medication	2	103	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-1.07, -0.28]
13 Fatigue	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
14 Thirst	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
15 Pulse wave velocity	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
16 Arterial vascular resistance [mmHg/mL/l00mL/s]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17 Venous tone [mmHg/mL/I00mL]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

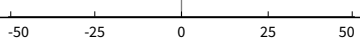
Analysis 1.1. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na +] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 1 Interdialytic weight gain.

Study or subgroup	Low d[Na+] N	Low d[Na+] Mean(SD)	Higher d[Na+] N	Higher d[Na+] Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ogden 1978	12	2.2 (1.1)	12	2.7 (1.6)		2.26%	-0.45[-1.56,0.66]
Beduschi 2013	20	2.5 (0.6)	18	2.8 (1.9)		3.24%	-0.29[-1.22,0.64]
Daugirdas 1985	7	2.2 (0.8)	7	2.6 (0.9)		3.6%	-0.39[-1.27,0.49]
MATCH-NA 2015	15	2.3 (1.1)	16	2.6 (0.9)		5.37%	-0.31[-1.03,0.41]
Quereda 1988	8	2 (0.7)	8	2 (0.7)		5.94%	-0.04[-0.73,0.65]
Henrich 1982	10	1.8 (0.6)	10	2.3 (0.6)		9.16%	-0.5[-1.05,0.05]
Chambers 2002	16	2.4 (0.7)	16	2.4 (0.7)		12.75%	-0.07[-0.54,0.4]
Akdag 2015	22	1.7 (0.6)	24	2.2 (0.8)		18.23%	-0.5[-0.89,-0.11]
Boquin 1977	37	2 (0.9)	37	2.5 (0.9)		18.62%	-0.57[-0.96,-0.18]
Liu 2016	28	2.8 (0.6)	29	3 (0.8)		20.82%	-0.2[-0.57,0.17]
Total * **	**175**		**177**			**100%**	**-0.35[-0.51,-0.18]**
Heterogeneity: Tau²=0; Chi²=4.96, df=9(P=0.84); I²=0%							
Test for overall effect: Z=4.06(P<0.0001)							



Analysis 1.2. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 2 Predialysis BP.

Study or subgroup	Low d[Na+] N	Low d[Na+] Mean(SD)	Higher d[Na+] N	Higher d[Na+] Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.2.1 Mean arterial pressure							
Henrich 1982	10	98 (8.2)	10	102 (16.7)		2.68%	-4[-15.51,7.51]
Ogden 1978	12	90.6 (10.9)	12	95.5 (14.1)		3.49%	-4.85[-14.94,5.24]
Beduschi 2013	20	102 (11.4)	18	109.2 (15.7)		4.57%	-7.2[-16.01,1.61]
Boquin 1977	37	102.7 (4.4)	37	106 (4.3)		89.26%	-3.33[-5.32,-1.34]
Subtotal * **	**79**		**77**			**100%**	**-3.58[-5.46,-1.69]**
Heterogeneity: Tau²=0; Chi²=0.78, df=3(P=0.86); I²=0%							
Test for overall effect: Z=3.72(P=0)							
1.2.2 Systolic BP							
Daugirdas 1985	7	137.8 (28)	7	136.4 (24)		9.37%	1.4[-25.92,28.72]
Beduschi 2013	20	137.2 (19.6)	18	149.2 (20.4)		42.98%	-12.02[-24.78,0.74]
MATCH-NA 2015	15	139.1 (16)	16	144.4 (18.4)		47.65%	-5.3[-17.42,6.82]
Subtotal * **	**42**		**41**			**100%**	**-7.56[-15.92,0.8]**
Heterogeneity: Tau²=0; Chi²=1.02, df=2(P=0.6); I²=0%							
Test for overall effect: Z=1.77(P=0.08)							



Study or subgroup	Low d[Na+] N	Mean(SD)	Higher d[Na+] N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.2.3 Diastolic BP							
Daugirdas 1985	7	75.6 (14)	7	77.3 (11)		43.14%	-1.7[-14.89,11.49]
Beduschi 2013	20	79.4 (10.2)	18	83.6 (22.9)		56.86%	-4.21[-15.7,7.28]
Subtotal ***	**27**		**25**			**100%**	**-3.13[-11.79,5.54]**
Heterogeneity: Tau²=0; Chi²=0.08, df=1(P=0.78); I²=0%							
Test for overall effect: Z=0.71(P=0.48)							

Lower with low d[Na+] -50 -25 0 25 50 Lower with higher d[Na+]

Analysis 1.3. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 3 Intradialytic BP.

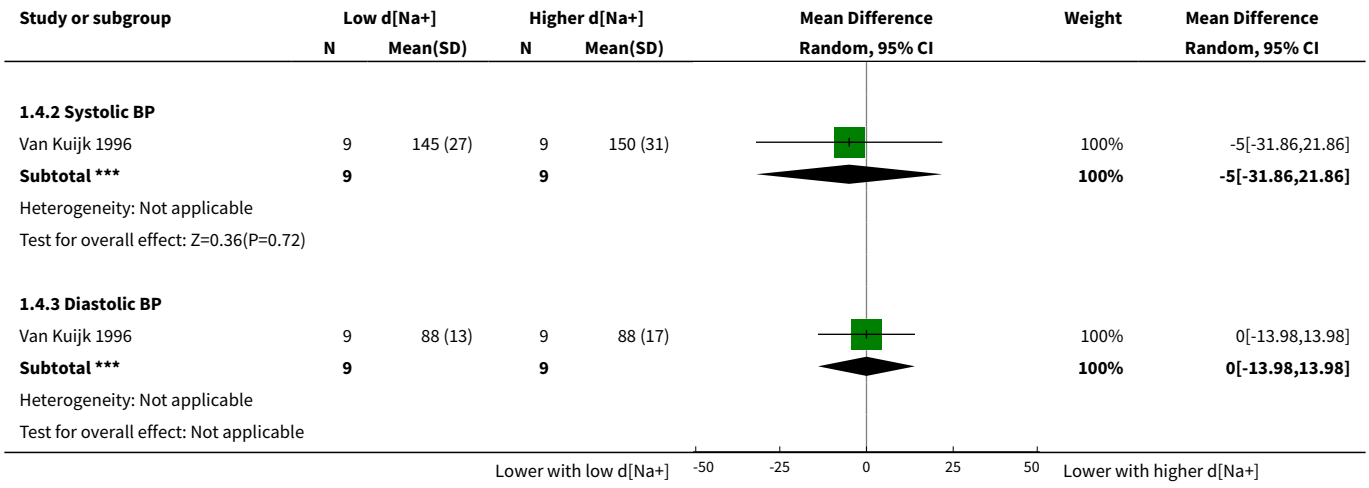
Study or subgroup	Low d[Na+] N	Mean(SD)	Higher d[Na+] N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.3.1 Mean arterial pressure							
Suckling 2013	10	91 (15)	10	95 (18)		100%	-4[-18.52,10.52]
Subtotal ***	**10**		**10**			**100%**	**-4[-18.52,10.52]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.54(P=0.59)							
1.3.2 Systolic BP							
Suckling 2013	10	127 (22)	10	139 (27)		41.93%	-12[-33.59,9.59]
Daugirdas 1985	7	127.4 (18)	7	125.6 (17)		58.07%	1.8[-16.54,20.14]
Subtotal ***	**17**		**17**			**100%**	**-3.99[-17.96,9.99]**
Heterogeneity: Tau²=0; Chi²=0.91, df=1(P=0.34); I²=0%							
Test for overall effect: Z=0.56(P=0.58)							
1.3.3 Diastolic BP							
Suckling 2013	10	73 (14)	10	73 (16)		33.43%	0[-13.18,13.18]
Daugirdas 1985	7	72.2 (9.4)	7	70.2 (8.4)		66.57%	2[-7.34,11.34]
Subtotal ***	**17**		**17**			**100%**	**1.33[-6.29,8.95]**
Heterogeneity: Tau²=0; Chi²=0.06, df=1(P=0.81); I²=0%							
Test for overall effect: Z=0.34(P=0.73)							

Lower with low d[Na+] -50 -25 0 25 50 Lower with higher d[Na+]

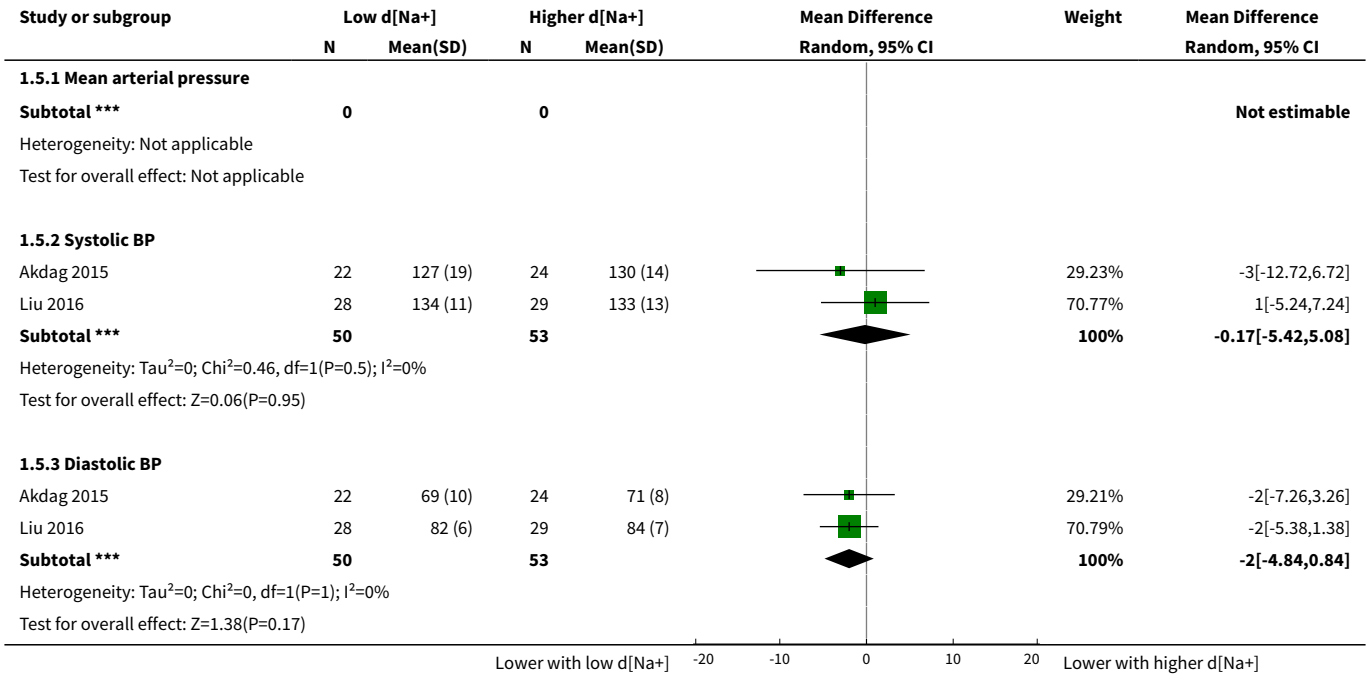
Analysis 1.4. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 4 Postdialysis BP.

Study or subgroup	Low d[Na+] N	Mean(SD)	Higher d[Na+] N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.4.1 Mean arterial pressure							
Van Kuijk 1996	9	109 (18)	9	111 (23)		0.67%	-2[-21.08,17.08]
Beduschi 2013	20	97 (12.3)	18	100.3 (12.4)		3.92%	-3.3[-11.17,4.57]
Henrich 1982	10	87 (6.3)	10	92 (3.1)		12.75%	-5[-9.36,-0.64]
Boquin 1977	37	98.3 (3.8)	37	101.3 (3.8)		82.66%	-3[-4.71,-1.29]
Subtotal ***	**76**		**74**			**100%**	**-3.26[-4.82,-1.7]**
Heterogeneity: Tau²=0; Chi²=0.72, df=3(P=0.87); I²=0%							
Test for overall effect: Z=4.1(P<0.0001)							

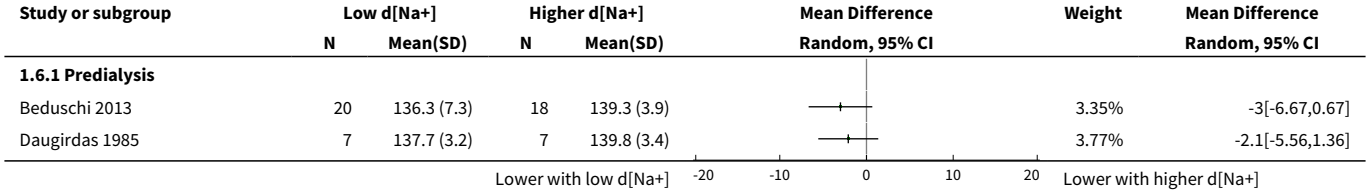
Lower with low d[Na+] -50 -25 0 25 50 Lower with higher d[Na+]

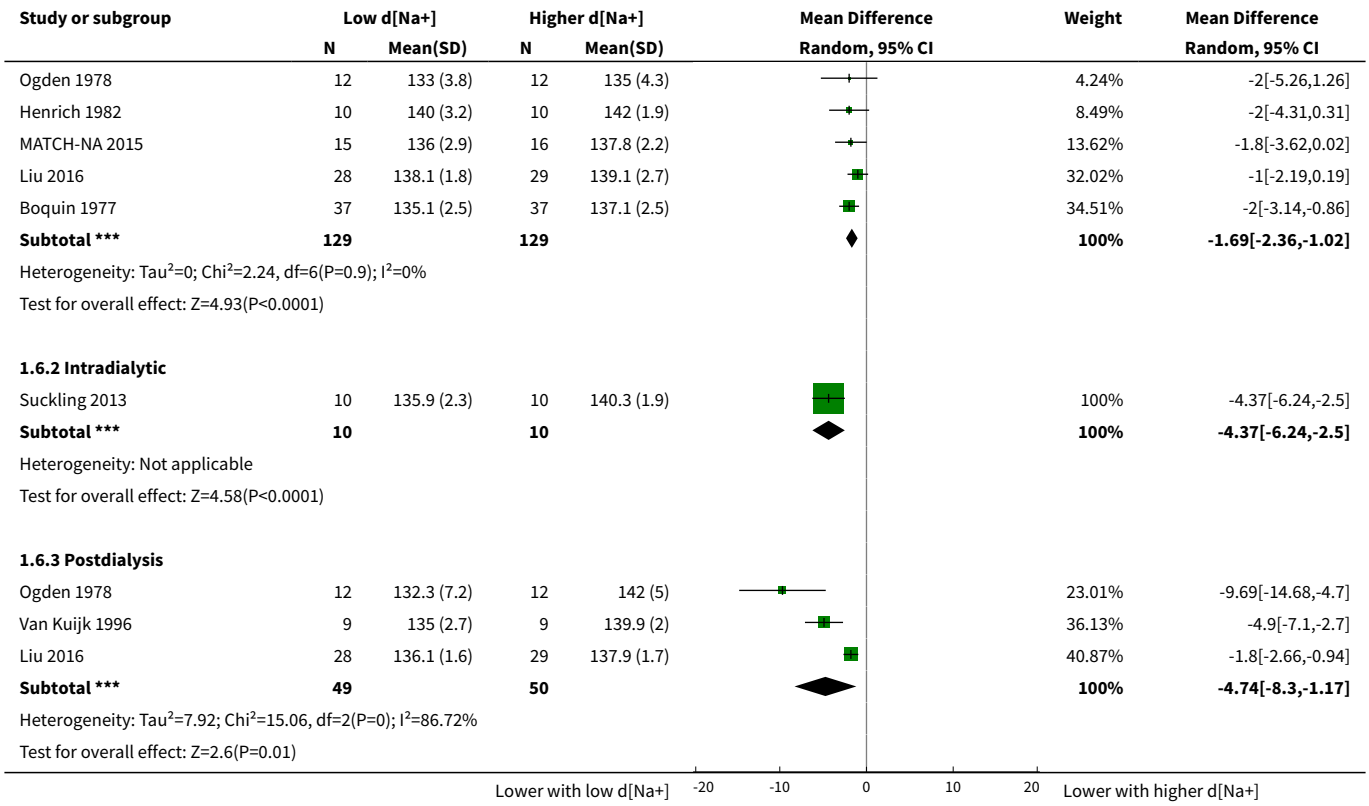


Analysis 1.5. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 5 Interdialytic BP.



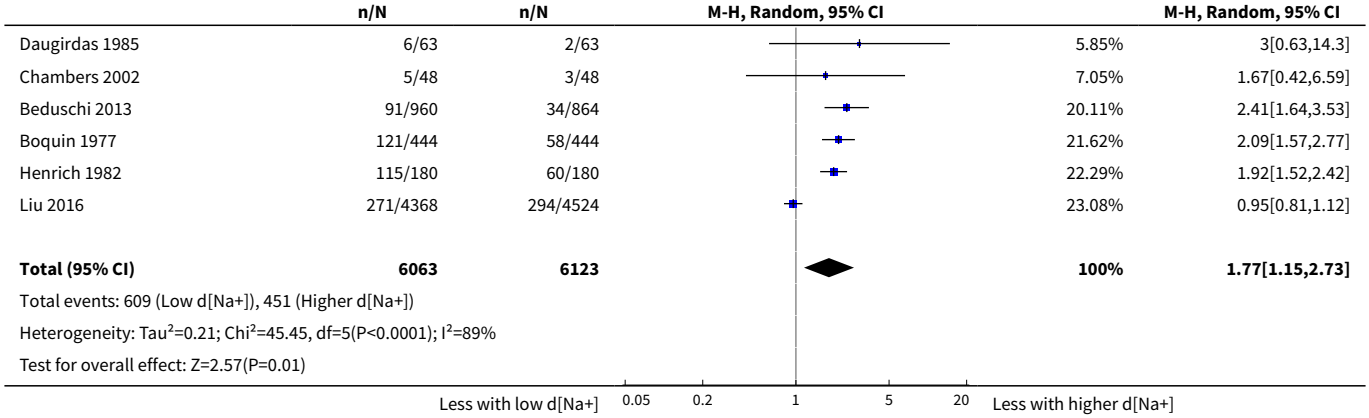
Analysis 1.6. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 6 Serum [Na+].





Study or subgroup	Low d[Na+] N	Low d[Na+] Mean(SD)	Higher d[Na+] N	Higher d[Na+] Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ogden 1978	12	133 (3.8)	12	135 (4.3)		4.24%	-2[-5.26,1.26]
Henrich 1982	10	140 (3.2)	10	142 (1.9)		8.49%	-2[-4.31,0.31]
MATCH-NA 2015	15	136 (2.9)	16	137.8 (2.2)		13.62%	-1.8[-3.62,0.02]
Liu 2016	28	138.1 (1.8)	29	139.1 (2.7)		32.02%	-1[-2.19,0.19]
Boquin 1977	37	135.1 (2.5)	37	137.1 (2.5)		34.51%	-2[-3.14,-0.86]
Subtotal ***	**129**		**129**			**100%**	**-1.69[-2.36,-1.02]**
Heterogeneity: Tau²=0; Chi²=2.24, df=6(P=0.9); I²=0%							
Test for overall effect: Z=4.93(P<0.0001)							
1.6.2 Intradialytic							
Suckling 2013	10	135.9 (2.3)	10	140.3 (1.9)		100%	-4.37[-6.24,-2.5]
Subtotal ***	**10**		**10**			**100%**	**-4.37[-6.24,-2.5]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.58(P<0.0001)							
1.6.3 Postdialysis							
Ogden 1978	12	132.3 (7.2)	12	142 (5)		23.01%	-9.69[-14.68,-4.7]
Van Kuijk 1996	9	135 (2.7)	9	139.9 (2)		36.13%	-4.9[-7.1,-2.7]
Liu 2016	28	136.1 (1.6)	29	137.9 (1.7)		40.87%	-1.8[-2.66,-0.94]
Subtotal ***	**49**		**50**			**100%**	**-4.74[-8.3,-1.17]**
Heterogeneity: Tau²=7.92; Chi²=15.06, df=2(P=0); I²=86.72%							
Test for overall effect: Z=2.6(P=0.01)							

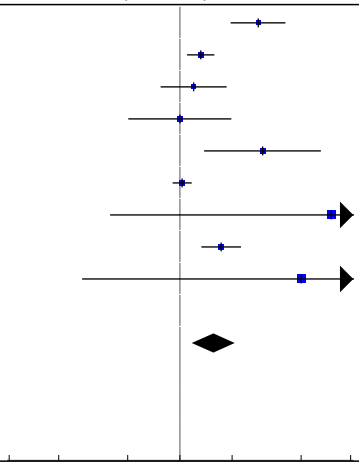
Analysis 1.7. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 7 HD sessions complicated by intradialytic cramps.



Study or subgroup	Low d[Na+] n/N	Higher d[Na+] n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Daugirdas 1985	6/63	2/63		5.85%	3[0.63,14.3]
Chambers 2002	5/48	3/48		7.05%	1.67[0.42,6.59]
Beduschi 2013	91/960	34/864		20.11%	2.41[1.64,3.53]
Boquin 1977	121/444	58/444		21.62%	2.09[1.57,2.77]
Henrich 1982	115/180	60/180		22.29%	1.92[1.52,2.42]
Liu 2016	271/4368	294/4524		23.08%	0.95[0.81,1.12]
Total (95% CI)	**6063**	**6123**		**100%**	**1.77[1.15,2.73]**
Total events: 609 (Low d[Na+]), 451 (Higher d[Na+])					
Heterogeneity: Tau²=0.21; Chi²=45.45, df=5(P<0.0001); I²=89%					
Test for overall effect: Z=2.57(P=0.01)					

Analysis 1.8. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 8 HD sessions complicated by intradialytic hypotension.

Study or subgroup	Low d[Na+] n/N	Higher d[Na+] n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Beduschi 2013	113/960	36/864		14.7%	2.83[1.96,4.06]
Boquin 1977	174/444	132/444		17.92%	1.32[1.1,1.58]
Chambers 2002	24/48	20/48		13.25%	1.2[0.77,1.86]
Daugirdas 1985	13/63	13/63		9.09%	1[0.5,1.98]
Henrich 1982	24/180	8/180		7.94%	3[1.38,6.5]
Liu 2016	428/4368	430/4524		18.66%	1.03[0.91,1.17]
MATCH-NA 2015	3/45	0/48		0.89%	7.46[0.4,140.45]
Quereda 1988	97/192	56/192		16.65%	1.73[1.33,2.25]
Van Kuijk 1996	2/9	0/9		0.91%	5[0.27,91.52]
Total (95% CI)	**6309**	**6372**		**100%**	**1.56[1.17,2.07]**
Total events: 878 (Low d[Na+]), 695 (Higher d[Na+])					
Heterogeneity: Tau^2=0.11; Chi^2=42.03, df=8(P<0.0001); I^2=80.96%					
Test for overall effect: Z=3.06(P=0)					



Less with low d[Na+] — Less with higher d[Na+]

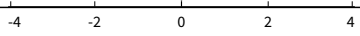
Analysis 1.9. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 9 Postdialysis extracellular fluid status.

Study or subgroup	Low d[Na+] N	Low d[Na+] Mean(SD)	Higher d[Na+] N	Higher d[Na+] Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Beduschi 2013	20	15.3 (2.9)	20	15.6 (2.8)		-0.3[-2.07,1.47]

Lower with low d[Na+] — Lower with higher d[Na+]

Analysis 1.10. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na +] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 10 Dietary salt intake.

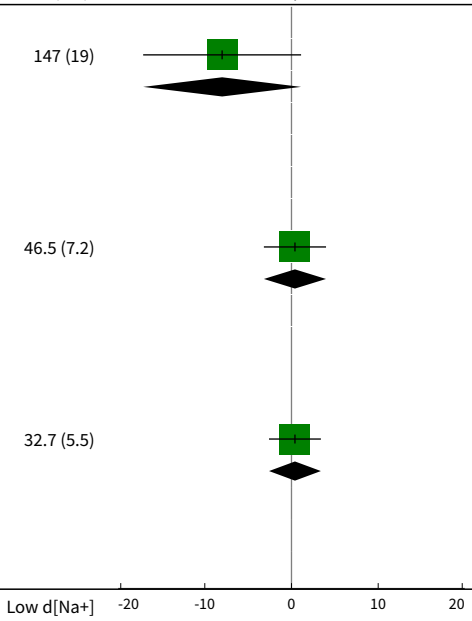
Study or subgroup	Low d[Na+] N	Low d[Na+] Mean(SD)	Higher d[Na+] N	Higher d[Na+] Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Liu 2016	28	3.9 (3)	29	4 (0.8)		5.42%	-0.1[-1.25,1.05]
Beduschi 2013	20	3.5 (0.3)	18	3.7 (0.5)		94.58%	-0.22[-0.49,0.06]
Total ***	**48**		**47**			**100%**	**-0.21[-0.48,0.06]**
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.85); I^2=0%							
Test for overall effect: Z=1.54(P=0.12)							



Lower with low d[Na+] — Lower with higher d[Na+]

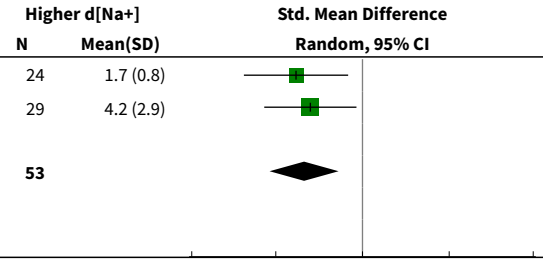
Analysis 1.11. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na +] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 11 Left ventricular structure.

Study or subgroup	Low d[Na+] N	Low d[Na+] Mean(SD)	Higher d[Na+] N	Higher d[Na+] Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.11.1 Mass index [g/m2]							
Liu 2016	28	139 (16)	29	147 (19)		100%	-8[-17.11,1.11]
Subtotal ***	**28**		**29**			**100%**	**-8[-17.11,1.11]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.72(P=0.09)							
1.11.2 End-diastolic dimension [mm]							
Liu 2016	28	46.9 (6.6)	29	46.5 (7.2)		100%	0.4[-3.18,3.98]
Subtotal ***	**28**		**29**			**100%**	**0.4[-3.18,3.98]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.22(P=0.83)							
1.11.3 End-systolic dimension [mm]							
Liu 2016	28	33.1 (6)	29	32.7 (5.5)		100%	0.4[-2.59,3.39]
Subtotal ***	**28**		**29**			**100%**	**0.4[-2.59,3.39]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.26(P=0.79)							
Test for subgroup differences: Chi^2=3.07, df=1 (P=0.22), I^2=34.91%							



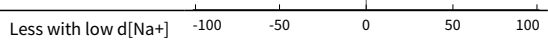
Analysis 1.12. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 12 Antihypertensive medication.

Study or subgroup	Low d[Na+] N	Low d[Na+] Mean(SD)	Higher d[Na+] N	Higher d[Na+] Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Akdag 2015	22	1.2 (0.4)	24	1.7 (0.8)		43.89%	-0.77[-1.37,-0.17]
Liu 2016	28	2.7 (1.9)	29	4.2 (2.9)		56.11%	-0.6[-1.13,-0.07]
Total ***	**50**		**53**			**100%**	**-0.67[-1.07,-0.28]**
Heterogeneity: Tau^2=0; Chi^2=0.16, df=1(P=0.69); I^2=0%							
Test for overall effect: Z=3.32(P=0)							



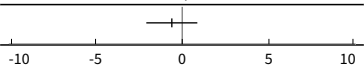
Analysis 1.13. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 13 Fatigue.

Study or subgroup	Low d[Na+] N	Low d[Na+] Mean(SD)	Higher d[Na+] N	Higher d[Na+] Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Chambers 2002	16	50.3 (36.2)	16	43.8 (36.2)		6.52[-18.57,31.6]



Analysis 1.14. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 14 Thirst.

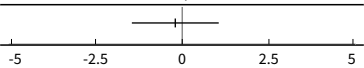
Study or subgroup	Low d[Na+] N	Low d[Na+] Mean(SD)	Higher d[Na+] N	Higher d[Na+] Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Daugirdas 1985	7	0.8 (1.3)	7	1.4 (1.5)		-0.6[-2.07,0.87]



Less with low d[Na+] — Less with higher d[Na+]

Analysis 1.15. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na +] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 15 Pulse wave velocity.

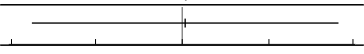
Study or subgroup	Low d[Na+] N	Low d[Na+] Mean(SD)	Higher d[Na+] N	Higher d[Na+] Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Liu 2016	28	10.9 (2.6)	29	11.1 (2.2)		-0.2[-1.45,1.05]



Slower with low d[Na+] — Slower with higher d[Na +]

Analysis 1.16. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 16 Arterial vascular resistance [mmHg/mL/l00mL/s].

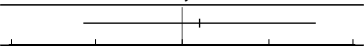
Study or subgroup	Low d[Na+] N	Low d[Na+] Mean(SD)	Higher d[Na+] N	Higher d[Na+] Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Van Kuijk 1996	9	3380 (874)	9	3363 (1033)		17[-867.03,901.03]



Less with low d[Na+] — Less with higher d[Na+]

Analysis 1.17. Comparison 1 Low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) or high dialysate [Na+] (> 140 mM), Outcome 17 Venous tone [mmHg/mL/l00mL].

Study or subgroup	Low d[Na+] N	Low d[Na+] Mean(SD)	Higher d[Na+] N	Higher d[Na+] Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Van Kuijk 1996	9	12.9 (3)	9	12.5 (2.8)		0.4[-2.28,3.08]



Less with low d[Na+] — Less with higher d[Na+]

ADDITIONAL TABLES

Table 1. Summary of included studies

Study ID	Year of study[a]	Dialysate [Na+] in mM (control/ intervention)	Study design	ITT population (analysed population)	No. analysed in low dialysate [Na+] arm	No. analysed in higher dialysate [Na+] arm	Mean follow-up (weeks)
Akdag 2015	2013	137/140	P	50 (46)	22	24	26
Beduschi 2013	2013	135/138	P	52 (38)	20	18	16
Boquin 1977	1977	130/140	X	51 (37)	37	37	4
Chambers 2002	2002	136/140[b]	X	16 (16)	16	16	1
Daugirdas 1985	1985	135/143	X	10 (7)	7	7	4
Henrich 1982	1982	132/144	X	10 (10)	10	10	6
Liu 2016	2016	136/138	P	64 (57)	28	29	52
MATCH-NA 2015	2012	134.3/142.9	X	18 (16)	15	16	1
Ogden 1978	1978	131/146	X	12 (12)	12	12	1
Quereda 1988	1988	133/139	X	8 (8)	8	8	2
Suckling 2013	2013	135/145	X	10 (10)	10	10	1[c]
Van Kuijk 1996	1996	134/144	X	9 (9)	9	9	1[c]

Abbreviations: X - cross-over study; P - parallel group study; ITT - intention to treat
[a] year of patient accrual if available, year of study publication otherwise
[b] profiled dialysate [Na+]
[c] one session intervention and follow-up

Table 2. Summary of included patients

Study ID	Year of study[a]	Mean age, years (SD)	Mean time on dialysis, months (SD)	% male	% with diabetic kidney disease
Akdag 2015	2013	44.4 (2.6)	53.9 (35.1)	42.3	28.3
Beduschi 2013	2013	62.5 (14)	40.7 (44.6)	46.8	34.2
Boquin 1977	1977	Not reported	Not reported	Not reported	Not reported
Chambers 2002	2002	75.8 (not reported)	Not reported	Not reported	Not reported
Daugirdas 1985	1985	Not reported	Not reported	Not reported	Not reported
Henrich 1982	1982	57.2 (24.7)	31.5 (25.3)	Not reported	30
Liu 2016	2016	58 (10.5)	64.6 (55.4)	54.4	19
MATCH-NA 2015	2012	58.8 (9.5)	Not reported	93.8	69
Ogden 1978	1978	Not reported	Not reported	Not reported	Not reported
Quereda 1988	1988	58 (9)	27 (22)	25	0
Suckling 2013	2013	60.9 (5.1)	Not reported	50	40
Van Kuijk 1996	1996	46 (not reported)	46 (not reported)	88.9	0

[a] year of patient accrual if available, year of study publication otherwise

Table 3. Definitions of intradialytic hypotension in included studies

Study ID	Definition
Akdag 2015	Fall in intradialytic systolic BP by ≥ 20 mmHg associated with symptoms requiring medical attention
Beduschi 2013	Fall in intradialytic BP to < 90/60
Boquin 1977	"Hypotension requiring intervention"
Chambers 2002	Fall in intradialytic systolic BP by ≥ 30 mmHg or to < 90 mmHg
Daugirdas 1985	Fall in intradialytic MAP by > 15% plus intervention (defined as reduction in UF, administration of medication/intravenous saline)
Henrich 1982	Fall in intradialytic systolic BP to < 90 mmHg
Liu 2016	Fall in intradialytic systolic BP to < 90 mmHg or a decrease in MAP by ≥10 mmHg associated with symptoms or the need for nursing interventions
MATCH-NA 2015	Fall in intradialytic systolic BP to < 90 mmHg
Ogden 1978	Not reported

Table 3. Definitions of intradialytic hypotension in included studies *(Continued)*

Quereda 1988	Fall in intradialytic systolic BP to < 90 mmHg
Suckling 2013	Not reported
Van Kuijk 1996	Fall in intradialytic systolic BP by ≥ 20 mmHg

BP - blood pressure; UF - ultrafiltration

Table 4. Outcomes reported for low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM)

Outcomes	No. of studies	Low dialysate [Na+]	Neutral dialysate [Na+]	MD or RR (95% CI)	I^2	Certainty of evidence
IDWG (kg)	6	131	132	-0.33 (-0.51 to -0.14)	0%	High
Predialysis MAP (mmHg)	2	57	55	-3.52 (-5.46 to -1.57)	0%	Low
Predialysis systolic BP (mmHg)	1	20	18	-12.02 (-24.78 to 0.74)	-	Very low
Predialysis diastolic BP (mmHg)	1	20	18	-4.21 (-15.70 to 7.28)	-	Very low
Intradialytic MAP (mmHg)	0	-	-	-	-	-
Intradialytic systolic BP (mmHg)	0	-	-	-	-	-
Intradialytic diastolic BP (mmHg)	0	-	-	-	-	-
Postdialysis MAP (mmHg)	2	57	55	-3.01 (-4.69 to -1.34)	0%	Low
Postdialysis systolic BP (mmHg)	0	-	-	-	-	-
Postdialysis diastolic BP (mmHg)	0	-	-	-	-	-
Interdialytic MAP (mmHg)	0	-	-	-	-	-
Interdialytic systolic BP (mmHg)	2	50	53	-0.12 (-6.45 to 6.21)	0%	Low
Interdialytic diastolic BP (mmHg))	2	51	52	-2.00 -4.85 to 0.85)	0%	Low
Predialysis serum [Na+] (mM)	3	85	84	-1.59 (-2.40 to -0.78)	0%	Low
Intradialytic serum [Na+] (mM)	0	-	-	-	-	-
Postdialysis serum [Na+] (mM)	1	28	29	-1.80 (-2.66 to -0.94)	-	Very low
Intradialytic cramps	4	5820 sessions	5880 sessions	1.66 (0.92 to 2.98)	91%	Low
Intradialytic hypotension	5	6012 sessions	6072 sessions	1.49 (1.09 to 2.03)	88%	Moderate
Predialysis ECF status (L)	0	-	-	-	-	-

Table 4. Outcomes reported for low dialysate [Na+] (< 138 mM) versus neutral dialysate [Na+] (138 to 140 mM) *(Continued)*

Postdialysis ECF status (L)	1	20	18	-0.30 (-2.11 to 1.51)	-	Very low
Dietary salt intake	2	48	47	-0.21 (-0.48 to 0.06)	0%	Low
LVMI (g/m^2)	1	28	29	-8.00 (-17.11 to 1.11)	-	Very low
LVEDD (cm)	1	28	29	0.40 (-3.18 to 3.98)	-	Very low
LVESD (cm)	1	28	29	0.40 (-2.59 to 3.39)	-	Very low
Antihypertensive medication	2	50	53	-0.67 (-1.07 to -0.28)	0%	Low
Fatigue	1	16	16	6.52 (-18.57 to 31.60)	-	Very low
Thirst	0	-	-	-	-	-
Pulse wave velocity (m/s)	1	28	29	-0.20 (-1.45 to 105)	-	Very low
Vascular resistance (mmHg/mL/100 mL)	1	9	9	0.02 (-0.91 to 0.94)	-	Very low
Venous tone (mmHg/mL/100 mL)	1	9	9	0.40 (-2.28 to 3.08)	-	Very low
Hospitalisation	0	-	-	-	-	-
Myocardial infarction	0	-	-	-	-	-
Stroke	0	-	-	-	-	-
Cardiovascular death	0	-	-	-	-	-
Death (all causes)	0	-	-	-	-	-

BP - blood pressure; ECF - extracellular fluid; IDWG - intradialytic weigh gain; LVMI - left ventricular mass index; LVED - left ventricular end diastolic dimension, LVESD - left ventricular end systolic dimension; MAP - mean arterial pressure

Table 5. Outcomes reported for low dialysate [Na+] (< 138 mM) versus high dialysate [Na+] (> 140 mM)

Outcome	No. of studies	Low dialysate [Na+]	High dialysate [Na+]	MD or RR (95% CI)	I^2	Certainty of evidence
IDWG (kg)	4	44	45	-0.42 (-0.80 to -0.05)	0%	Moderate
Predialysis MAP (mmHg)	2	22	22	-4.48 (-12.07 to 3.10)	0%	Low
Predialysis systolic BP (mmHg)	2	23	23	-4.22 (-15.17 to 6.72)	0%	Low
Predialysis diastolic BP (mmHg)	1	7	7	-1.70 (-14.89 to 11.49)	-	Very low
Intradialytic MAP (mmHg)	2	17	17	-0.04 (-10.32 to 10.24)	0%	Low

Table 5. Outcomes reported for low dialysate [Na+] (< 138 mM) versus high dialysate [Na+] (> 140 mM) *(Continued)*

Intradialytic systolic BP (mmHg)	2	17	17	-3.99 (-17.96 to 9.99)	0%	Low
Intradialytic diastolic BP (mmHg)	2	17	17	1.33 (-6.29 to 8.95)	0%	Low
Postdialysis MAP (mmHg)	2	19	19	-4.85 (-9.10 to -0.60)	0%	Low
Postdialysis systolic BP (mmHg)	2	25	25	-10.74 (-24.04 to 2.57)	0%	Low
Postdialysis diastolic BP (mmHg)	1	9	9	0 (-13.98 to 13.98)	-	Very low
Interdialytic MAP (mmHg)	0	-	-	-	-	-
Interdialytic systolic BP (mmHg)	0	-	-	-	-	-
Interdialytic diastolic BP (mmHg))	0	-	-	-	-	-
Predialysis serum [Na+] (mM)	4	44	45	-1.92 (-3.15 to -0.70)	0%	Low
Intradialytic serum [Na+] (mM)	1	10	10	-4.37 (-4.79 to -3.95)	-	Very low
Postdialysis serum [Na+] (mM)	2	21	21	-6.75 (-11.32 to -2.18)	66%	Very low
Intradialytic cramps	2	243 sessions	243 sessions	1.94 (1.54 to 2.44)	0%	Low
Intradialytic hypotension	2	243 sessions	243 sessions	1.71 (0.57 to 5.07)	78%	Low
Predialysis ECF status (L)	0	-	-	-	-	-
Postdialysis ECF status (L)	0	-	-	-	-	-
Dietary salt intake	0	-	-	-	-	
LVMI (g/m^2)	0	-	-	-	-	-
LVEDD (mm)	0	-	-	-	-	-
LVESD (mm)	0	-	-	-	-	-
Antihypertensive medication	0	-	-	-	-	-
Fatigue	0	-	-	-	-	-
Thirst	1	7	7	-0.40 (-1.46 to 0.66)	-	Very low
Pulse wave velocity (m/s)	0	-	-	-	-	-
Vascular resistance (mmHg/mL/100 mL)	1	9	9	0.02 (-0.91 to 0.94)	-	Very low
Venous tone (mmHg/mL/100 mL)	1	9	9	0.40 (-2.28 to 3.08)	-	Very low

Table 5. Outcomes reported for low dialysate [Na+] (< 138 mM) versus high dialysate [Na+] (> 140 mM) *(Continued)*

Hospitalisation	0	-	-	-	-	-
Myocardial infarction	0	-	-	-	-	-
Stroke	0	-	-	-	-	-
Cardiovascular death	0	-	-	-	-	-
Death (all causes)	0	-	-	-	-	-

BP - blood pressure; ECF - extracellular fluid; IDWG - interdialytic weigh gain; LVMI - left ventricular mass index; LVEDD - left ventricular end diastolic dimension; LVESD - left ventricular end systolic dimension; MAP - mean arterial pressure

Table 6. "Dose effect" for intervention of lower versus higher dialysate [Na+]

Outcome	Overall effect	Neutral dialysate [Na+] (138 to 140 mM)	High dialysate [Na+]	P value*
IDWG	-0.35 [-0.51, -0.18]	-0.33 [-0.51, -0.14]	-0.42 [-0.80, -0.05]	0.65
Predialysis mean MAP	-3.58 [-5.46, -1.69]	-3.52 [-5.46, -1.57]	-4.48 [-12.07, 3.10]	0.74
Postdialysis mean MAP	-3.26 [-4.82, -1.70]	-3.01 [-4.69, -1.34]	-4.85 [-9.10, -0.60]	0.34
Predialysis serum [Na+]	-1.69 [-2.36, -1.02]	-1.59 [-2.40, -0.78]	-1.92 [-3.15, -0.70]	0.65
Postdialysis serum [Na+]	-4.74 [-8.30, -1.17]	-1.80 [-2.66, -0.94]	-6.75 [-11.32, -2.18]	0.02
Intradialytic cramps	1.77 [1.15, 2.73]	1.66 [0.92, 2.98]	1.94 [1.54, 2.44]	0.63
Intradialytic hypotension	1.52 [1.14, 2.02]	1.49 [1.09, 2.03]	1.71 [0.57, 5.07]	0.81

IDWG - interdialytic weigh gain; MAP pressure
*P values refer to hypothesis testing of the means for "vs. neutral dialysate [Na+]" compared to "vs. high dialysate [Na+]"

Table 7. A priori definitions of intradialytic hypotension in the literature

Source	Definition
Nadir90	Minimum intradialytic SBP < 90 mmHg
Nadir100	Minimum intradialytic SBP < 100 mmHg
Fall20	Pre-HD SBP minus minimum intradialytic SBP ≥ 20 mmHg
Fall30	Pre-HD SBP minus minimum intradialytic SBP ≥ 30 mmHg
Fall20Nadir90	Minimum intradialytic SBP < 90 mmHg and pre-HD SBP-minimum intradialytic SBP ≤ 20 mmHg
Fall30Nadir90	Minimum intradialytic SBP < 90 mmHg and pre-HD SBP-minimum intradialytic SBP ≤ 30 mmHg

Table 7. A priori definitions of intradialytic hypotension in the literature *(Continued)*

KDOQI Guideline	Pre-HD SBP minus minimum intradialytic SBP ≥ 20 mmHg plus symptoms of cramping, headache, light-headedness, vomiting or chest pain during dialysis
HEMO Study	Fall in SBP resulting in intervention of UF reduction, blood flow reduction, or saline administration.

Adapted from Flythe 2015
HD - haemodialysis; SBP - systolic blood pressure; UF - ultrafiltration

Table 8. Methods for measuring [Na+] in included studies

Study ID	Serum [Na+]	Dialysate [Na+]
Akdag 2015	Not reported	Not reported
Beduschi 2013	Reflectance spectrophotometry[a]	Dialysate conductivity[a]
Boquin 1977	Not reported	Not reported
Chambers 2002	Not reported	Not reported
Daugirdas 1985	Flame photometry[b]	Flame photometry[b]
Henrich 1982	Flame photometry	Flame photometry
Liu 2016	Ion selective electrode	Dialysate conductivity
MATCH-NA 2015	Ion selective electrode[c]	Dialysate conductivity[c]
Ogden 1978	Flame photometry	Dialysate conductivity
Suckling 2013	Ion selective electrode	Ion selective electrode
Van Kuijk 1996	Ion selective electrode	Dialysate conductivity
Quereda 1988	Not reported	Not reported

[a]Personal communication Pasqual Barretti 18 July 2018
[b]Personal communication John T Daugirdas 17 July 2018
[c]Personal communication Jula Inrig 17 July 2018

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. ultrafiltration:ti,ab,kw

(Continued)

	6. {or #1-#5} 7. (dialysis next solution*):ti,ab,kw 8. (dialysis next fluid*):ti,ab,kw 9. dialysate*:ti,ab,kw 10.{or #7-#9} 11.sodium:ti,ab,kw 12.{and #6, #11} 13.{and #10-#11} 14.{or #12-#13}
MEDLINE	1. Renal Dialysis/ 2. exp Ultrafiltration/ 3. dialysis.tw. 4. (hemodialysis or haemodialysis).tw. 5. (hemodiafiltration or haemodiafiltration).tw. 6. (hemofiltration or haemofiltration).tw. 7. ultrafiltration.tw. 8. or/1-7 9. exp dialysis solutions/ 10.dialysate*.tw. 11.dialysis solution*.tw. 12.dialysis fluid*.tw. 13.or/9-12 14.Sodium/ 15.(sodium adj5 (concentration* or level or levels or load or loading)).tw. 16.(sodium adj5 (low* or reduc* or decreas* or high* or increas* or alter*)).tw. 17.(sodium adj5 (profil* or ramp* or model*)).tw. 18.or/14-17 19.and/13,18 20.and/8,18 21.or/19-20
EMBASE	1. Hemodialysis/ 2. Hemofiltration/ 3. Hemodiafiltration/ 4. Dialysis/ 5. Ultrafiltration/ 6. (hemodialysis or haemodialysis).tw. 7. (hemofiltration or haemofiltration).tw. 8. (hemodiafiltration or haemodiafiltration).tw. 9. dialysis.tw. 10.ultrafiltration.tw. 11.or/1-10 12.Hemodialysis Fluid/ 13.Dialysate/ 14.dialysate*.tw. 15.dialysis solution*.tw. 16.dialysis fluid*.tw. 17.or/12-16 18.Sodium/ 19.Sodium Balance/ 20.Sodium Load/

(Continued)

21.(sodium adj5 (concentration* or level or levels or load or loading)).tw.
22.(sodium adj5 (low* or reduc* or decreas* or high* or increas* or alter*)).tw.
23.(sodium adj5 (profil* or ramp* or model*)).tw.
24.or/18-23
25.and/17,24
26.and/11,24
27.or/25-26

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.

(Continued)

	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention Mean difference; 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.
	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 Mean difference; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: JD, MM
2. Study selection: JD, MM
3. Extract data from studies: MM, JD, AV
4. Enter data into RevMan: MM, JD
5. Carry out the analysis: JD, MM, AV
6. Interpret the analysis: JD, MM, AV
7. Draft the final review: JD, MM
8. Disagreement resolution: AV

9. Update the review: MM

DECLARATIONS OF INTEREST

JD: None known

AV: None known

MM: is currently employed by Baxter Healthcare as the Director of Medical Affairs Asia-Pacific, Renal Therapeutic Area

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Internal sources

- No sources of support supplied

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- Royal Australasian College of Physicians, New Zealand.

  Jacquot Research Establishment Award (MM)

  Jacquot Research Entry Award (JD)
- Health Research Council of New Zealand, New Zealand.

  Project grant 11/583, 13/442

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the review; due to the small number of eligible studies, the profiled and non-profiled dialysate sodium interventions were combined and not analysed separately, as was planned in the protocol.

In the review; low (< 138 mM) dialysate [Na+] was compared with the pooled results from both neutral (138-140mM) and high (>140mM) dialysate [Na+] interventions. This comparison was not pre-specified in the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

*Weight Gain; Antihypertensive Agents [therapeutic use]; Blood Pressure; Dialysis Solutions [adverse effects] [*chemistry]; Hypertension [chemically induced] [drug therapy] [*prevention & control]; Hypotension [epidemiology] [etiology]; Muscle Cramp [epidemiology] [etiology]; Randomized Controlled Trials as Topic; Renal Dialysis [*adverse effects] [methods]; Sodium [*administration & dosage] [adverse effects] [blood]

MeSH check words

Humans