Techniques to improve intradialytic haemodynamic stability

V.R. Latha Gullapudi[a], *Isma Kazmi*[a], *and Nicholas M. Selby*[a,b]

Purpose of review
Intra-dialytic hypotension (IDH) remains a significant problem for patients undergoing chronic haemodialysis. IDH causes symptoms that degrade patients' experience, compromises dialysis delivery and is strongly associated with adverse patient outcomes. Greater understanding of the link between IDH and dialysis-induced ischaemia in heart and brain has characterized mechanistic pathways, with repeated episodes of ischaemia resulting in organ dysfunction. This review provides updates from published evidence over the last 2 years across the range of potential interventions for IDH.

Recent findings
A literature search was undertaken to identify articles published in peer review journals between January 2016 and April 2018 using terms 'intradialytic hypotension,' 'haemodynamic instability,' 'ESRF,' 'renal replacement therapy,' 'dialysis' in Medline and EMBASE and identified 58 references from which 15 articles were included in this review. Interventions included: cooling the dialysate; sodium profiling; convective therapies; strategies to minimize inter-dialytic weight gain (IDWG) and improve accuracy of target weight assessment; prescribing of antihypertensive medications; and carnitine supplementation.

Summary
IDH remains a significant clinical problem. Recent evidence from the last 2 years does not support any major changes to current practice, with cooling of the dialysate and reduction of IDWG remaining cornerstones of management.

Keywords
cool temperature dialysate, haemodiafiltration, interdialytic weight gain, intradialytic hypotension, sodium

INTRODUCTION

Haemodynamic instability, most commonly manifested as intradialytic hypotension (IDH), is one of the most frequent complications of haemodialysis. IDH is generally accepted to complicate 10–20% of haemodialysis sessions, but reported prevalence ranges between 7 and 40% of haemodialysis sessions and varies depending on patient characteristics, and which definition of IDH is used [1,2]. IDH has clear associations with adverse outcomes; for example, in a US-based cohort of 112 013 patients, IDH occurring in more than 40% of dialysis sessions had a hazard ratio for mortality of 1.49 (1.42–1.57) [3] and in a landmark study by Shoji *et al.* [4], the adjusted odds ratio for death was 1.5 (95% CI 0.90–2.48) with fall in SBP during haemodialysis by 40 mmHg or greater. Several factors underlie the relationship between IDH and adverse outcomes, but one potential causal link has been the demonstration of subclinical ischaemia during dialysis occurring in various organs including heart and brain, with repeated episodes of ischaemia resulting in chronic organ dysfunction [5,6]. IDH also leads to unpleasant symptoms including abdominal discomfort; yawning; sighing; nausea; vomiting; muscle cramps; restlessness; dizziness or fainting; and anxiety [7]. Dialysis time may be cut short as a result of these symptoms with failure to achieve adequate solute or fluid removal.

Despite this, there remains uncertainty around optimal preventive strategies for an individual. One practical problem is that the definition of IDH for use in clinical practice or research studies is not well

[a]Centre for Kidney Research and Innovation, Division of Medical Sciences and Graduate Entry Medicine, University of Nottingham and [b]Department of Renal Medicine, Royal Derby Hospital, Derby, UK

Correspondence to Dr Nicholas M. Selby, BMBS, DM, MRCP, Associate Professor of Nephrology and Honorary Consultant Nephrologist, Centre for Kidney Research and Innovation, Division of Medical Sciences and Graduate Entry Medicine, University of Nottingham, Uttoxeter Road, DE22 3NE Derby, UK. E-mail: nicholas.selby@nottingham.ac.uk

Curr Opin Nephrol Hypertens 2018, 27:413–419
DOI:10.1097/MNH.0000000000000449

KEY POINTS

- Cooling the dialysate reduces IDH, is safe and does not occur any cost. It is a first line strategy in IDH prevention.
- Reducing IDWG and accurate determination of target weight are important on an individual patient basis, and there may also be benefit from organizational level changes.
- Levocarnitine supplementation may be tried as a last resort in patients with IDH who are unresponsive to other measures.
- Sodium profiling is not recommended to reduce IDH as it may result in sodium loading, increased thirst and larger IDWGs.

established, and definitional variation permeates the current evidence base. European Best Practice Guidelines (EBPG) define IDH as a decrease in SBP of at least 20 mmHg or a decrease in mean arterial pressure (MAP) by 10 mmHg associated with clinical events and need for nursing interventions [8]. Kidney Diseases Outcomes Quality Initiative (KDOQI) recommends the same blood pressure changes but in association with symptoms [7]. However, concern remains that smaller or asymptomatic changes in blood pressure (BP) may still be clinically relevant. Recently Flythe *et al.* [9▪▪] have studied the association of eight commonly used IDH definitions with mortality in two large US dialysis cohorts. Their results showed that nadir BP during dialysis retained the strongest association with mortality (nadir intradialytic BP <90 mmHg for those with a predialysis BP of <160mmHg; nadir of <100mmHg for those with a predialysis BP of ≥160 mmHg). Further studies to definitively define BP thresholds based on patient outcomes, symptoms and pathophysiological consequences of IDH are needed to build on this work.

The fundamental process that leads to IDH is a reduction in circulating blood volume that exceeds plasma refill rate and cardiovascular compensatory mechanisms; these have been discussed in multiple previous reviews [10,11]. Established preventive strategies for IDH recommended in current guidelines include regular review of target weight; minimizing inter-dialytic weight gain (IDWG) by dietary fluid and salt restriction; optimizing dialysate composition (use of bicarbonate buffer; avoidance of low-calcium dialysis concentration); cooling the dialysate; review of antihypertensive medications; and longer/more frequent dialysis schedules. However, even with these interventions, some patients remain prone to IDH.

This review aims to provide a summary of new and emerging evidence in the management of IDH from the last 2 years. A literature search was undertaken to identify articles published in peer review journals between January 2016 and April 2018 using terms 'intradialytic hypotension,' 'haemodynamic instability,' 'ESRF,' 'renal replacement therapy,' 'dialysis' in Medline and EMBASE and identified 58 references from which 15 articles were selected for this review.

REDUCING DIALYSATE TEMPERATURE

Cooling the dialysate is one of the more widely studied interventions to reduce intradialytic hypotension, and is a first line recommendation in the EBPG guidelines [8]. A 2016 meta-analysis combined results from 26 randomized or cross-over trials, consisting of 484 patients [12▪▪]. Of note, only five of these studies had been published in the last 10 years since the previous systematic review [13]. The authors confirmed previous results, showing that cooled dialysis reduces the rate of IDH by as much as 70% [95% confidence interval (CI) 49–89%] and that intra-dialytic blood pressure is significantly higher. Importantly, the intervention is widely available on all haemodialysis machines, confers no additional cost and does not affect dialysis adequacy [pooled Kt/V mean difference compared with standard dialysis of −0.05 (95% CI −0.09 to 0.01)] [12▪▪]. The improved intradialytic haemodynamics with cooled dialysate have also been shown to translate into amelioration of dialysis-induced ischaemia in the heart (as measured by a reduction in new left ventricular regional wall motion abnormalities [14]) and brain (prevention of ischaemic cortical white matter changes as detected by MRI [6,15]). Although entirely safe, there are some patients who do not tolerate a reduction of dialysate temperature; Mustafa *et al.* [12▪▪] reported that uncomfortable thermal symptoms were approximately three times more likely. One potential way to address this may be through individualizing dialysate temperature manually [16] or using isothermic dialysis [17].

Therefore, reducing dialysate temperature is a safe and effective way to prevent IDH and may lessen end-organ injury; the stage would appear to be set for clinical trials to determine whether this approach also translates into improved patient outcomes.

SODIUM PROFILING

It remains controversial whether sodium profiling provides overall benefit in the setting of IDH. The concept evolved to combat the faster reduction in

plasma osmolality and subsequent reduction in plasma refill rate that can occur at the start of dialysis when plasma:dialysate ratio of uraemic solutes is the highest. Several studies have shown improvement in the haemodynamic stability in the short-term [18,19]; however, this may come at the expense of increased thirst, larger IDWG and higher predialysis SBP [19,20].

A 2017 study from Iran reported favourable results with sodium modelling [21]. The study had a complex cross-over design in which 80 patients received four different combinations of sodium profiling and/or dialysate temperature reduction in different orders. Dialysate temperatures of 35 and 37 °C were compared as were a fixed dialysate sodium of 138 mmol/l and sodium profiling (linear sodium profiling, reducing from 150 to 138 mmol/l by the third hour of haemodialysis). The authors reported that IDH was least frequent in the two treatment schedules that included sodium profiling, that there was no additive effect of dialysate cooling, and that cooling was protective as compared with standard dialysis. However, patients only experienced each dialysis modification for 1 week (three treatments) and change in IDWG was not reported, so potential adverse consequences of sodium profiling were not adequately assessed. In addition, a 1-week washout period between study sessions is too short to exclude carry-over effects, particularly related to changes in dialysate sodium.

Some of the arguments around relative benefits and harms of sodium profiling originate from the many different methods that have been employed (e.g. linear, step-wise or exponential reductions) and whether differences in application explain conflicting results. This variation was highlighted in a recent meta-analysis that included 10 cross-over studies; whilst the author concluded that IDH was less with sodium profiling (but only with stepwise regimes), the significant heterogeneity and small size of studies were notable; this makes it difficult to draw any firm conclusions [22].

In summary, it remains controversial as to whether sodium profiling reduces IDH, and in view of potential negative effects in terms of increasing thirst and IDWG, its use is not currently recommended [8]. Recent data do not justify a change in this position.

HAEMODIAFILTRATION

Convective therapies have long been suggested to reduce IDH [23], although previous studies investigating the impact of haemodiafiltration (HDF) have yielded conflicting results. Unfortunately, recent studies have not dispelled this.

The 'FRENCHIE' study was a prospective, multicentre randomized controlled trial that compared tolerability of haemodialysis and HDF in the elderly [24▪▪]. Three hundred and eighty-one patients aged more than 65 years were randomized to either high-flux haemodialysis (HF-HD) or online haemodiafiltration (OL-HDF). OL-HDF treatments were mainly performed in postdilution mode, but predilution was allowed; convection volumes in the HDF arm were reasonably high, between 19.32 ± 4.46 and 22.53 ± 6.76 l over the course of the study. Over 80% of patients had at least one adverse event (asymptomatic hypotension, symptomatic hypotension, headache, muscle cramps, nausea, vomiting, fever, chest pain, arrhythmia, others) with no significant difference between study arms [odds ratio OR 0.94, 95% CI 0.51–1.76, $P = 0.85$]. Furthermore, there were no significant differences in health-related quality of life, morbidity or mortality. An exploratory analysis, from which results have to be interpreted with caution, compared all 11 981 treatment sessions as the unit of analysis (as opposed to the patient) and found a lower rate of asymptomatic IDH with HDF (20.6% of sessions versus 18.4%, $P = 0.002$), although there was no difference in symptomatic IDH.

In contrast, Koda *et al.* [25] reported more positive outcomes with intermittent back-filtrate infusion HDF (I-HDF) when compared with standard haemodialysis. I-HDF uses on-line ultrapure dialysate that is intermittently reinfused (back-filtered), which theoretically helps to preserve blood volume and blood pressure. A total of 74 hypotension-prone patients were exposed to both treatments for 4-week periods in a cross-over study design. From 816 sessions in both groups, the total number of interventions for symptomatic IDH was less with I-HDF and there was a lower median IDH frequency, 3.0 times per person per month versus 4.5 with haemodialysis ($P = 0.003$). There was no reported change in pre- or post-dialysis body weight or target weight throughout the study.

Smith *et al.* [26] reported a paradoxical increase in IDH with HDF. In a randomized cross-over study, 100 patients received 8 weeks of both haemodialysis and HDF (mean convection volume for HDF treatments was 20.6 l). Ultrafiltration volumes were similar in both groups. Symptomatic hypotension occurred in 8% of HDF treatments as compared with only 5.3% of haemodialysis sessions (relative risk, 1.52; 95% CI 1.2–1.9; $P = 0.001$), although 80% of IDH episodes were 'mild,' managed only with temporary cessation of ultrafiltration.

Finally, Buchanan *et al.* used intra-dialytic functional MRI to compare effects of haemodialysis and HDF on cardiac function and perfusion in a randomized cross-over study. Whilst significant reductions in left ventricular systolic function and

myocardial perfusion were observed during treatment, these changes did not differ between haemodialysis and HDF [27▪].

Therefore, whilst the evidence remains conflicted, HDF is not a first line option in the prevention of IDH, although convective techniques may be trialled in patients who have not responded to simpler, first line manoeuvres. It should be noted that two large, multicentre randomized controlled trials of high-volume HDF are currently underway that may provide definitive answers as to whether HDF reduces IDH and more importantly improves patient outcomes (H4RT trial, ISRCTN10997319; CONVINCE trial, Netherlands Trial Registry NTR7138).

BUFFER COMPOSITION

Historically, acetate was a major cause of IDH [28]. Whilst modern dialysis uses bicarbonate buffer, a small amount of acetate is still present in dialysate (to prevent calcium precipitation). Whilst the concentration is low, the absence of acetate in the blood creates a dialysate:blood concentration gradient. Acetate-free techniques have, therefore, been developed to eliminate acetate transfer completely in an attempt to reduce IDH. A recent single-centre cross-over study reported a large reduction in IDH with a combined acetate free biofiltration and potassium profiling technique as compared with acetate-free haemodialysis and HDF [29]; however, such positive results are tempered by the small study size (only 14 patients) and practical aspects that may limit clinical translation.

Viegas *et al.* [30] reported a randomized trial in which 93 patients received dialysis with either standard dialysate bicarbonate concentration (34 mmol/l) or lower bicarbonate (30 mmol/l). Over a follow-up period of 9 months, no differences in IDH or IDWGs were observed.

REDUCING ULTRAFILTRATION VOLUME/RATE

Reducing IDWG and ultrafiltration volume is a key strategy in prevention of IDH, although often challenging to achieve in practice. Whilst this is usually attempted on an individual patient basis, Pirkle *et al.* [31] reported an organizational approach by applying a ultrafiltration limit of 13 ml/kg/h within a single US facility. There was a small reduction in IDH after implementation (event rate per treatment 0.06 versus 0.07; OR 0.78, 95% CI 0.62–1.00, $P = 0.05$). Time was extended in 62 treatments and 28 additional treatments were performed to achieve ultrafiltration needs. Predialysis and postdialysis weights and ultrafiltration volumes were lower with the intervention, raising the possibility that improvements may have resulted from a Hawthorne effect; however, it was reassuring that there were no signals around increases in fluid overload.

Reducing dietary salt intake is also crucial to reducing IDWG and ultrafiltration volumes. Colson *et al.* assessed the impact of reducing the salt content of sandwiches provided by the dialysis unit from 2.4 to 1.4 g. Over a 4-month period, IDWG decreased significantly and number of treatments with symptomatic IDH episodes were reduced from 6.1 to 3.3% ($P = 0.004$) [32]. Again, study design makes it difficult to be certain about causal relationships in this study, as it is possible that additional unmeasured factors were present (e.g. raised awareness of dietary sodium in general). Whilst these two studies may not provide definitive evidence, the principle of applying quality improvement approaches to the dialysis unit should be lauded, and may offer a practical way to effect change.

TARGET WEIGHT ASSESSMENT

Regular assessment of target weight is part of essential care of patients on dialysis, and with respect to IDH aims to avoid excessive fluid removal. Whilst historically this is based on clinical examination, a number of objective measures exist including bioimpedance, lung ultrasonography and measurement of inferior vena cava diameter. Previous studies have suggested that the use of bioimpedance is associated with improved BP control, left ventricular mass and pulse wave velocity [33]. However, use of bioimpedance in clinical practice is not universal. In a recent randomized multicentre centre study from Taiwan, Huan-Sheng *et al.* [34] compared the use of bioimpedance to standard care in 298 prevalent haemodialysis patients. Bioimpedance was used once per month to determine a postdialysis target weight based on correcting the degree of measured 'fluid overload' according to an algorithm. After 6 months, blood pressure control improved in the bioimpedance group as compared with baseline; this was achieved with fewer antihypertensive medications and a reduction in IDH was observed (intervention 6.1% versus control 6.62%, $P < 0.05$). Further studies are required to validate these results and the use of the specific bioimpedance algorithm in non-Asian populations, as the approach of defining thresholds for use of bioimpedance in clinical practice would be an important step forwards.

RELATIVE BLOOD VOLUME AND BIOFEEDBACK SYSTEMS

Online feedback systems using relative blood volume (RBV) changes have been used to modify

ultrafiltration volumes in an attempt to prevent IDH. Although a number of studies have suggested their effectiveness, technical complexity has prevented widespread clinical adoption. Leung *et al.* [35] have recently reported a randomized cross-over study in 32 patients (26 completed the study) comparing haemodialysis to blood volume based biofeedback dialysis over 16 weeks (8 weeks per modality). Critical RBV was set on a weekly basis in the intervention arm; however, this process also included weekly review of patients' target weight. Although there was reduction in the rate of symptomatic IDH from run-in to the eighth week in the biofeedback period (0.15 episodes/h reducing to 0.07 episodes/h; $P = 0.01$) there was no difference between the two arms at 8 weeks. In addition, a number of other endpoints were unchanged by biofeedback dialysis. Results from this study showing a lack of effectiveness in combination with technical complexity may reduce enthusiasm for this approach, although it should be noted that patients included in this study had fairly modest average ultrafiltration volumes.

PHARMACOLOGICAL INTERVENTIONS

Surprisingly, relatively little is known about effects of antihypertensive medications during dialysis. EBPG guidelines [8] suggest in patients prone to IDH that 'antihypertensive agents should be given with caution prior to dialysis depending on pharmacodynamics, but should not be routinely withheld on the day of haemodialysis treatment,' a statement supported by only grade III evidence. A recent retrospective study using a clinical database of a large US dialysis organization examined IDH rates in patients receiving the two most commonly prescribed beta-blockers in the United States, metoprolol and carvedilol [36]. An active comparator new-user study design was used (this compares the drug of interest to another commonly used agent for the same indication, rather than a 'non-user' group [37]). In 27 064 haemodialysis patients over a 1-year follow up, the rate of intradialytic hypotension was somewhat higher among patients who started carvedilol (57.5 vs 55.2 episodes/1000 person-treatments; adjusted incident rate ratio 1.10, 95% CI 1.09–1.11). A second recent study also reported rates of IDH with carvedilol within the bounds of a randomized, double-blind, placebo-controlled feasibility study [38]. Seventy-two patients entered a run-in period, 49 patients were randomized to either carvedilol or placebo but only 16 in the carvedilol group completed the study. As such, results should be treated with extreme caution and the study is obviously underpowered; the authors reported a nonsignificant trend to more IDH in the carvedilol group (incidence rate ratio 2.94, 95% CI 0.70–12.28; $P = 0.1$). It is clear, therefore, that more research is needed in this area. At present, prescribing decisions must be made on an individual patient basis, factoring in uncertainty about optimal blood pressure targets in haemodialysis populations, and that evidence for the use of betablockers and RAAS inhibitors for cardiovascular benefit is often extrapolated from nondialysis populations, and weigh this against IDH risk.

Levocarnitine supplementation has been proposed to improve dyslipidaemia, malnutrition and quality of life in patients on dialysis. A trial of levocarnitine is recommended in current guidelines [7,8] as a last resort in patients who are resistant to other interventions for IDH. Recent data appear to tentatively support this position. A small single-centre randomized controlled trial compared intravenous levocarnitine prior to dialysis (30 mg/kg per session) with placebo [39]. The total number of IDH episodes were fewer in the levocarnitine group (60 events complicating 9.3% of treatments versus 179 events in 33.1% of treatments; $P < 0.001$). Zhang *et al.* [40] reported data from an observational study that included dialysis patients who were and were not receiving levocarnitine supplementation. Whilst causal associations cannot be assessed in this study, lower rates of IDH and intra-dialytic symptoms were seen in those receiving levocarnitine. Paradoxically, the authors observed that IDH rates were increased in patients receiving levocarnitine with plasma-free carnitine levels greater than 300 μmol/l when compared to plasma-free carnitine levels less than 80–199 μmol/l ($P < 0.05$); whilst it is difficult to draw firm conclusions from this, further work to establish optimal dosing may be required.

NOVEL/OTHER INTERVENTIONS

Whilst a long way from clinical adoption, there have been some recent small studies describing novel approaches to preventing IDH. These include: pneumatic compression devices designed to increase venous return from the lower limbs [41,42]; immersion therapy (dialysis is performed with patients immersed in water) also aimed at improving venous return [43]; and herbal acupuncture [44].

CONCLUSION

IDH remains a significant clinical problem, impacting negatively on patient symptoms, dialysis adequacy and treatment time, and is strongly associated with worse patient outcomes. Over the last 2 years, there have been few significant studies and recent

evidence does not support any major changes to current practice. However, this should not deflect from the ongoing clinical need; it remains a priority for dialysis care that better strategies are developed for monitoring and detecting IDH, for defining optimal definitions of IDH with respect to pathophysiological consequences, and ultimately for more effective preventive strategies.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Sands Jeffrey J, Usvyat Len A, Sullivan T, *et al.* Intradialytic hypotension: frequency, sources of variation and correlation with clinical outcome. Hemodial Int 2014; 18:415–422.
2. Yu J, Liu Z, Shen B, *et al.* Intradialytic hypotension as an independent risk factor for long-term mortality in maintaining hemodialysis patients: a 5-year follow-up cohort study. Blood Purif 2018; 45:320–326.
3. Chou JA, Streja E, Nguyen DV, *et al.* Intradialytic hypotension, blood pressure changes and mortality risk in incident hemodialysis patients. Nephrol Dial Transplant 2018; 33:149–159.
4. Shoji T, Tsubakihara Y, Fujii M, Imai E. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. Kidney Int 2004; 66:1212–1220.
5. Polinder-Bos HA, Garcia DV, Kuipers J, *et al.* Hemodialysis induces an acute decline in cerebral blood flow in elderly patients. J Am Soc Nephrol 2018; 29:1317–1325.
6. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. J Am Soc Nephrol 2015; 26:957–965.
7. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis 2005; 45(4 Suppl 3):16–153.
8. Kooman J, Basci A, Pizzarelli F, *et al.* EBPG guideline on haemodynamic instability. Nephrol Dial Transplant 2007; 22(Suppl 2):ii22–ii44.
9. ■■ Flythe JE, Xue H, Lynch KE, *et al.* Association of mortality risk with various definitions of intradialytic hypotension. J Am Soc Nephrol 2015; 26:724–734.

Well conducted study comparing different defintions of IDH to clinical outcome (mortality). More studies with this approach would help provide an evidence-based, standardised defintion of IDH.

10. van der Sande FM, Dekker MJ, Leunissen KML, Kooman JP. Novel insights into the pathogenesis and prevention of intradialytic hypotension. Blood Purif 2018; 45:230–235.
11. Reeves PB, Mc Causland FR. Mechanisms, clinical implications, and treatment of intradialytic hypotension. Clin J Am Soc Nephrol 2018. [Epub ahead of print]
12. ■■ Mustafa RA, Bdair F, Akl EA, *et al.* Effect of lowering the dialysate temperature in chronic hemodialysis: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2016; 11:442–457.

Systematic review, confirming that cooling the dialysate is an effective and safe intervention for reducing IDH

13. Selby NM, McIntyre CW. A systematic review of the clinical effects of reducing dialysate fluid temperature. Nephrol Dial Transplant 2006; 21:1883–1898.
14. Selby NM, Burton JO, Chesterton LJ, McIntyre CW. Dialysis-induced regional left ventricular dysfunction is ameliorated by cooling the dialysate. Clin J Am Soc Nephrol 2006; 1:1216–1225.
15. Odudu A, Eldehni MT, McCann GP, McIntyre CW. Randomized controlled trial of individualized dialysate cooling for cardiac protection in hemodialysis patients. Clin J Am Soc Nephrol 2015; 10:1408–1417.
16. Jefferies HJ, Burton JO, McIntyre CW. Individualised dialysate temperature improves intradialytic haemodynamics and abrogates haemodialysis-induced myocardial stunning, without compromising tolerability. Blood Purif 2011; 32:63–68.
17. Maggiore Q, Pizzarelli F, Santoro A, *et al.* The effects of control of thermal balance on vascular stability in hemodialysis patients: results of the European randomized clinical trial. Am J Kidney Dis 2002; 40:280–290.
18. Acchiardo SR, Hayden AJ. Is Na+ modeling necessary in high flux dialysis? ASAIO Trans 1991; 37:M135–M137.
19. Sadowski RH, Allred EN, Jabs K. Sodium modeling ameliorates intradialytic and interdialytic symptoms in young hemodialysis patients. J Am Soc Nephrol 1993; 4:1192–1198.
20. Barre PE, Brunelle G, Gascon-Barre M. A randomized double blind trial of dialysate sodiums of 145 mEq/L, 150 mEq/L, and 155 mEq/L. ASAIO Trans 1988; 34:338–341.
21. Ebrahimi H, Safavi M, Saeidi Marzieh H, Emamian Mohammad H. Effects of sodium concentration and dialysate temperature changes on blood pressure in hemodialysis patients: a randomized, triple-blind crossover clinical trial. Ther Apher Dial 2017; 21:117–125.
22. Dunne N. A meta-analysis of sodium profiling techniques and the impact on intradialytic hypotension. Hemodial Int 2016; 21:312–322.
23. Locatelli F, Altieri P, Andrulli S, *et al.* Hemofiltration and hemodiafiltration reduce intradialytic hypotension in ESRD. J Am Soc Nephrol 2010; 21:1798–1807.
24. ■■ Morena M, Jaussent A, Chalabi L, *et al.*, FRENCHIE Study Investigators. Treatment tolerance and patient-reported outcomes favor online hemodiafiltration compared to hemodialysis in the elderly. Kidney Int 2017; 91:1495–1509.

A randomized controlled trial of online haemodiafiltration and haemodialysis, showing few differences in terms of symptoms or haemodynamic stability between modalities.

25. Koda Y, Aoike I, Hasegawa S, *et al.* Feasibility of intermittent back-filtrate infusion hemodiafiltration to reduce intradialytic hypotension in patients with cardiovascular instability: a pilot study. Clin Exp Nephrol 2017; 21:324–332.
26. Smith JR, Zimmer N, Bell E, *et al.* A randomized, single-blind, crossover trial of recovery time in high-flux hemodialysis and hemodiafiltration. Am J Kidney Dis 2017; 69:762–770.
27. ■ Buchanan C, Mohammed A, Cox E, *et al.* Intradialytic cardiac magnetic resonance imaging to assess cardiovascular responses in a short-term trial of hemodiafiltration and hemodialysis. J Am Soc Nephrol 2017; 28:1269–1277.

Important study from a methodological point of view as the first time that intradialytic magnetic resonance scanning has been successfully performed to assess consequences of dialysis

28. Leenen Frans HH, Buda Andrew J, Smith Donna L, *et al.* Hemodynamic changes during acetate and bicarbonate hemodialysis. Artificial Organs 1984; 8:411–417.
29. Kosmadakis G, Correia EDC, Albaret J, *et al.* Comparison of the hemodynamic tolerance and the biological parameters of four acetate-free hemodialysis methods. Nephrol Ther 2017; 13:532–536.
30. Viegas M, Cândido C, Felgueiras J, *et al.* Dialysate bicarbonate variation in maintenance hemodiafiltration patients: impact on serum bicarbonate, intradialytic hypotension and interdialytic weight gain. Hemodial Int 2016; 21:385–392.
31. Pirkle James L, Comeau Mary E, Langefeld Carl D, *et al.* Effects of weight-based ultrafiltration rate limits on intradialytic hypotension in hemodialysis. Hemodial Int 2017; 22:270–278.
32. Colson A, Brinkley A, Braconnier P, *et al.* Impact of salt reduction in meals consumed during hemodialysis sessions on interdialytic weight gain and hemodynamic stability. Hemodial Int 2018. [Epub ahead of print]
33. Hur E, Usta M, Toz H, *et al.* Effect of fluid management guided by bioimpedance spectroscopy on cardiovascular parameters in hemodialysis patients: a randomized controlled trial. Am J Kidney Dis 2013; 61:957–965.
34. Huan-Sheng C, Yeong-Chang C, Ming-Hsing H, *et al.* Application of bioimpedance spectroscopy in Asian dialysis patients (ABISAD-III): a randomized controlled trial for clinical outcomes. Int Urol Nephrol 2016; 48:1897–1909.
35. Leung KCW, Quinn RR, Ravani P, *et al.* Randomized crossover trial of blood volume monitoring–guided ultrafiltration biofeedback to reduce intradialytic hypotensive episodes with hemodialysis. Clin J Am Soc Nephrol 2017; 12:1831–1840.
36. Assimon MM, Brookhart MA, Fine JP, *et al.* A comparative study of carvedilol versus metoprolol initiation and 1-year mortality among individuals receiving maintenance hemodialysis. American Journal of Kidney Diseases 2018. [Epub ahead of print]
37. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. Nat Rev Rheumatol 2015; 11:437–441.
38. Roberts MA, Pilmore HL, Ierino FL, *et al.* The β-Blocker to Lower Cardiovascular Dialysis Events (BLOCADE) feasibility study: a randomized controlled trial. Am J Kidney Dis 2016; 67:902–911.

39. Ibarra-Sifuentes H, Del Cueto-Aguilera Á, Gallegos-Arguijo DA, *et al.* Levocarnitine decreases intradialytic hypotension episodes: a randomized controlled trial. Ther Apher Dial 2017; 21:459–464.
40. Zhang Y-M, Zhuo L, Hu J, *et al.* Clinical significance of different carnitine levels for improving the prognosis of patients undergoing hemodialysis. Ren Fail 2016; 38:1654–1658.
41. Álvares VRC, Ramos CD, Pereira BJ, *et al.* Pneumatic compression, but not exercise, can avoid intradialytic hypotension: a randomized trial. Am J Nephrol 2017; 45:409–416.
42. Dang M, Sia C, Wong K. Pneumatic compression devices in the prevention of intradialytic hypotension. Nephrology 2017. [Epub ahead of print]
43. Doenyas-Barak K, Garra N, Beberashvili I, Efrati S. Immersion-enhanced fluid redistribution can prevent intradialytic hypotension: a prospective, randomized, crossover clinical trial. Hemodial Int 2018. [Epub ahead of print]
44. Tsai M-Y, Wu C-H, Huang Y-C, *et al.* Treatment of intradialytic hypotension with an herbal acupoint therapy in hemodialysis patients: a randomized pilot study. Complementary Ther Med 2018; 38:67–73.