Blood pressure and volume management in dialysis: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Blood pressure (BP) and volume control are critical components of dialysis care and have substantial impacts on patient symptoms, quality of life, and cardiovascular complications. Yet, developing consensus best practices for BP and volume control have been challenging, given the absence of objective measures of extracellular volume status and the lack of high-quality evidence for many therapeutic interventions. In February of 2019, Kidney Disease: Improving Global Outcomes (KDIGO) held a Controversies Conference titled *Blood Pressure and Volume Management in Dialysis* to assess the current state of knowledge related to BP and volume management and identify opportunities to improve clinical and patient-reported outcomes among individuals receiving maintenance dialysis. Four major topics were addressed: BP measurement, BP targets, and pharmacologic management of suboptimal BP; dialysis prescriptions as they relate to BP and volume; extracellular volume assessment and management with a focus on technology-based solutions; and volume-related patient symptoms and experiences.

The overarching theme resulting from presentations and discussions was that managing BP and volume in dialysis involves weighing multiple clinical factors and risk considerations as well as patient lifestyle and preferences, all within a narrow therapeutic window for avoiding acute or chronic volume-related complications. Striking this challenging balance requires individualizing the dialysis prescription by incorporating comorbid health conditions, treatment hemodynamic patterns, clinical judgment, and patient preferences into decision-making, all within local resource constraints.

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During the past decade, mounting evidence has highlighted blood pressure (BP) and volume status as key mediators of outcomes among individuals receiving maintenance dialysis.[1–6] Qualitative data suggest that suboptimal BP and volume management negatively affect quality of life.[7–9] Efforts to develop consensus best practices in managing BP and volume in dialysis have been hampered by an absence of widely available, accurate, and objective measures of extracellular volume status, as well as a lack of high-quality

evidence. As such, related practice patterns vary considerably, both within local communities and throughout the world.

In February 2019, Kidney Disease: Improving Global Outcomes (KDIGO) held a Controversies Conference, *Blood Pressure and Volume Management in Dialysis*, in Lisbon, Portugal (https://kdigo.org/conferences/bp-volume-management-in-dialysis/). The conference is the second of 4 conferences planned on dialysis (see Chan *et al.*[10] for the first report, on dialysis initiation). Participants, who included both physicians and patients, considered how BP and volume management can be optimized and individualized across dialysis modalities and resource settings.

MAJOR THEMES

As participants addressed specific issues relating to BP and volume in dialysis, multiple crosscutting themes emerged. First was the substantial heterogeneity of the dialysis population (e.g., incident vs. prevalent status, comorbid conditions, residual kidney function [RKF], and nutritional status) and the treatment setting (in-center vs. home therapies, medication use, etc.) that must be considered when prescribing dialysis. Second was the ever-present tension in balancing multiple, interlinked, volume-related factors within a narrow therapeutic window for avoiding complications (Figure 1). In some instances, correcting one volume-related abnormality (e.g., hypervolemia) may result in increasing risk associated with another volume-related parameter (e.g., ultrafiltration [UF] rate and RKF). Data to guide these decisions are limited. Third was recognition of the impact that poorly managed BP and volume have on patient lives, and the importance of incorporating patient priorities into management decisions. Fourth, availability of local resources and technologies vary globally and often dictate the bounds of dialysis prescriptions. Therefore, individualizing the dialysis prescription to manage BP and volume for each patient and setting is essential and requires incorporating numerous factors into decision-making. Finally, there was broad-based recognition of the lack of quality evidence to inform recommendations for the management of many of the BP and volume complications discussed, resulting in few strong recommendations, and calls for additional research. In many regions of the world, the dialysis community is well positioned to fill these knowledge gaps. Investigators and dialysis organizations must collaborate to leverage the predictable nature of dialysis treatments, large volumes of collected data, and research and clinical implementation capacities inherent to well-resourced dialysis delivery systems to address these fundamental questions.

BP MEASUREMENT AND TARGETS

The diagnosis and management of hypertension in patients receiving hemodialysis (HD) are often based on pre- and post-dialysis BP measurements.[11] However, assessment of cardiovascular risk based on these measurements may be not be fully informed, as observational studies have shown that pre- and post-dialysis BP have either no association or a U- or J-shaped association with mortality.[12–14] These findings may stem in part from the inaccuracy of pre- and post-dialysis BP measurements. Pre- and post-dialysis BPs, even if measured using a standardized protocol, are imprecise estimates of interdialytic BPs[15,16] and generally should not be used alone for diagnosing and managing hypertension. However, pre-, post- (i.e., peridialytic), and intradialytic BP measurements do have clinical importance for assessing and managing hemodynamic stability during the HD session.

Ambulatory BP monitoring is considered the gold-standard method for BP evaluation.[17–19] Compared with peridialytic BP, 44-hour interdialytic BP has superior risk prediction for all-cause and cardiovascular mortality.[20,21] Ambulatory BP monitoring use may be limited by patient intolerance, availability, and financial constraints in some countries.[19] When ambulatory BP monitoring is unavailable, home BP measurements may be taken twice a day, covering interdialytic days over 1–2 weeks or twice a day for 4 days following the midweek treatment.[19,22] Compared with peridialytic BP measurement in HD, home BP measurement has superior agreement with mean 44-hour ambulatory BP monitoring,[23] higher short-term reproducibility,[24] and improved prediction of adverse outcomes.[20,21] Key disadvantages of home BP monitoring are the absence of information on nocturnal dipping, and in some settings, cost.

A third alternative is BP measurement in-office, not in the dialysis unit. Increased systolic BPs (SBPs) outside of the dialysis unit are an independent risk factor for mortality.[25] Another alternative is mean or median peridialytic BP (pre-, inter-, and post-HD BP values), which has greater sensitivity and specificity in detecting interdialytic hypertension than pre- or post-dialysis BP measurements alone.[26] However, no studies have assessed the association of this approach with outcomes.

Data assessing the validity of peridialytic, office, and home BP in patients receiving home HD or peritoneal dialysis (PD) are limited, and no studies have been conducted in these populations on the associations of out-of-unit BP measurements and the risk of cardiovascular outcomes. Research to identify valid methods for BP measurement in all dialysis modalities is recommended (Table 1).

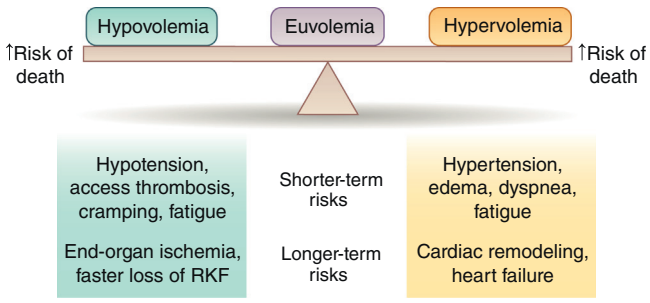

Figure 1 | Tension in balancing volume status within a narrow therapeutic window. RKF, residual kidney function.

Table 1 | Research recommendations[a]

Modality	Recommendations
BP measurements, targets, and pathophysiology	
HD and PD	Investigate the optimal BP target/threshold for hypertension treatment
HD and PD	Assess the agreement and prediction of standardized (attended or unattended) in-office BP readings, averaged intradialytic BP readings, and scheduled home BP readings with ABPM and clinical outcomes
HD and PD	Assess the acceptability and feasibility of ABPM
HD and PD	Investigate strategies to reduce BP variability
BP agent selection	
HD and PD	Hypertension: Conduct head-to-head RCTs of different medication classes on BP, including 44-h ABPM, and clinical and patient-reported outcomes (i.e., ARB vs. BB or ARB vs. BB vs. CCB)
HD and PD	Hypertension: Conduct RCTs on the effect of diuretics on RKF, BP, and CV outcomes
HD	Hypotension: Conduct larger, longer RCTs on effectiveness of midodrine
Dialysis prescription	
HD and PD	Perform studies that incorporate patient preferences and test individualized treatment approaches
HD and PD	Compare outcomes of strategies that focus on volume control vs. those that focus on RKF preservation
HD and PD	Investigate strategies for preserving RKF, including: • Impact of incremental dialysis on RKF
HD	• Impact of frequent/long hours dialysis on RKF
HD and PD	Investigate whether routine monitoring of RKF impacts clinical outcomes
HD and PD	Investigate spot biomarkers and urine volume for simple assessment of RKF
HD	Assess how to establish an individualized, *safe* UF rate for patients with different risk profiles
HD	Investigate the roles of dialysate composition—sodium, magnesium, and calcium—in intradialytic hypotension
PD	Evaluate whether minimizing dialysate glucose is preferable to reducing antihypertensive medication in PD patients with hypotension
PD	Assess whether routine monitoring of peritoneal membrane function impacts clinical outcomes
Technologies	
HD and PD	Investigate whether bioimpedance-guided volume management improves patient-centered and hard clinical outcomes
HD and PD	Investigate whether lung ultrasound-guided volume management improves patient-centered and hard clinical outcomes
HD	Investigate whether blood volume monitoring, temperature cooling, hemodiafiltration, UF profiling, and isolated UF have a benefit in hemodynamic stability, and whether this translates into benefits in hard outcomes
Volume-related patient symptoms and experiences	
HD and PD	Collect data on quality of life and symptoms in all future studies related to BP and/or volume management
HD and PD	Investigate the underlying physiology of symptoms[27]
HD and PD	Test different approaches to routine symptom assessment (e.g., smartphones, tablets)
HD and PD	Investigate correlations between symptoms and intradialytic or ambulatory BP, imaging (e.g., ultrasound, cardiac magnetic resonance), cerebral blood flow measurements, and bioimpedance spectroscopy
HD and PD	Develop symptom surveys that utilize computerized adaptive testing to decrease burden and tailor questions to individual patient priorities

ABPM, ambulatory blood pressure monitoring; ARB, angiotensin receptor blocker; BB, ß-blocker; BP, blood pressure; CCB, calcium channel blocker; CV, cardiovascular; HD, hemodialysis; PD, peritoneal dialysis; RCT, randomized controlled trial; RKF, residual kidney function; UF, ultrafiltration.
[a]Research recommendations within each topic area are listed in order of priority, stratified by modality type.

Definition of hypertension and BP treatment targets

Accepted definitions of hypertension and BP treatment targets in the dialysis population have not been determined, with just one relevant randomized controlled trial (RCT). The Blood-Pressure-in-Dialysis pilot (BID) study randomized 126 participants to either an intensive pre-dialysis SBP goal of 110–140 mm Hg *or* a standard SBP goal of 155–165 mm Hg, with the primary objective of assessing feasibility and safety to inform a larger RCT assessing hard clinical outcomes.[28] The study demonstrated intervention feasibility; however, despite the protocol calling for site investigators to challenge post-dialysis weight as the initial step in attaining the assigned target SBP, the intensive SBP goal was achieved by use of additional antihypertensive medications. Target weights actually increased in the intervention group, suggesting inadequate management of the extracellular volume status.

No population-specific evidence has established BP thresholds and targets for interdialytic BP (i.e., not pre- or post-dialysis) for the dialysis population. Extrapolating from current general population hypertension guidelines may be reasonable, but such guidelines do not account for differences in cardiovascular risk in dialysis patients. Specifically, numerous observational studies[12–14] and the Blood-Pressure-in-Dialysis study[28] have suggested harm from lower BPs. Targeting too low of a threshold may heighten cardiovascular risk in some patients. The 2017 American College of Cardiology/American Heart Association Guidelines[29] BP threshold and target is 130/80 mm Hg; in contrast, the 2018 European Society of Hypertension/European Society of Cardiology Guidelines[30] recommend an SBP target of <130 mm Hg for ages <65 years, and an SBP target range of 130–140 mm Hg for all others. Based on existing evidence, definitive recommendations regarding BP treatment targets cannot be made. An individualized approach is *a priori* necessary for all patients receiving dialysis, with a particular focus on avoiding overly low BPs, and special consideration regarding

Table 2 | Definitions of intradialytic hypotension and intradialytic hypertension

Guideline definition	Other definitions and notes	Suggested definition
Intradialytic hypotension		
KDOQI 2005 Guidelines[11] Decrease in SBP ≥ 20 mm Hg or mean BP ≥ 10 mm Hg with associated symptoms (cramping, headache, lightheadedness, vomiting, or chest pain) or need for intervention (reduction in UF or administration of fluids)	• SBP drop accompanied by interventions (saline bolus administration, UF reduction, or blood pump flow reduction) • SBP drop of a certain degree (20, 30, or 40 mm Hg) • Nadir intradialytic SBP below a threshold value (90, 95, or 100 mm Hg) A nadir SBP < 90 mm Hg and a nadir SBP < 100 mm Hg in patients with pre-dialysis SBP > 160 mm Hg is most potently associated with mortality.[4]	Any symptomatic decrease in SBP or a nadir intradialytic SBP < 90 mm Hg should prompt reassessment of BP and volume management.
Intradialytic hypertension		
None	• BP rise of any degree during the second or third intradialytic hour • SBP rise > 15 mm Hg within or immediately post-dialysis • SBP rise > 10 mm Hg from pre- to post-dialysis • Rising intradialytic BP that is unresponsive to volume removal	An SBP rise >10 mm Hg from pre- to post-dialysis in the hypertensive range in at least 4 of 6 consecutive dialysis treatments should prompt a more extensive evaluation of BP and volume management, including home and/or ABPM.

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative; SBP, systolic blood pressure; UF, ultrafiltration.

intradialytic and interdialytic BP patterns, volume management, and ccomorbidities.

Definitions of intradialytic hypotension and hypertension

In a typical dialysis treatment session, BP decreases from pre- to post-dialysis; the magnitude of this reduction most closely relates to the magnitude of UF.[19] Intradialytic hypotension is a serious complication of HD, associated with vascular access thrombosis, inadequate dialysis dose, and mortality.[4,31,32] Intradialytic hypotension prevalence ranges from 15% to 50% of HD treatments, depending on the definition (Table 2).

Any symptomatic decrease in BP or a nadir intradialytic SBP of <90 mm Hg should prompt reassessment of BP management. This reassessment includes, but is not limited to, UF rate, dialysis treatment time, interdialytic weight gain (IDWG), dry-weight estimation, and antihypertensive medication use, in concordance with discussions in the following sections. Avoidance of intradialytic hypotension should not come at the expense of maintaining euvolemia or ensuring adequate dialysis time. Data on intradialytic hypotension during home HD or intermittent PD techniques are scarce.

Intradialytic hypertension is the phenomenon of BP increase during or immediately after a dialysis session, and it involves activation of the sympathetic nervous and renin–angiotensin systems, endothelial stiffness, volume excess, and other mechanisms.[33,34] Intradialytic hypertension has an estimated prevalence of 5%–15%, depending on the definition used (Table 2). Defining it as an SBP increase of >10 mm Hg from pre- to post-dialysis accurately identifies persons with persistently elevated interdialytic BP[35] and demonstrates an association with hospitalization and mortality.[36,37] An SBP increase of >10 mm Hg from pre- to post-dialysis into the hypertensive range in at least 4 of 6 consecutive dialysis treatments should prompt a more extensive evaluation of BP and volume management, including out-of-unit BP measurements and a critical assessment of dry weight. Currently, there are no data on intradialytic hypertension in home HD or PD.

BP variability

Fluctuations of BP over the very short-term (beat-by-beat), short-term (within 24 hours), mid-term (day-by-day), and long-term (visit-to-visit) are associated with target-organ damage, cardiovascular events, and mortality in patients on HD.[38–41] However, whether BP variability is a modifiable risk factor or a marker of underlying pathology (e.g., volume shifts, arterial stiffness) remains uncertain. There are no studies of interventions targeting BP variability, so no treatment recommendations can be made, and further research is needed (Table 1).

Pharmacologic approaches to suboptimal BP and volume control

Use of antihypertensive medications. Deciding when to use antihypertensive medications requires consideration of indication (e.g., BP lowering alone or cardioprotection). In the first case, nonpharmacologic treatments should be considered first, as volume overload underlies most cases of BP elevation in dialysis.[18,19,42,43] If BP remains above target after nonpharmacologic measures directed at volume control, then initiation or up-titration of antihypertensive medications is necessary. If BP is well controlled and antihypertensive medications interfere with UF, reducing medications to allow for enhanced UF is reasonable. When antihypertensive medications are already being used for BP control and cardioprotection, it is reasonable to continue them unless they interfere with targeting euvolemia.

Choice of antihypertensive medications. Patient heterogeneity and scarcity of comparative evidence preclude recommending any one medication class over another for all patients. Antihypertensive medications considered first-line in the general population (e.g., angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and calcium channel blockers) can also be considered first-line to lower BP in patients receiving dialysis. It is reasonable to choose medications based on patient characteristics, cardiovascular indications, and availability (Table 3).

Pharmacokinetics and dialyzability are also important considerations. For example, one retrospective study found that nondialyzable β-blockers (e.g., propranolol) but not highly dialyzable β-blockers (e.g., atenolol, metoprolol) are associated with lower mortality risk, possibly due to preserved intradialytic protection against arrhythmias.[66] In contrast, another retrospective study showed higher mortality rates with the nondialyzable carvedilol versus the highly dialyzable metoprolol, which was attributed to a higher likelihood of intradialytic hypotension with carvedilol.[67] Additionally, the data assessing drug dialyzability contain uncertainties. For example, a recent study suggests that bisoprolol may in fact be dialyzable, contrary to what had been previously thought.[68] It is reasonable to consider intradialytic BP patterns with regard to drug dialyzability, and it may be prudent to avoid nondialyzable medications in the setting of frequent intradialytic hypotension. For relatively stable intradialytic BP, use of longer-acting, once-daily medication may improve adherence and reduce pill burden.

The timing of antihypertensive medication administration should be individualized, taking into account interdialytic BP and the frequency of intradialytic hypotension. The effectiveness of withholding antihypertensive agents before dialysis in reducing intradialytic hypotension is unknown[69] and is being investigated in an ongoing RCT (NCT03327909).[70]

Medications to raise BP in intradialytic hypotension. Nonmedication strategies for treating intradialytic hypotension, such as cardiovascular status optimization, UF rate minimization, and target-weight reassessment, should be prioritized. Medication options include midodrine,[71] arginine-vasopressin,[72–76] sertraline,[77,78] droxidopa, amezinium metilsulfate,[79] fludrocortisone, and carnitine.[71] In general, the evidence base for these strategies is relatively weak, with most studies being small and of short duration.[71] The most widely used is midodrine, an oral vasoconstrictor, although efficacy data are limited,[65] as is its availability outside the US (Table 3).

THE DIALYSIS PRESCRIPTION AS IT RELATES TO BP AND VOLUME

Target weight

A critical element of the dialysis prescription is the target weight; a target weight that is too low may lead to hypotension and faster loss of RKF, whereas a weight that is too high

Table 3 | Medication classes for blood pressure management in dialysis

Medication class	Evidence for use
Hypertension	
ACEis/ARBs	• RCT: Fosinopril did not reduce cardiovascular events and death compared with placebo in patients on HD with left ventricular hypertrophy[44] • RCT: Inconsistent results related to ARBs and cardiovascular outcomes[45–48] • Meta-analysis: ACEis/ARBs may reduce left ventricular mass index[49] • RCT: May preserve residual kidney function, especially in PD patients[50,51]
β-blockers	• RCT: Fewer heart failure hospitalizations with the β-blocker atenolol compared to the ACEi lisinopril in HD patients with hypertension and left ventricular hypertrophy[52] • RCT: Lower risk of death and cardiovascular death with carvedilol versus placebo in HD patients with dilated cardiomyopathy who were also receiving digoxin and ACEi or ARB[53]
Calcium channel blockers	• RCT: Amlodipine reduced cardiovascular events compared with placebo in HD patients with hypertension[54]
Diuretics	• Prospective: May help preserve residual diuresis and limit fluid overload[55,56] • Prospective: Minimal effect on central hemodynamic indices and should not be considered an antihypertensive medication in the setting of dialysis[57] • Observational: Continuation of loop diuretics after HD initiation is associated with lower IDWG and lower intradialytic hypotension and hospitalization rates[58]
Mineralocorticoid receptor antagonists	• RCT: Some trials in patients on dialysis have shown benefit on cardiovascular outcomes with spironolactone vs. placebo,[59–61] whereas others have not[62] • Ongoing RCTs: spironolactone and cardiovascular outcomes in HD patients (ACHIEVE and ALCHEMIST)[63]
Hypotension	
Midodrine	• Meta-analysis: Nadir SBP improved by an average of 13 mm Hg (95% CI: 9–18 mm Hg, $P < 0.0001$), and 6 of the 10 studies reported an improvement in symptoms associated with intradialytic hypotension with use of midodrine vs. control.[64] Included studies were all of short duration and had small sample sizes (6–21 patients), and none examined clinical endpoints such as death or cardiovascular events. • Observational: Matched midodrine users to non-users (including matching by mean peridialytic BP level) found that midodrine use was associated with significantly higher risks of cardiovascular events, all-cause hospitalization, and mortality.[65]

ACEi, angiotensin-converting enzyme inhibitor; ACHIEVE, Aldosterone Blockade for Health Improvement Evaluation in End-stage Renal Disease; ALCHEMIST, ALdosterone Antagonist Chronic HEModialysis; ARB, angiotensin receptor blocker; BP, blood pressure; CI, confidence interval; HD, hemodialysis; IDWG, interdialytic weight gain; PD, peritoneal dialysis; RCT, randomized controlled trial; SBP, systolic blood pressure.

results in hypervolemia (Figure 2). The result is a narrow therapeutic window in which to avoid acute and chronic complications of volume depletion and overload. Target weight differs in concept and in practice from the estimated dry weight, as target weight can vary from treatment to treatment. In some cases (e.g., acute illness, severe symptoms), it may be appropriate to maintain an individual slightly above the estimated dry weight; however, the long-term risks from chronic volume overload in this setting must be weighed carefully.[80]

Intradialytic hypotension and the HD prescription

Major contributors to intradialytic hypotension are insufficient intravascular volume to support the desired UF rate, and inadequate cardiovascular compensatory responses. The UF rate is a function of dialysis treatment time and volume removal.[81] In observational data, higher UF rates, even as low as 6 ml/h per kg, are associated with higher mortality risk.[3,82] Although no RCTs have demonstrated that lowering UF rates improves outcomes, biologic plausibility data support a relationship between higher UF rates and end-organ ischemia (heart, brain, liver, gut, kidneys).[83–89] A critical unanswered question is how to balance the potential risks from higher UF rates with the potential risks from volume overload.[80] In the absence of conclusive data, using one specific UF rate threshold for all patients at all times is likely inappropriate. Instead, clinicians should consider a range of factors, including intradialytic hemodynamics, comorbid medical conditions, symptoms, current conditions, and other factors as a means to weigh the potential harms of higher UF rates against their potential benefits. Decisions may differ on a treatment-to-treatment basis.

Although questions about how to individualize UF rate prescriptions remain, patient and clinician awareness and frequent consideration of the UF rate are critically important to BP- and volume-related decisions. UF rates can be lowered by increasing HD time and/or decreasing IDWG (Table 4). Increased UF time can be accomplished by lengthening or adding treatments. Patient preference and local logistics and resources are important considerations.

Strategies aimed at improving vascular compensation and/or tolerance of UF may also lower the risk of UF-induced intradialytic hypotension and are listed in Tables 4 and 5. Altering dialysate sodium concentration is the most debated approach (Table 5). Prospective studies suggest that use of lower dialysate sodium is associated with lower IDWG and BP[90,91] but also show an association with intradialytic hypotension and symptoms, including cramps.[92] Observational studies have yielded mixed results regarding the association of dialysate sodium and mortality.[93–95] The Sodium Lowering in Dialysate (SoLID) RCT[96,97] assesses the effects of low versus standard dialysate sodium concentration on regression of left ventricular mass, with results pending. Therefore, the ideal dialysate sodium concentration remains uncertain. A large multinational, pragmatic trial is ongoing (RESOLVE, NCT02823821). Moreover, the prescribed and delivered dialysate sodium concentrations can differ, rendering individualization of prescriptions challenging and potentially unsafe.[98] In general, sodium balance should be negative during an HD treatment,[1] given the tension between

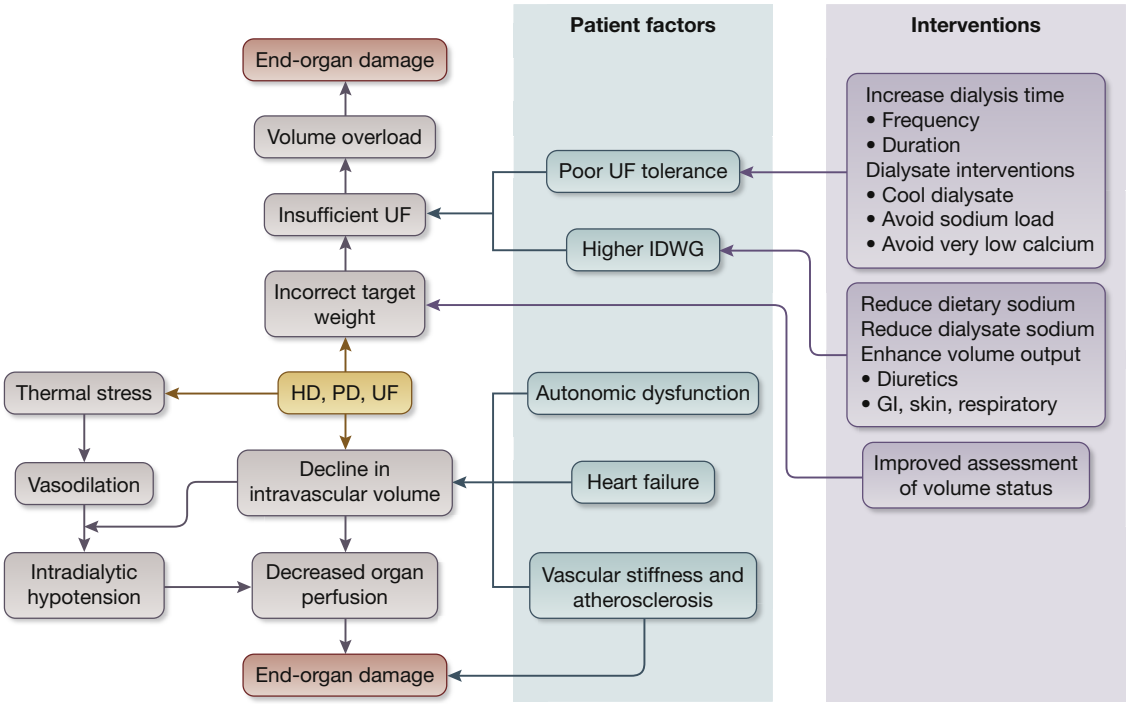

Figure 2 | Contributors to and consequences of blood pressure and volume abnormalities in dialysis. GI, gastrointestinal; HD, hemodialysis; IDWG, interdialytic weight gain; PD, peritoneal dialysis; UF, ultrafiltration.

Table 4 | Nonpharmacologic interventions to prevent intradialytic hypotension

Concept	Specific intervention	Challenges
Reduce UF rate		
Increase dialysis time	Lengthen dialysis treatments	Facility logistics; patient preference; infeasible in resource-poor regions
	Increase frequency of dialysis treatments	Facility logistics; patient preference; infeasible in resource-poor regions
	Utilize home dialysis modalities	Not available in all regions
Decrease weight gain	Decrease sodium intake	Patient preferences and adherence; difficult in setting of high-salt diets
	• Dietary counseling, including family members/food preparers	Limited food choices; poverty; lack of dietician, registered nurse, and physician skills
	• Dietary sodium restriction	
	• Avoid sodium loading during dialysis	Imprecise dialysate sodium prescriptions; increased cramping and hypotension
	Enhance nondialytic volume loss	
	• Diuretics	Viable strategy only among individuals with residual kidney function
	• Gastrointestinal, sweat, and respiratory	Patient preference and symptom burden; limited evidence
Improve tolerability of a specific UF rate		
Enhance vascular space viability	Cooled dialysate	Patient tolerance, although data suggest well tolerated
	Higher dialysate sodium[a]	May improve single-treatment BP but often leads to more IDWG and volume overload in the long-term
	Higher dialysate calcium[a]	Possible positive calcium balance and vascular calcification promotion
	UF profiling	Exposure to time-limited higher UF rate; limited evidence
	Isolated UF, followed by HD	Exposure to time-limited higher UF rate; potential decrement in clearance; limited evidence
	Hemodiafiltration	Limited availability; cost
	Improve venous tone (compression stockings)	Patient comfort
	Supine dialysis	Limited availability of beds for in-center HD
Improve overall health		
	Prevent protein energy wasting	Chronic intervention that cannot be applied acutely
	Preserve residual kidney function	Chronic intervention that cannot be applied acutely; may occur at the expense of volume overload; limited evidence
	Intradialytic exercise	Chronic intervention that cannot be applied acutely; infeasible in resource-poor regions; limited evidence

BP, blood pressure; HD, hemodialysis; IDWG, interdialytic weight gain; UF, ultrafiltration.
[a]Dialysate sodium and calcium are discussed in more detail in Table 5.

enhanced vascular space viability during a single treatment and lower IDWG across many treatments.

Additional questions include whether there is a role for UF profiling or isolated UF followed by HD (i.e., *sequential* dialysis) and how to address logistic issues such as the 3-day gap in some regions and limited access to thrice-weekly HD in resource-poor settings.

Chronic hypotension and the HD prescription

Chronically hypotensive patients are a particularly challenging group to manage. For many of these individuals, the same principles hold, most notably increasing dialysis time. Patients with chronic hypotension may tolerate PD better than HD, yet further study is required to confirm whether outcomes are better after a transition in modalities.

Hypotension and the PD prescription

Conditions associated with hypotension in PD include aggressive UF and/or failure to adjust PD prescription with decreased dietary intake or hypovolemia; failure to adjust antihypertensive medications; overly stringent salt restriction; and low cardiac output. Strategies to prevent hypotension include reducing UF volume by adjusting solutions (e.g., using less hypertonic glucose solutions or changing icodextrin to conventional 1.5% glucose solution); omitting day dwell (in automated PD [APD]) or night dwell (in continuous ambulatory PD) in those with significant RKF without compromising clearance; withholding antihypertensive medications; and liberalizing salt intake.

Hypertension and the HD prescription

Dialytic management of hypertension in patients receiving HD begins with addressing volume overload. Options include gently probing the prescribed target weight,[99] increasing treatment time and/or frequency (possibly through home HD or center-based nocturnal HD), decreasing IDWG, and improving vascular stability during HD (Figure 2).

Hypertension and the PD prescription

As among HD patients, volume is a significant contributor to hypertension among PD patients. The principle behind preventing or treating hypertension in PD is to maximize peritoneal UF and urine output to achieve euvolemia with a prescription that has the lowest glucose load to patients and without jeopardizing RKF. Strategies to maximize UF for the long dwell include shortening the dwell with glucose-based

Table 5 | Hemodialysate composition and blood pressure and volume status

Dialysate	Effects	Notes
Sodium (Na^+)	• Higher dialysate Na^+ increases IDWG and BP • Higher dialysate Na^+ reduces hypotension and symptoms	• Avoid hypernatremic HD • Prescribed dialysate Na^+ and delivered dialysate Na^+ may be discrepant • Further research needed regarding the optimal serum to dialysate Na^+ gradient • Further research needed to assess whether lower dialysate Na^+ has benefits for longer-term clinical outcomes
Calcium (Ca^{++})	• Higher dialysate Ca^{++} associated with greater hemodynamic stability • Higher dialysate Ca^{++} may result in net calcium gain and greater Ca^{++} loading	• Generally avoid very low dialysate Ca^{++} • Optimal balance between risk of lower BP and increased heart failure and sudden cardiac death risk with lower dialysate Ca^{++} needs to be weighed against the potential for increased vascular calcification and chronic loss of vascular elasticity resulting in maladaptive vascular and heart remodeling
Potassium (K^+)	• Unlikely that dialysate potassium has significant BP effects	N/A
Magnesium (Mg^{++})	• Higher dialysate Mg^{++} may reduce intradialytic hypotension and arrhythmia risk	• Minimal data and requires further evaluation
Glucose	• Unlikely that dialysate glucose has significant BP effects	N/A
Bicarbonate (HCO_3^-)	• Minimal BP effects with varying dialysate HCO_3^-	• Dated literature showing improved hemodynamic effects of HCO_3^- likely reflects harm of acetate rather than benefits of varying the dialysate HCO_3^-

BP, blood pressure; IDWG, interdialytic weight gain; HD, hemodialysis; N/A, not applicable.

solutions (high transporter), using higher tonicity glucose-based solutions (but this is less preferable), using icodextrin for long day dwell for APD or long overnight dwell for continuous ambulatory PD, restricting dietary salt, and in those with RKF, using diuretics to increase urine volume (Figure 3).[55,100] Experimental approaches include using a low-sodium dialysate,[101] a bimodal solution with glucose and icodextrin,[102] 2 icodextrin exchanges per day,[103] and incorporating intermittent hybrid therapy, all of which require further evaluation.

Assessment of membrane function may be considered as adjunctive to clinical measures of UF volume. The peritoneal equilibration test is used in solute removal modelling prediction software. However, this test alone should not guide PD prescriptions. The correlation between solute transport characteristics and UF capacity is poor. The test may be useful in identifying true membrane failure versus other causes of impaired UF and volume excess (such as mechanical causes or excess intake).[104]

No robust data suggest that continuous ambulatory PD or APD results in superior volume control relative to the other.[105] Therefore, PD modality selection considerations should go beyond BP and volume control, centering on broader concerns, such as patient preferences and local resources. APD has a potential for greater UF than continuous ambulatory PD, and mostly observational data suggest that APD may have a greater benefit for rapid transporters.[105] Changing the PD solution type, exchange number, and dwell time are important PD prescription strategies to optimize BP and volume management.

Compared with standard glucose solutions, the more biocompatible, neutral pH, or low glucose degradation products solutions may prolong the time to anuria when used for more than 12 months, and this may indirectly benefit volume control.[106,107] The more biocompatible PD solutions have also been associated with stable peritoneal membrane function and UF capacity over time, compared with conventional glucose-based solutions, which have been associated with a progressive decline in UF capacity over time.[108–110]

Icodextrin. Moderate-certainty evidence indicates that icodextrin augments peritoneal UF compared with standard glucose solutions.[106] Three RCTs have examined the effect of icodextrin in high or high-average transporters[111–113]; in general, higher transporters derived greater UF benefit from icodextrin.

4.25% PD solutions. Animal[114] and clinical data[115] suggest that hypertonic glucose solutions are deleterious to peritoneal health and may cause adverse metabolic effects.[114–116] Frequent use of 4.25% solutions should prompt evaluation of dietary salt and fluid intake, PD prescription, mechanical problems, and peritoneal membrane failure.

Preserving residual kidney function

In observational PD[117,118] and HD[119] studies, better-preserved RKF is associated with better survival rates and patient outcomes. Preserving RKF allows the incorporation of diuretics into regimens to help reduce IDWG. In addition, RKF preservation allows consideration of incremental PD prescriptions that reduce treatment burden. Likewise, the presence of significant RKF is an important consideration in incremental HD,[120] although the purported benefits are untested by adequately powered RCTs. What the optimal approach is for measuring RKF is controversial.[121,122] In many cases, urine volume measurement or potentially patient-reported urine volume[123] may be adequate. RCT data on RKF preservation strategies beyond the common-sense strategies of hypotension and nephrotoxin avoidance are limited (Table 6). Moreover, the cardioprotective strategies of more intensive volume control and more frequent HD may

hasten RKF loss.[131] Thus, individualized approaches are necessary.

EXTRACELLULAR VOLUME MANAGEMENT AND TECHNOLOGIES RELEVANT TO VOLUME MANAGEMENT

Measuring extracellular volume

There are no widely available, precise methods for measuring extracellular volume. Evaluation of any approach to measuring volume is complicated by the absence of an accessible gold standard. In most instances, volume assessment relies on clinical markers, including patient history and physical examination. Volume assessment includes examining trends in weights, BPs, and signs and symptoms. The physical examination is the mainstay of volume assessment, but data suggest that BP, jugular vein distension, and edema may not correlate well with volume status.[132–134] Despite these limitations, a physical examination should include evaluation for the presence of edema, degree of filling of the jugular vein, and lung auscultation. Physical examination paired with review of longitudinal weights, BPs, and symptoms should be performed at least once per month, with the optimal frequency individualized based on patient circumstances.

Other tools for evaluating extracellular volume are listed in Table 7. Major challenges are limited availability and the lack of evidence-based protocols. Certain tools, such as bioimpedance spectroscopy and lung ultrasound, can be used to confirm clinical suspicion of extracellular excess and are of prognostic value.[136–139] The use of bioimpedance to guide target weight estimation may improve BP and left ventricular mass.[140] Data on the effectiveness of bioimpedance-guided volume management on symptoms and hospitalizations are mixed.[136,141,142] Lung ultrasound–guided volume management improves BP control,[143] and an ongoing trial of lung ultrasound–guided treatment and cardiovascular outcomes is underway (LUST Study, NCT02310061). The biggest barriers to using these technologies are cost (of the test itself and time to administer it) and availability. In resource-constrained environments, clinical examination remains the mainstay of volume assessment.

Technical intradialytic strategies for managing BP and volume

Temperature biofeedback. Cooling the dialysate temperature through various methods (e.g., lowering temperature relative to measured body temperature or lowering

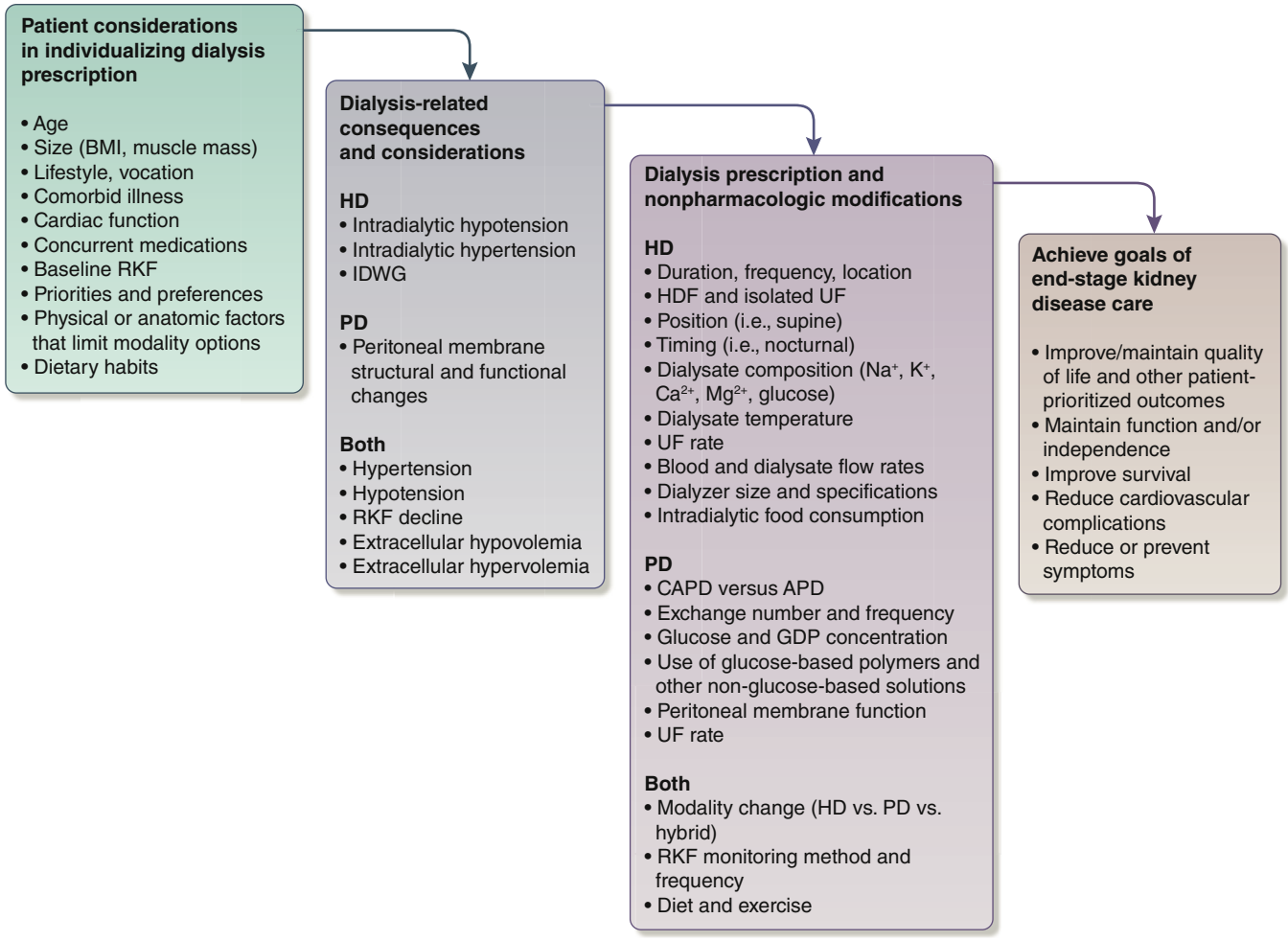

Figure 3 | Conceptual framework for individualizing dialysis prescriptions. APD, automated peritoneal dialysis; BMI, body mass index; CAPD, continuous ambulatory peritoneal dialysis; GDP, glucose degradation product; HD, hemodialysis; HDF, hemodiafiltration; IDWG, interdialytic weight gain; PD, peritoneal dialysis; RKF, residual kidney function; UF, ultrafiltration.

Table 6 | Residual kidney function

	Peritoneal dialysis	Hemodialysis
When to assess[124]	Limited consensus about frequency, which ranges from quarterly to far less frequent	Limited consensus about frequency; not consistently measured in HD patients
How to assess	Mean of urea and creatinine clearance using 24-h urine collection and simultaneous one-off blood sampling[125]	24-h urine collection only for volume vs. both urine collection and serum samples for clearance determination[126] • Entire interdialytic period preferable • Clearance of urea or creatinine or mean of urea and creatinine
Strategies to preserve	*RCT evidence* • RAS blockers[127] • Neutral pH Low GDP solution[76] • Diuretics (increase urine volume and thus reduce UF rate, but do not specifically preserve RKF)[55] • Low-protein diet with keto acid supplementation[128] *Other* • Avoid hypotension[129] • Avoid nephrotoxins	*RCT evidence* • High flux vs. low flux (benefit)[130] • Frequent nocturnal dialysis may increase rate of loss (harm)[131] *Other* • Avoid intradialytic hypotension[129] • Avoid nephrotoxins

GDP, glucose degradation product; HD, hemodialysis; RAS, renin–angiotensin system; RCT, randomized controlled trial; RKF, residual kidney function; UF, ultrafiltration.

temperature to a set threshold—35 °C or 36 °C—irrespective of body temperature) has been associated with hemodynamic stability,[144–147] and lowering temperature to 0.5 °C below body temperature is well tolerated by most patients. An ongoing trial (MY TEMP, NCT02628366) is evaluating the effect of dialysate cooling on cardiovascular events.

Blood volume monitoring. Evidence is conflicting regarding whether relative blood volume monitoring can predict intradialytic hypotension[148–151]; however, evidence suggests that relative blood volume monitoring is of prognostic value.[152] In the randomized Crit-Line Intradialytic Monitoring Benefit (CLIMB) trial, mortality and hospitalization rates were higher among patients undergoing intradialytic blood volume monitoring versus conventional clinical monitoring. However, the interpretation of the trial is limited by the atypically low hospitalization and mortality rates and questions regarding study protocol adherence.[153,154] In children, although there are no RCT data, evidence indicates that a relative blood volume–guided UF algorithm improves BP control.[155]

UF profiling. RCT data on UF profiling, independent of relative blood volume monitoring and sodium profiling, are scarce, with a crossover RCT published in 2000 demonstrating no benefit.[156]

Isolated UF. Isolated UF is commonly used,[147] but currently there is limited evidence to support this approach.

Sodium profiling. Although data to support sodium profiling are scant, one meta-analysis suggests that stepwise versus linear sodium profiling is associated with greater hemodynamic stability.[157] Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) suggest that the routine use of sodium modelling/profiling to limit or prevent intradialytic hypotension is associated with increased all-cause mortality.[147] Sodium profiling must be used judiciously, as it may result in sodium loading and hypervolemia.

Bioimpedance. Data from a study of 15 patients indicate that bioimpedance may have a role for assessing the relationship between plasma refilling and tissue hydration during dialysis,[158] but evidence is currently insufficient to justify routine use for intradialytic volume management. As reported above, bioimpedance may have a role in extracellular volume management.

Hemodiafiltration. Convective therapies such as hemodiafiltration may have a role in preventing intradialytic hypotension. An RCT including 146 patients demonstrated a significant reduction in intradialytic hypotension in the hemodiafiltration group compared with regular HD,[159] and others have demonstrated better hemodynamic stability with increasing convection volume prescriptions.[160] Further research is needed.

Remote monitoring and wearable health technologies

For home-based dialysis, older technologies, such as telephone calls, remain important. However, systems are advancing, and many modern dialysis machines can transmit data, such as BP, weight, oxygen saturation, and UF rate, back to central locations. None of these tools has been proven to enhance outcomes, but more investigation is needed. Wearable devices, including dialysis apparatuses and cardiac tools for measuring volume status, heart rhythm, and other factors, are currently in development. Their roles in dialysis management remain nascent. These tools have the potential to improve patient autonomy and risk-factor management but will need to be aligned with local health and payment systems to realize widespread uptake.

VOLUME-RELATED PATIENT EXPERIENCES AND NONPHARMACOLOGIC INTERVENTIONS FOR SUBOPTIMAL BP AND VOLUME CONTROL

Signs and symptoms of volume overload or depletion

Various signs and symptoms are associated with volume overload or depletion: breathlessness, orthopnea, edema, elevated jugular venous pressure, cardiomegaly, lung congestion, light-headedness, cramps, erectile dysfunction, thirst, and weight gain and loss, among others. Small studies suggest that better BP and volume management may improve symptoms.[161] Some dialysis patients have symptom clusters that relate to volume status, and it is helpful for both

Table 7 | Volume-assessment parameters and tools

Method	Comments
History and symptoms	• Mainstay of clinical care • Lack standardized approaches to data collection
Physical examination	• Mainstay of clinical care • Data supporting associations between physical signs and volume status are weak
Blood pressure	• Studies suggest weak correlation between BP and volume status • Useful in monitoring patient safety • Minimal data on relative effectiveness of various BP measurements as they relate to volume assessment
Inferior vena cava diameter	• Low accuracy • Low repeatability • High patient burden
Lung water ultrasound	• Good for evaluating for hypervolemia (but not hypovolemia) • Role in routine volume assessment is underway (NCT02310061) • Time- and personnel-intensive
Bioimpedance	• Medium to high accuracy • High reproducibility • Some challenges in interpretation owing to reading variation across some patient subpopulations • Not universally available • Time- and personnel-intensive
Relative blood-volume monitoring	• Low accuracy and repeatability • Only applicable in hemodialysis • Requires interpretation • Not universally available
Biochemical markers (BNP/NT-proBNP, CD146, cGMP)	• Generally low accuracy • Cost is variable and depends upon laboratory availability at centers • Not universally available, mainly used as a research tool
Extracellular volume (NaBr)	• High accuracy • High cost and time burden • Not universally available, mainly used as a research tool
Chest x-ray	• Low accuracy • Low risk • Easy to perform and accessible
Echocardiography (RVSP and LV filling pressure via E/E′ ratio)	• Higher left and right atrial enlargement and RVSP elevation correspond to pulmonary circulation overload[135] • Not performed in dialysis clinics, impacting feasibility • High cost and time burden • Not universally available

BNP, brain natriuretic peptide; BP, blood pressure; CD146, cluster of differentiation 146; cGMP, cyclic guanosine monophosphate; LV, left ventricular; NT-proBNP, N-terminal-pro hormone BNP; RVSP, right ventricular systolic pressure.

clinicians and patients to recognize these individualized indicators. Research aimed at understanding symptom constellations is needed.[162]

Incorporating volume-related symptoms into dialysis prescription decision-making

National guidelines suggest UF rate thresholds and dietary restrictions,[18,19,163] but none address the relationship between volume status and symptoms. In consensus-building exercises, patients prioritize symptoms that plausibly relate to volume, such as fatigue and cramping, for treatment and new research.[7,164] Symptoms, especially when new or escalating, should trigger review of volume-related aspects of the dialysis prescription. However, symptoms are seldom formally assessed on a frequent basis, and patients describe underreporting their symptoms.[8] Patients should be engaged, educated, and encouraged to report symptoms routinely.[8] Symptom assessment surveys have been developed for dialysis patients,[165] but most instruments assess symptoms over 1 to 4 weeks, obscuring links between symptoms and the dialysis prescription. Ideally, a symptom measurement tool would capture relevant symptoms and their severity in real time, without being burdensome to patients.

Incorporating symptoms into dialysis prescription considerations may focus discussions on aspects of care that are most important to patients. In considering symptoms, risk-versus-benefit tradeoffs must be carefully explained and weighed. Good communication, both among the dialysis team members and between the team and the patient, is essential to ensure that changes in target weight (or other prescription aspects) are carefully monitored. Inclusion of patient experience and well-being in benchmarking could help align the goals of patients and providers.

Salt and fluid restrictions for BP and volume control

Salt and fluid restrictions are the cornerstone nonpharmacologic strategies for BP and volume management; however, data supporting their effectiveness are surprisingly

scant. A systematic review evaluated 16 studies of psychological interventions for addressing nonadherence to fluid restrictions in HD patients,[166] including behavior modification, cognitive therapy, social reinforcement, and stress management. At best, these studies indicated only a modest postintervention decrease in IDWG. However, small studies have shown that restricting salt intake can reduce IDWG in patients receiving HD,[167] and BP in patients receiving PD.[168] Although the serum sodium level that triggers thirst varies across individuals,[169] most patients maintain their pre-dialysis sodium levels within the normal range. This finding suggests that water intake is adjusted to match salt intake, underscoring the importance of emphasizing salt restriction, rather than the overly simplistic advice to just restrict fluid intake. For patients with low pre-dialysis sodium level, other issues should be considered, such as poorly controlled glucose levels or excessive drinking.

Effects of dietary restrictions on quality of life. According to a review of qualitative studies, dietary and fluid restrictions are disorienting and intensely burdensome to patients.[170,171] Conference patient participants emphasized how eating and drinking are integral to social and familial interactions, noting that dietary restrictions can further isolate patients, who are already isolated by chronic illness. Moreover, patients reported feeling *blamed* for their fluid gains, often despite their best efforts at adherence.

Improving adherence to dietary restrictions. Empowering patients to adapt to dietary restrictions requires a multifaceted approach. Salt literacy must be promoted, and dietary guidance should be appropriate for local settings. Motivational interviewing with frequent follow-up has been shown to improve adherence, leading to better BP and volume control.[172] Education should be tailored to a patient's health literacy level and provided throughout treatment phases. Interventions that increase patient activation (through education, shared decision-making, and other means of empowerment) may increase adherence; these require further evaluation.[173]

Dietary restrictions and nutritional status. Dietary interventions to reduce IDWG must be made cautiously so as not to compromise nutritional status. Such caution is particularly important in frail patients, who may tolerate UF poorly even when hypervolemic. In growing children, it is important to monitor volume status and body composition regularly to ensure that the target weight is adjusted to match growth. If fluid gains between treatments persist despite dietary changes, an augmented dialysis regimen should be considered. Goals of care should be reviewed frequently.

Exercise for BP and volume control

Although there are few studies of exercise and volume,[174] combined aerobic and resistance training has been associated with SBP and diastolic BP reductions.[175] Although many dialysis patients want to exercise,[176] barriers to exercise of any type include fatigue, dialysis access, time constraints, comorbidities, fear, and (for intradialytic exercise) clinic personnel workload.[177,178]

CONCLUSION

Managing BP and volume in dialysis requires an individualized approach with integration of numerous clinical, dialysis treatment, and patient factors. Bolstered by shared commitments to improving volume management and focusing on patient-stated priorities, the conference participants identified numerous strategies and technologies that should be considered in the design and implementation of future RCTs in this critical, yet understudied area.

APPENDIX

Other conference participants

Teresa Adragão, Portugal; Samaya J. Anumudu, USA; Christopher T. Chan, Canada; Alfred K. Cheung, USA; Maria Rosa Costanzo, USA; Indranil Dasgupta, UK; Andrew Davenport, UK; Simon J. Davies, UK; Marijke J.E. Dekker, The Netherlands; Laura M. Dember, USA; Daniel Gallego, Spain; Rafael Gómez, Colombia; Carmel M. Hawley, Australia; Manfred Hecking, Austria; Kunitoshi Iseki, Japan; Vivekanand Jha, India; Jeroen P. Kooman, The Netherlands; Csaba P. Kovesdy, USA; Eduardo Lacson, Jr, USA; Adrian Liew, Singapore; Charmaine E. Lok, Canada; Christopher W. McIntyre, Canada; Rajnish Mehrotra, USA; Dana C. Miskulin, USA; Ezio Movilli, Italy; Fabio Paglialonga, Italy; Roberto Pecoits-Filho, Brazil; Jeff Perl, Canada; Carol A. Pollock, Australia; Miguel C. Riella, Brazil; Patrick Rossignol, France; Rukshana Shroff, UK; Laura Solá, Uruguay; Henning Søndergaard, Denmark; Sydney C.W. Tang, Hong Kong, China; Allison Tong, Australia; Yusuke Tsukamoto, Japan; Suzanne Watnick, USA; Matthew R. Weir, USA; James B. Wetmore, USA; Caroline Wilkie, USA; and Martin Wilkie, UK.

DISCLOSURE

JEF declared having received consultancy fees from AstraZeneca and Fresenius Kidney Care North America; having served on the advisory board of NxStage Medical; having received speaker honoraria from American Renal Associates, American Society of Nephrology, Dialysis Clinic, Inc., National Kidney Foundation, and multiple universities; and having received research support from Renal Research Institute, a subsidiary of Fresenius Kidney Care North America. TIC declared having received consultancy fees from Janssen Research & Development, LLC and Novo Nordisk; is expected to receive fees from Tricida, Vascular Dynamics, Inc., and Gilead Sciences for future consultancy work; declared having served on the advisory board of Fresenius Medical Care Renal Therapies Group, LLC; and declared having received research support from Satellite Health Care. MPG declared having received speaker honoraria from AstraZeneca. EL declared having received speaker honoraria from Fresenius Medical Care Asia Pacific. MPG declared having received speaker honoraria from AstraZeneca. AY-MW declared having received speaker honoraria from Fresenius Kabi and Sanofi Renal; and travel support from Fresenius Kabi. DEW declared having received consultancy fees from Janssen Biopharmaceuticals and Tricida. MJ declared having received consultancy fees from Amgen, AstraZeneca, Mundipharma, MSD, and Vifor Fresenius Medical Care; speaker honoraria from Amgen, Menarini, MSD, and Vifor Fresenius Medical Care; and research support from Amgen, MSD, and Otsuka. WCW declared having received consultancy fees from Akebia, AMAG, Amgen, AstraZeneca, Bayer, Daichii-Sankyo, Relypsa, and ZS Pharma; speaker honoraria from FibroGen; and research support from the National Institutes of Health. KRP declared having received consultancy fees from Medtronic Australasia Pty Ltd. All the other authors declared no competing interests.

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