

Ultrafiltration-profiled hemodialysis to reduce dialysis-related cardiovascular stress: Study protocol for a randomized controlled trial

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ABSTRACT

Rapid fluid removal (ultrafiltration, UF) is associated with higher cardiovascular morbidity and mortality among individuals receiving maintenance hemodialysis (HD). Fluid removal rates that exceed vascular refill rates can result in hemodynamic instability, end-organ damage to the heart, kidneys, gut and brain, among other organs, and patient symptoms. There are no known evidence-based HD treatment strategies to reduce harm from higher UF rates. Ultrafiltration profiling, the practice of varying UF rates to maximize fluid removal during periods of greatest hydration and plasma oncotic pressure, has been proposed as an HD treatment intervention that may reduce UF rate-related complications. This study is a randomized 4-phase cross-over trial in which participants are successively alternated between study arms with intervening washout periods, and treatment order is randomized. After 4-week screening and 6-week baseline periods, participants are randomized to HD with conventional UF or HD with UF profiling for a period of 3 weeks followed by a 1-week washout period before crossing over. Participants cross into conventional UF and UF profiling phases twice (2 phases per arm). The primary outcomes of interest are intradialytic hypotension (nadir intradialytic systolic blood pressure < 90 mmHg), pre-to post-HD change in troponin T (expressed as a percentage), change in left ventricular global longitudinal strain (an echocardiographic measure of left ventricular systolic function), and development of intradialytic left ventricular stunning (worsening of contractile function in ≥ 2 segments). This study will determine the impact of UF profiling on UF rate-related cardiovascular complications in prevalent, maintenance HD patients.

1. Introduction

There are over 500,000 individuals in the United States (U.S.) who receive maintenance hemodialysis (HD) therapy. These individuals have exceedingly high mortality (166.3 deaths/1000 person-years), driven largely by cardiovascular causes [1]. Many difficult to modify factors such as a high burden of co-morbid disease, chronic inflammation, and poor nutrition contribute to the morbidity and mortality experienced by HD patients. However, HD treatment factors also affect outcomes. Over the last decade, a growing body of literature has shown an association between aspects of volume management and adverse outcomes [2–6].

Specifically, higher rates of fluid removal (ultrafiltration, UF)

during HD are associated with higher cardiovascular morbidity and mortality [2,7,8]. The mechanism likely relates to blood pressure (BP) perturbations, myocardial ischemia, systemic inflammation, and other end-organ ischemic damage [9–11]. In cases where fluid removal rates outpace vascular refill rates, UF induces both subclinical end-organ hypoperfusion and frank hypotension and associated ischemia. Hypoperfusion leads to regional myocardial hypoxia as evidenced by myocardial ischemia, or “stunning”, on transthoracic echocardiography (TTE) and troponin elevation [10,12]. Moreover, higher UF rates have been associated with patient-reported outcomes such as prolonged recovery time after treatment [13].

Hemodialysis procedural strategies such as UF profiling, the practice of varying UF rates to maximize fluid removal during periods of

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greatest hydration and plasma oncotic pressure, may reduce UF rate-related cardiovascular complications and patient-reported symptoms. While UF profiling has been available for decades, it has been studied primarily in the context of concomitant sodium profiling. Sodium profiling uses a higher dialysate sodium concentration to increase plasma osmolality. While sodium profiling (\pm UF profiling) often reduces hypotension, it also disadvantageously results in a positive sodium balance that leads to increased thirst, weight gain, and interdialytic hypertension [14–16]. Sodium profiling has been dismissed as a viable treatment option in most circumstances because of these adverse consequences. Alternatively, UF profiling may reduce UF rate-related hemodynamic instability and associated cardiovascular consequences without altering sodium balance, but its potential effects in this regard have not been firmly established.

The objective of this study is to investigate the comparative effect of HD with conventional UF and HD with UF profiling on select cardiovascular and patient-reported outcomes.

2. Methods

2.1. Study design overview

This study is a randomized 4-phase cross-over trial in which participants are successively alternated between dialysis strategies with intervening washout periods, and treatment order is randomized (Fig. 1). Screening and baseline periods precede the intervention period. Patient eligibility for the study will be determined during the 4-week screening period. The screening period will be followed by a 6-week baseline period that will consist of recruitment, baseline data collection (i.e. laboratory testing, medical history, physical examination, and medication review), and standardization of the HD prescription.

Following the baseline period, participants will be randomized to either HD with conventional UF (control arm) or HD with UF profiling (intervention arm) for a 9-treatment phase, followed by a 3-treatment washout period. Then participants will cross over to the other study arm for a 9-treatment phase. Following another washout period, the same sequence of treatment and washout phases will be repeated (Fig. 1). The study includes a total of 45 treatments: 18 conventional UF (2 9-treatment phases), 18 UF-profiled (2 9-treatment phases), and 9 washout treatments (3 3-treatment periods).

2.2. Study participants

2.2.1. Selection criteria

All patients receiving maintenance HD at participating outpatient dialysis clinics will be screened for eligibility. Participants must be > 18 and < 85 years-old, have received in-center HD treatments for at least 90 days, and have UF rates > 10 mL/h/kg in at least 30% of treatments during the 4-week screening period. Fig. 2 displays the study flow diagram and complete list of exclusion criteria. In brief, exclusion criteria include sodium profiling or UF profiling in routine HD prescription, active infection, unstable angina, end-stage cirrhosis, New York Heart Association class IV heart failure, treatment non-adherence (defined as > 2 unexcused treatment absences during the screening period), and inability to undergo all study testing.

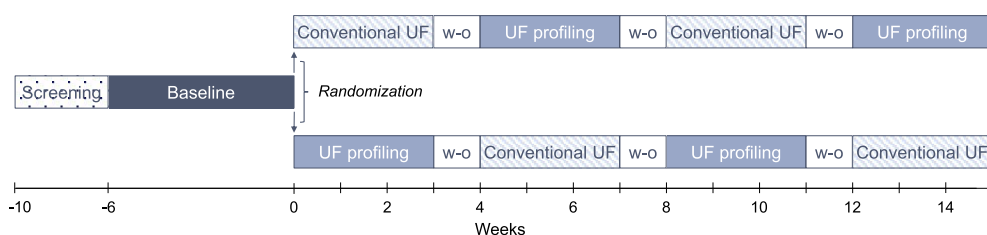


Fig. 1. Study design.

2.2.2. Participant recruitment

Participants will be recruited from 2 central North Carolina outpatient dialysis clinics affiliated with the University of North Carolina (UNC) at Chapel Hill. Based on our preliminary data, we anticipate that 30% of the 175 HD patients in the participating clinics will meet study selection criteria, and 75% (40 patients) will be willing to participate. The recruitment goal is 36 total participants. If the recruitment goal is not met at the first 2 clinics, we will expand to a third UNC-affiliated clinic.

2.2.3. Randomization

After providing informed consent, participants will be randomized to a study intervention arm: the sequence beginning with conventional UF or the sequence beginning with UF profiling. Randomization of allocation sequence will be completed using computer-generated random numbers. At the conclusion of the baseline period and following randomization, the dialysis clinic nurse manager will be provided the allocation sequence for each enrolled participant. The nurse manager will enter the correct dialysis prescription orders into the electronic health record, and the clinic medical director, who is unaffiliated with the research, will cosign the treatment orders.

2.3. Interventions

All participants will be dialyzed using the Fresenius 2008T machine (Fresenius Kidney Care North America, Waltham, MA) with a dialysate temperature of 37°C . All other treatment parameters (e.g. dialysate composition, blood flow rate, dialysate flow rate) will be per the participant's baseline, attending nephrologist-prescribed HD prescription.

2.3.1. Intervention: hemodialysis with ultrafiltration profiling

The study intervention arm will be HD + linear UF profiling (profile 2 on the Fresenius 2008T machine). Under profile 2, the machine automatically changes the UF rate in a linear, down-sloping fashion (Fig. 3). The treatment begins at a UF rate 40% higher than the baseline rate (determined by UF volume and prescribed treatment time). Over the course of the treatment, the UF rate declines, reaching 100% of the baseline rate at treatment midpoint and 60% of the baseline rate at treatment end. For example, a participant with a prescribed UF rate of 923 mL/h (3000 mL UF over 3.25 h treatment time) would begin treatment at a UF rate of 1292 mL/h, decline to a UF rate of 923 mL/h by mid-treatment, and conclude treatment with a UF rate of 554 mL/h.

2.3.2. Control: hemodialysis with conventional ultrafiltration

The study control arm will be HD with conventional UF, the participant's standard HD prescription with a constant UF rate (i.e. without UF profiling).

2.3.3. Wash-out hemodialysis treatments

Study wash-out treatments will be HD with conventional UF, the participant's standard HD prescription with a constant UF rate (i.e. without UF profiling, same as control treatments).

2.3.4. Clinical decision-making

The attending nephrologist will determine the baseline UF rate for both conventional UF and UF-profiled treatments by considering

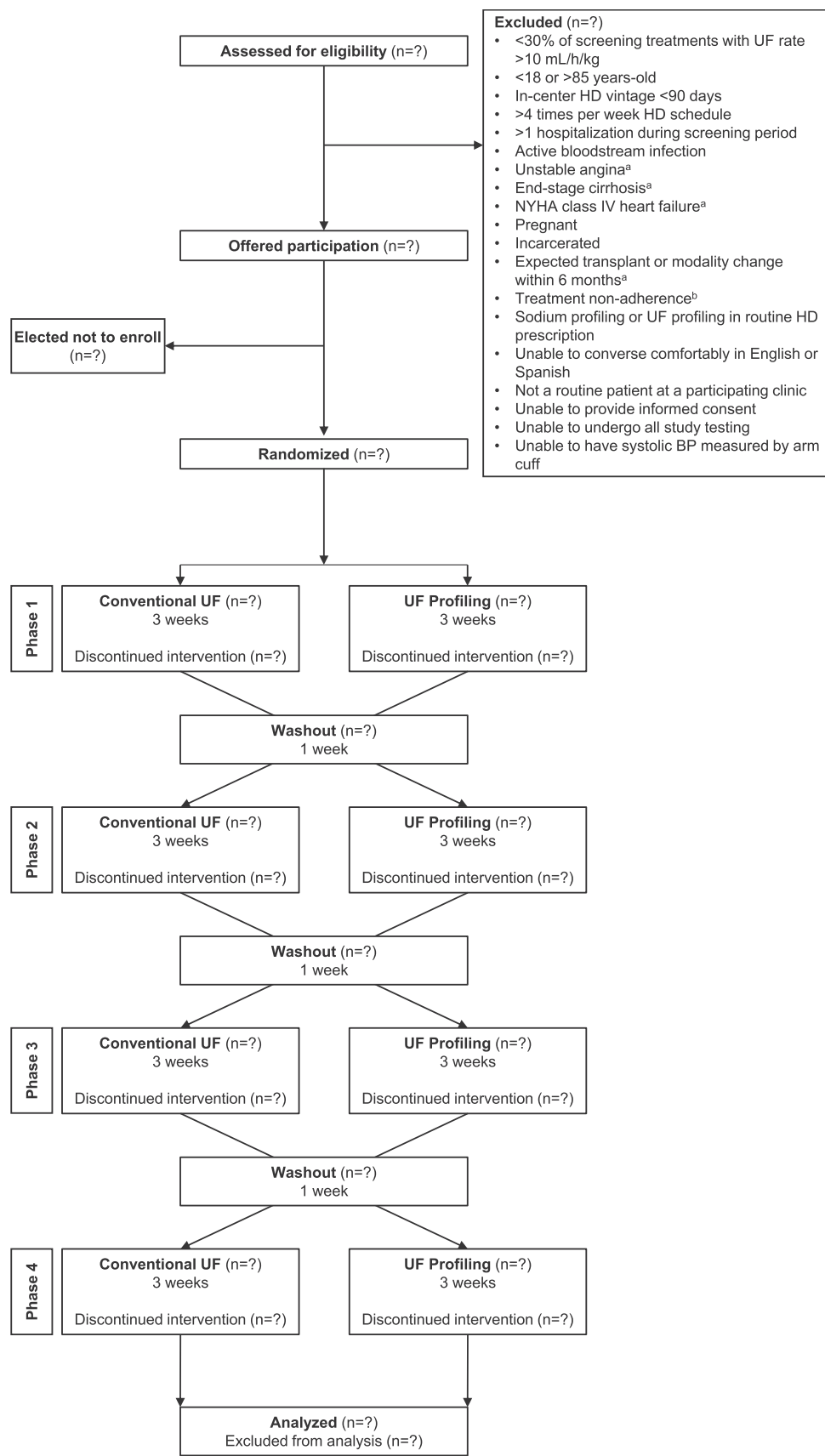


Fig. 2. Study flow diagram.

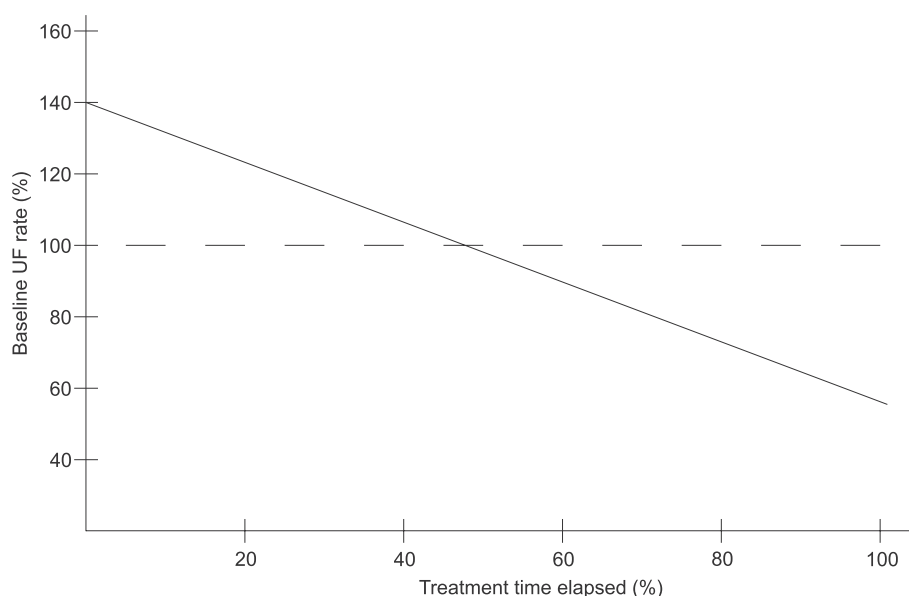


Fig. 3. Ultrafiltration profile 2.

interdialytic weight gain (IDWG), prescribed target weight and other clinical factors (i.e. BP, health status, symptoms, etc.). The attending nephrologist will prescribe the dialysate composition and medications administered during HD. Sodium profiling will not be used in either arm of the study. Any hemodynamic instability experienced during study treatments will be managed per routine protocols with standard interventions (e.g. saline administration, reduction in UF rate or blood flow). Upon resolution of hemodynamic instability, UF will be resumed at a constant UF rate for participants in the conventional UF arm and at a profiled rate via re-enablement of UF profile 2 for participants in the UF-profiled arm.

2.3.5. Blinding

The study will be double-blinded. The study participants, investigators, cardiac sonographers, and cardiologist will be blind to allocation sequence. The HD clinic personnel (i.e. medical director, nurse manager, nurses, and patient care technicians) will be aware of the study arm assignment and prescribed treatment type for each HD treatment.

2.4. Data collection and outcomes

2.4.1. Data collection procedures

Study data will be collected according to the schedule displayed in Table 1. Clinical data including BP, heart rate, and weights will be obtained per routine care protocols and extracted from the electronic health record. Additional HD data such as dialysate sodium, potassium and calcium concentrations, medication administration, and hypotension interventions (e.g. saline administration, UF cessation, UF rate change) will be recorded by clinic personnel per standard clinical protocols and obtained from the electronic health record. Baseline laboratory testing (e.g. electrolytes, albumin, complete blood count, Kt/V, iron stores, bone-mineral tests) will be drawn in the last week of the baseline period and processed at Spectra Laboratories (Rockleigh, NJ). Among participants producing > 100 mL urine/day, a 24-h urine collection will be performed during the baseline period.

2.4.2. Primary outcomes

Table 2 displays study primary, secondary and exploratory outcomes and definitions. The primary outcomes of interest are intradialytic hypotension (binary), troponin T percentage change (continuous), left ventricular global longitudinal strain (GLS) change (%,

continuous), and intradialytic cardiac stunning (binary).

Blood pressure will be machine-measured pre- and post-HD and every 15 min during HD by clinic personnel per standard clinic protocols. The presence or absence of intradialytic hypotension will be determined on a per treatment basis (36 total measurements, 18 per study arm). Treatments with intradialytic hypotension will be defined as treatments in which the lowest intradialytic systolic BP is < 90 mmHg. Treatments without intradialytic hypotension will be those treatments in which the lowest intradialytic systolic BP is ≥ 90 mmHg. Intradialytic hypotension defined by a nadir systolic BP < 90 mmHg has been associated with higher mortality compared to intradialytic hypotension defined by other definitions (e.g. BP fall of some requisite amount, occurrence of symptoms) [17].

Troponin T percentage change will be assessed once during each study phase (4 total measurements, 2 per study arm). Troponin T assessment will occur at the 7th HD treatment of each phase. The 7th treatment was selected to facilitate capture of data from the treatment following the 72-h interdialytic break. Blood samples for Troponin T will be collected via the vascular access by clinic personnel before and after the HD treatment using a lithium heparin tube. Pre-HD samples will be collected after insertion of access needles, and post-HD samples will be collected after the blood pump is set to minimum. Blood samples will be processed in the clinic's centrifuge (Spectra Laboratories, Rockleigh, NJ) by a research team member. Processed serum will be refrigerated within 2 h of collection. Troponin T analysis will be performed using a fifth-generation assay (Mayo Medical Laboratories, Rochester, MN). Troponin T percentage change will be defined as $[(\text{post-HD troponin} - \text{pre-HD troponin}) / \text{pre-HD troponin}] \times 100$.

Echocardiograms will be performed during the baseline period on a non-dialysis day and 30 min before the end of the 7th HD treatment in the first phase of each treatment type. Prior studies have identified this timeframe as the period of "peak intradialytic stress." [10,18] The 7th treatment was selected to facilitate capture of data from the treatment following the 72-h interdialytic break. Images will be acquired by a trained sonographer using a Samsung HM70A cardiac ultrasound machine (Seoul, South Korea) with a phased array transducer. Digital clips of two-dimensional, pulsed Doppler, and tissue Doppler images will be recorded from the apical 4-chamber view, the apical 2-chamber view and the apical long axis view. Ultrasound data will be optimized and analyzed offline by a blinded cardiologist using a dedicated computer workstation equipped with TomTec software (TOMTEC Corporation, Chicago, IL). Left ventricular systolic function will be quantified by 2-

Table 1
Data collection schedule.

Weeks from study start	– 6 to 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Study assessments	Baseline	Phase 1			Wash-out	Phase 2			Wash-out	Phase 3		Wash-out	Phase 4				End
Informed consent	X																
Laboratory testing	X																
Medical history and physical	X																
Medication review	X																
Pregnancy status inquiry	X																
Prescribed target weight optimization	X																
BP monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiogram	X			X				X				X ^a					X ^a
Plasma refill testing	X			X				X				X					X
Troponin T testing				X				X				X					X
Patient-reported symptoms assessment ^b	X		X	X	X		X	X	X		X	X	X		X	X	X
Patient-reported treatment acceptance assessment ^b					X				X				X				X

Abbreviations: BP, blood pressure.

^a If echocardiogram is missed during phases 1 and/or 2 (i.e. due to participant hospitalization, missed treatment, technical problem, etc.), imaging will be completed in phases 3 and/or 4 to capture intradialytic echocardiographic data under both treatment paradigms (UF profiling and conventional UF).

^b Patient-reported symptoms and treatment acceptance assessments consider the “last week” of treatments and “last three weeks” of treatments, respectively, and will be collected at the first treatment of the subsequent week.

dimensional speckle tracking echocardiography-derived global longitudinal strain. Regional myocardial function will be subjectively scored using a 16-segment model of the left ventricle. Intradialytic left ventricular stunning, a finding that has been associated with increased mortality [18], will be defined as worsening of contractile function in ≥ 2 segments from baseline to peak intradialytic stress.

2.4.3. Secondary outcomes

The secondary outcomes of interest are systolic BP change (mmHg, continuous), nadir systolic BP (mmHg, continuous), target weight achievement (binary), weight difference (kg, continuous), patient acceptance (binary), symptoms (categorical), time to recovery (hours, continuous), and left ventricular ejection fraction (EF) change (% continuous).

Patient acceptance will be assessed after the completion of each study phase (4 total measurements, 2 per study arm). The participant's response to the question, “If recommended by your physician, would you be willing to adopt the HD prescription you have received during the last 9 treatments?” will be recorded by a research team member. Acceptance will be defined as a response of “yes”, and non-acceptance will be defined by a response of “no.”

Symptoms will be assessed once weekly, 3 times per study phase (12 total measurements, 6 per study arm). The participants' responses to a 12-symptom 5-category severity Likert scale survey will be recorded by a research team member. Responses options are none, mild, moderate, severe, and very severe. Time to recovery after dialysis will be assessed at the same time and frequency as symptoms and will be defined as the participant's self-reported amount of time to recover after the previous week's HD treatments. A research team member will also record the participants' recovery time. Table 2 displays the additional secondary outcome definitions.

2.4.4. Exploratory outcomes

The exploratory outcomes of interest are hypoxemia (% continuous), plasma refill (binary), indices of left ventricular diastolic function and filling pressures (early diastolic myocardial velocity [cm/s, continuous] and mitral E/e' ratio [continuous]), a measure of right ventricular systolic function (tricuspid annulus systolic excursion velocity [cm/s, continuous]), assessments of segmental and global left ventricular systolic function (left ventricular wall motion score, [continuous], segmental vs. global worsening among those with segmental wall motion abnormalities [continuous], and affected left ventricular segment difference [continuous]), and vascular access thrombosis events [continuous].

Intradialytic arterial oxygen saturation will be machine-measured once per minute by the Crit-Line Monitor (Fresenius Medical Care North America, Waltham, MA), a blood volume monitoring device approved by the U.S. Food and Drug Administration for the measurement of hematocrit and oxygen saturation in the extracorporeal circuit. The manufacturer-reported accuracy of the measured oxygen saturation is 2%. Hypoxemia will be determined on a per treatment basis (36 total measurements, 18 per study arm) and will be defined as the difference between the starting oxygen saturation and the lowest intradialytic oxygen saturation. Hematocrit values will be machine-measured by the same device per standard clinical protocols.

Plasma refill will be assessed at the 7th HD treatment of each study phase (4 total measurements, 2 per study arm). At the beginning of these treatments, the UF time will be set 10 min shorter than the treatment run-time. Treatments with plasma refill will be defined as treatments in which the hematocrit decreases by $\geq 0.5\%$ from the termination of UF to the end of treatment. Treatments without plasma refill will be those treatments in which the hematocrit decreases by $< 0.5\%$ from the termination of UF to the end of treatment. Table 2 displays the complete list of exploratory outcome definitions.

2.5. Statistical analysis

To assess the difference of various outcomes between the UF-profiled intervention arm and the conventional UF control arm, we will perform likelihood ratio tests using various Generalized Linear Mixed Models (GLMM) depending on the outcome type. For binary outcomes, we will perform a repeated measure logistic regression using the binary treatment indicator (UF-profiled/control) as a fixed effect predictor and assigning each subject a random intercept term. A likelihood ratio test will then be carried out to test the significance of whether the coefficient corresponding to the binary treatment indicator equals to zero, i.e. whether the binary outcomes significantly differ between the two treatment groups. For continuous outcomes, we will perform a repeated measure linear regression. For continuous percentage outcomes, we will first log transform the outcome before performing the repeated measure linear regression. For categorical outcomes, we will perform a repeated measure multinomial regression. For all these models, the treatment indicator will also be treated as a fixed-effect predictor, and random intercept terms will be added in each model. Similar likelihood ratio tests will be conducted to test the significance of arm difference. P-values as well as confidence intervals will be given for the arm difference in all described models.

Table 2
Study outcomes.

Outcomes	Definitions
<i>Primary</i>	
Intradialytic hypotension	Intradialytic systolic BP < 90 mmHg
Troponin T percentage change	[(Post-HD troponin T – pre-HD troponin T)/pre-HD troponin T]x100
Left ventricular GLS change (%)	Peak intradialytic stress GLS – baseline GLS
Intradialytic left ventricular stunning	Worsening of systolic function in ≥ 2 segments from baseline to peak intradialytic stress
<i>Secondary</i>	
Systolic BP change (mmHg)	Pre-HD systolic BP – lowest intradialytic systolic BP
Nadir systolic BP (mmHg)	Lowest intradialytic systolic BP
Target weight achievement	Post-HD weight < 1 kg above or below prescribed target weight
Weight difference (kg)	Target weight – post-HD weight
Patient acceptance ^a	Patient-reported willingness to adopt prior treatment type (UF profiling or conventional UF) for future dialysis treatments
Symptoms ^b	Patient-reported 5-point severity Likert scales for cramping, nausea/upset stomach, vomiting, dizziness/lightheadedness, heart palpitations, chest pain, shortness of breath, thirst/dry mouth, headache, itching, restless legs, and tingling/numbness
Time to recovery ^b (hours)	Patient-reported length of time that it takes to recover after HD treatments
Left ventricular EF change (%)	Peak intradialytic stress EF – baseline EF
<i>Exploratory</i>	
Hypoxemia (%)	Starting O ₂ saturation – nadir O ₂ saturation per blood volume monitor
Plasma refill	Hematocrit decrease by $\geq 0.5\%$ per blood volume monitor
Early diastolic left ventricular myocardial velocity [e'] (cm/s)	Peak intradialytic stress e' – baseline e'
Mitral E/e' ratio	Peak intradialytic stress E/e' – baseline E/e'
Tricuspid annulus systolic excursion velocity [S _t] (cm/s)	Peak intradialytic stress S _t – baseline S _t
Left ventricular wall motion score	Peak intradialytic stress score – baseline score
Segmental vs. global worsening among those with WMA	Peak stress _{UF profiling} vs. peak stress _{conventional UF}
Affected segment difference	Peak intradialytic stress – baseline # of affected segments
Vascular access thrombosis	Vascular access thrombosis event

Abbreviations: BP, blood pressure; HD, hemodialysis; GLS, global longitudinal strain; EF, ejection fraction; UF, ultrafiltration.

^a Patient-reported treatment acceptance assessments consider the “last three weeks” of treatments.

^b Patient-reported symptoms and time to recovery consider the “last week” of treatments.

2.6. Sample size calculation

This study is designed as a pilot study to test for efficacy signals. However, with each participant acting as his or her own control in this cross-over design, we are powered to detect clinically and statistically significant differences across arms within patients. With a sample size of 30, we have 80% power to detect a 5.9 mmHg difference in nadir SBP (S.D. 8), a ≥ 0.07 ng/mL troponin T difference (S.D. 0.1) [19], a 2.2% strain difference (S.D. 3) [20], and 4% ejection fraction difference (S.D. 5); all clinically meaningful differences. We have 80% power to detect a 31% absolute difference in the binary endpoint of intradialytic hypotension (event rate = 20%).

3. Discussion

Despite substantial evidence that rapid fluid removal contributes substantially to adverse cardiovascular outcomes among HD patients, we lack evidence-based interventions to reduce these risks. Current approaches to UF risk reduction focus on patient-dependent factors such as adherence to dietary restrictions and willingness to extend HD treatment time. Clinical experience and research demonstrate that patients are averse to such strategies [21,22]. Dialysis patients are heavily burdened by dietary restrictions, medication requirements, and time required for dialysis [22,23]. It is thus not surprising that UF-related harm reduction strategies that entail additional patient demands have limited uptake. Dialysis treatment strategies such as linear UF profiling have been largely ignored, as the focus of UF risk mitigation has been on patient behavior. Identifying strategies that reduce cardiovascular risk and that are acceptable to patients is crucial to improving outcomes.

Randomized studies examining the effect of UF profiling on cardiovascular outcomes are few in quantity and generally of low quality. To our knowledge, only four studies, two of which had trivial sample sizes (N = 8 patients) [24,25], have evaluated UF profiling independent of

sodium profiling. Straver et al. tested a UF profile that removed 40% of total UF in the first hour followed by 20%, 30% and 10% respectively in the second, third and fourth hours of HD [24]. Donauer et al. examined 6 UF profiles (vs. conventional, non-profiled UF) but used each UF profile only once per patient and did not employ washout treatments. Despite these limitations, a trend toward less hypotension and symptoms was observed with a linear UF profile [26]. However, Zhou et al. did not observe differences in BP or achieved UF volume when comparing linear UF profiling to conventional, non-profiled UF. Findings were potentially influenced by the longer HD treatment times (5-h) and resultant lower UF rates [25]. In a recent randomized, single-blind cross-over trial, Leung et al. examined blood volume-monitoring-guided UF biofeedback whereby the UF rate was automatically adjusted in response to the real-time relative blood volume. Compared to control (conventional, non-profiled UF), there was no difference in the rate of symptomatic hypotension or in secondary outcomes including interdialytic weight gain, cardiac troponins and dialysis recovery time across treatment arms.

All prior UF profiling studies defined hypotension as a BP decline plus symptoms. Observational cohort studies have shown that nadir-based definitions (e.g. nadir intradialytic BP < 90 mmHg) have significant associations with mortality, while symptom-based definitions do not [17]. Cardiac imaging studies have demonstrated that asymptomatic BP decline has important structural and functional cardiac consequences. To our knowledge, no study has investigated the effect of UF profiling on nadir intradialytic BPs, cardiac ischemic markers such as troponin and intradialytic global longitudinal strain, or patient-reported outcomes such as intradialytic symptoms and time to recovery.

We will fill this evidence gap with the afore-described double-blinded cross-over clinical trial of HD with linear UF profiling. We have carefully designed the study to account for common challenges in dialysis clinical trials including loss to follow-up due to hospitalizations or dialysis clinic transfer. This study is a 4-phase cross-over trial in which participants are successively alternated between study arms

across 4 phases with intervening washout periods, and treatment order is randomized. Design advantages include: 1) enabling blinding that would not be possible if a single sequence was used for all patients, 2) averting potential period effects by ensuring equal patient numbers in each arm for any given period, and 3) maximizing the ability to gain information in instances of censoring (i.e., if a patient is lost to follow-up after 21 treatments, outcome data for both intervention and control will be available for analysis).

We anticipate that this study will provide key comparative effectiveness data about UF profiling, a pragmatic and low-cost intervention. Nonetheless, we anticipate some potential limitations of the study. First, the study is a single-center study (2 North Carolina dialysis clinics) and includes patients with histories of frequent exposure to higher UF rates. Findings may not generalize to all populations of patients, including patients with UF rates lower than 10 mL/h/kg. Second, carry-over effect is a threat to cross-over studies [27]. We have employed wash-out treatments (3 treatments between each of the 4 phases) to minimize carry-over effect from prior phases. Third, study echocardiograms will be performed 30 min prior to the end of HD under each dialysis strategy, consistent with the published literature [10,18]. In the case of HD with UF profiling, peak UF-induced stress may occur earlier in the treatment coincident with the maximum UF rate. It is possible that associated transient ischemia may not be captured by the echocardiogram. However, data from studies examining serial, peridialytic echocardiograms suggest that transient, HD-induced ischemic changes persist for 2–3 h [28]. Fourth, the patients' treating nephrologists and dialysis nurses and technicians will not be blinded. Finally, recruitment for dialysis studies can be challenging. We will expand recruitment to additional affiliated clinics if recruitment goals are not met. Moreover, we will account for potential dropout by enrolling 36 participants in order to reach our target of 30 participants. Despite these potential limitations, we believe that our study will provide important data regarding the effectiveness of UF profiling in the improvement of UF-related cardiovascular stress.

4. Conclusion

This trial may provide key evidence on the effectiveness of linear UF profiling in the mitigation of risk of harm from higher UF rates. If HD with linear UF profiling is effective at improving intermediate cardiovascular outcomes, UF profiling could be broadly disseminated with little to no impact on dialysis clinic operations.

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Clinical trial registration

Clinicaltrials.gov identifier: NCT03301740.

Disclosures

In the last 2 years, Dr. Flythe has received speaking honoraria from American Renal Associates, American Society of Nephrology, Dialysis Clinic, Incorporated, National Kidney Foundation, and multiple universities as well as research funding for studies unrelated to this project from the Renal Research Institute, a subsidiary of Fresenius Kidney Care North America. Dr. Flythe is on the medical advisory board to NxStage Medical and has received consulting fees from AstraZeneca and

Fresenius Kidney Care North America. Dr. Brunelli is an employee of DaVita Kidney Care. The disclosed organizations had no role in the design, funding or execution of the reported study.

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