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DESIGN OF THE BLOOD PRESSURE IN DIALYSIS (BID) PILOT STUDY

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Abstract

Background—Cardiovascular disease (CVD) is markedly increased among hemodialysis (HD) patients. Optimizing blood pressure among HD patients may present an important opportunity to reduce the disparity in CVD rates between HD patients and the general population. The optimal target pre-dialysis systolic blood pressure (SBP) among HD patients is unknown. Current international guidelines, calling for a pre-dialysis SBP <140 mm Hg, are based on opinion and extrapolation from the general population. Existing randomized controlled trials (RCTs) were small and did not include pre-specified blood pressure targets.

Methods—We describe the design of the Blood Pressure in Dialysis (BID) Study; a pilot, multi-center, RCT where HD patients are randomized to either a target standardized pre-dialysis SBP of 110 to 140 mm Hg or 155 to 165 mm Hg. This is the first study in HD patients to randomize patients to two different SBP targets.

Results—Primary outcomes are feasibility and safety. Feasibility parameters include recruitment and retention rates, adherence with prescribed blood pressure measurements and achievement and maintenance of selected blood pressure targets. Safety parameters include rates of hypotension, other adverse and serious adverse events. We obtain preliminary data on changes in left

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ventricular mass, aortic pulse wave velocity, vascular access thromboses and health related quality of life across study arms, which may be secondary outcomes in the full-scale study.

Conclusions—The data acquired in the pilot will determine the feasibility and safety and inform the design of a full-scale trial, powered for hard outcomes, which may require 2000 participants.

Keywords

blood pressure; cardiac MRI; dialysis; randomized controlled trial

INTRODUCTION

Background

Hypertension is a major risk factor for cardiovascular disease (CVD) in the general population.^{1,2} Hypertension may contribute to the increased risk for CVD morbidity and mortality among hemodialysis (HD) patients.^{3,4} Results from observational studies of blood pressure (BP) and mortality in HD patients suggest a “U” shaped relationship.⁵ Mortality may be increased among HD patients who meet the current systolic blood pressure (SBP) goal of <140 mm Hg.^{6,7} The increased mortality among HD patients with normal SBP versus those with mild to moderate increases in SBP may reflect cardiac dysfunction among the normotensive patients. To date no randomized controlled trials (RCT) have been published, which randomized HD patients to different SBP goals. Therefore, high quality evidence to guide management of BP in HD patients is lacking. We describe the design of a pilot study of two SBP goals in HD patients. This study looks at longitudinal changes in four different types of BP measurements, pre-dialysis routine dialysis unit measurements of SBP (RDUSBPM), pre-dialysis standardized dialysis unit SBP (SDUSBPM), home blood pressure measurements (HBPM) and ambulatory blood pressure (ABPM) in HD patients. We are not aware of another RCT comparing two different SBP targets that uses MRI to assess changes in aortic pulse wave velocity in HD patients.

Study Design

The Blood Pressure in Dialysis (BID) study is an un-blinded, multi-center, pilot RCT. Eligible HD patients are randomized in a 1:1 allocation to a SDUSBPM goal of 110-140 mm Hg or 155-165 mm Hg. We plan to achieve the assigned targets by each patient's post-randomization month and maintain it through post-randomization month 12. The organization of the study is shown (Figure 1).

Outcomes of the BID Pilot Study

The primary outcomes are to assess our ability to recruit and retain participants and determine the feasibility and safety of achieving and maintaining the assigned SBP in each arm over the one-year intervention period. We also assess the differences in the changes from baseline to the end of the one-year intervention in left ventricular mass (LVM), aortic pulse wave velocity (APWV), vascular access thromboses and health related quality of life (HRQOL) across study arms.

METHODS

Human Subjects

Subjects (n=120) are recruited from dialysis units affiliated with the University of New Mexico, Tufts University, Medical University of South Carolina, University of Pittsburgh, Satellite Health Care and DaVita Boston. The racial/ethnic mix of eligible patients in the

participating units is approximately African American (27%), American Indian (7%), Asian (6%), Hispanic (36%) and non-Hispanic white (21%).

Eligibility Criteria

We review pre-dialysis routine dialysis unit measurements of SBP (RDUSBPM) and medical records to identify subjects meeting the eligibility criteria (Table 1). A two-week averaged SDUSBPM ≥ 155 mm Hg is the SBP criterion for randomization. If the two-week averaged SDUSBPM is <155 mm Hg, anti-hypertensive medications (AHT) are back titrated.

Blood Pressure Measurements (BPM)

There is controversy about which BPM should guide therapy in practice and in the full-scale study. RDUSBPM do not follow American Heart Association (AHA) guidelines, are not standardized across facilities and exhibit significant intra- and inter-patient variability.⁸ In a cross-sectional study, the mean intra-individual difference between pre-dialysis RDUSBPM and SDUSBPM was 14.2 mm Hg and the individual difference exceeded 10 mm Hg in 50% of participants.⁹ Studies have shown that HBPM and ABPM exhibit less variability and are stronger predictors of clinical outcomes than RDUSBPM.^{9,10} However, Zoccali et al. demonstrated that the average of 12 RDUSBPM was as strong a predictor of left ventricular hypertrophy (LVH) as ABPM.¹¹ Conversely, Agarwal et al. reported that RDUSBPM and SDUSBPM were significantly weaker than home blood pressure measurements (HBPM) and ambulatory blood pressure (ABPM) as predictors of LVH¹² and all-cause mortality.¹³ ABPM monitoring can be cumbersome, disturb sleep patterns and be associated with reduced physical activity and poor adherence.¹² Due to uncertainty about patient adherence with HBPM and ABPM, SDUSBPM will guide therapy in the BID Pilot. We will also obtain HBPM and ABPM to assess patient and staff adherence with these measures, compare BP values and intra-patient variability in BP, and relationships with cardiac parameters. These results will inform which measure will be used in the full-scale study.

Dialysis Unit BP Measurements

SDUSBPM is measured pre-dialysis, in accord with AHA guidelines after five minutes of rest. These measures are taken in all centers using the auto-inflating oscillometric LifeSource 767 PV or 789 devices with the appropriate cuff attached. Participants do not eat, smoke, consume caffeine or engage in vigorous activity in the 30 minutes prior to the SDUSBPM. Arteriovenous fistulas or grafts are not cannulated and if a participant is dialyzed with a catheter the bloodlines are not connected until after the pre-dialysis SDUSBPM is measured. RDUSBPM are obtained during and after dialysis in accord with usual practice.

Home Blood Pressure Measurements (HBPM)

Participants take their HBPM in accord with AHA guidelines, the morning and evening on the day after the midweek dialysis. In order to optimize consistency all HBPM are obtained using auto-inflating oscillometric LifeSource UA-767, 767 PV or 789 devices. The day after the midweek treatment is chosen because a prior study, in which patients took twice daily readings for a week, showed that the systolic and diastolic BP obtained the morning after the mid-week HD session correlated most strongly with the weekly average BP.¹⁴

Ambulatory Blood Pressure Measurements (ABPM)

ABPM is performed during a 44-hour mid-week inter-dialytic period once during the screening period and quarterly thereafter. ABPM is performed using a SpaceLabs 90207 ABP monitor in all study participants who obtain these measurements. The study coordinator places the monitor on the participant's non-access arm post-dialysis. We record

BPM every 30-minutes between 0600h and 2200h and every 60-minutes between 2200 and 0600h. The schedules for SDUBPM, HBPM and ABPM are shown in Table 2.

Rationale for SDUSBPM Goal of 110-140 mm Hg or 155-165 mm Hg

The lower BP goal (SBP <140 mm Hg) is consistent with current K/DOQI-US, CARI-Australia, UK and KDIGO guidelines. In order to ensure adequate separation in the blood pressures obtained in the intensive versus usual arms of BID we set the lower bound of the higher goal 15 mm Hg above the upper bound of the lower goal. Separation of target blood pressures is standard practice in the design of clinical trials of different blood pressure targets. This design was used in the Frequent Hemodialysis Network (FHN) study¹⁵ and the Hypertension Optimal Treatment (HOT) trial¹⁶ and is currently being done in SPRINT¹⁷.

Assessment of Cardiac Structure and Function and Measurement of Aortic Pulse Wave Velocity (APWV) by Magnetic Resonance Imaging (MRI)

We assess the relationships of BP with cardiac structure and function by MRI, without contrast, during the baseline period and after the one-year intervention period. We measure the following parameters: (1) left ventricular (LV) end systolic volume; (2) LV end diastolic volume; (3) LV ejection fraction; (4) LVM; and (5) APWV. APWV, an integrated index of vascular structure and function, is an independent predictor of mortality among HD patients. Receiver operator characteristic (ROC) curve analysis indicated a cutoff value of 10.75 m/s with 84% sensitivity, 73% specificity, 87% negative and 72% positive predictive value for CV mortality.¹⁸ Therefore, APWV may improve CVD risk stratification.

Stepped Care Algorithm to Achieve Blood Pressure Targets

Many participants will have two-week averaged SDUSBPM above the targeted range at the first follow-up visit. Interventions to achieve the assigned target are implemented using the stepped care algorithm described below. We anticipate achievement of BP goals by the fourth month of follow-up.

Step 1: Restrict dietary sodium and fluid intake and reduce dialysate sodium

We instruct participants to restrict dietary sodium to 2 grams per day and fluid intake to 1.5 liters per day. Dialysate sodium is reduced to within 2 mEq/L of the most recent serum sodium concentration. Instituting a low or zero sodium gradient dialysate has been associated with decreased thirst, inter-dialytic weight gain and decreased pre-dialysis SBP.¹⁹

Step 2: Challenge Estimated Dry Weight (EDW)

The usual EDW challenge is 0.5 kg, but may be modified if clinically indicated. We observe participants for two weeks after an EDW reduction before instituting another challenge, unless obviously fluid overloaded. Intradialytic hypotension is diagnosed if the SBP falls below 90 mm Hg. To minimize intradialytic hypotension cool dialysate, ultrafiltration profiling and sodium neutral profiling maybe used. Crit-Line™ (Hema Metrics; Salt Lake City UT) may be used to help assess dry weight and optimize volume status.²⁰ There is limited data on the use of other technologies in the assessment of dry weight during hemodialysis. Therefore, Crit-Line is the only equipment we use to estimate dry weight in BID. AHT medications may be given post-dialysis. If intradialytic hypotension persists, we may increase EDW.

Step 3: Up-titrate AHT medications

The study formulary is shown (Table 3). Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are first line therapy due to the high prevalence of cardiomyopathy among dialysis patients. We continue β -adrenergic blocking agents in

participants with a recent myocardial infarction. The titration schedule is a recommendation, not a requirement, and participants may remain on non-formulary AHT medication(s) if there are compelling indication(s). Existing AHT therapy is maximized, if tolerated, before adding a new drug. The choice of therapy after ACEi/ARB is at the physician's discretion. Medication adjustments occur biweekly until the target SBP is reached. We administer AHT medications post-dialysis to minimize intradialytic hypotension and optimize fluid removal. We may modify this if clinically indicated.

Step 4: Extend Treatment Time

If reducing EDW or adjusting AHT medications does not achieve the target SBP we may extend treatment time in 15 minute increments up to 30 minutes. Agreeing to extend treatment time is not an inclusion criterion.

Health Related Quality of Life (HRQOL)

We assess HRQOL using the Quality Metrics SF-36, the FACIT-F Questionnaire²¹ and a question about time to recovery following HD.²² The SF-36 has eight sub-scales, which have been tested extensively for reliability, validity and responsiveness to interventions in HD patients. The FACIT-F consists of 13 items and uses a five-point rating scale. It has excellent internal consistency and test-retest reliability.²³ The HRQOL questionnaires are self-administered during the baseline period and at six and twelve months following randomization. We monitor the number of patients who successfully complete the HRQOL questionnaires.

Assessing Feasibility of Conducting a Full-Scale Trial

Achievement of the following parameters will be considered evidence supporting the feasibility of conducting a full-scale study: (1) 80% of participants in each arm, excluding those who die or are transplanted, complete the study and provide 12 months of data; (2) 75% of participants in each arm obtain the minimum number of SDUSBPM per month; (3) 80% of participants achieve their target SBP within four months; (4) mean separation in pre-dialysis SDUSBPM between treatment arms exceeds 10 mm Hg; (5) rate of intradialytic hypotension in the intensive arm is not more than 20% higher than in the usual arm; and (6) rates of serious adverse events (SAEs) are not greater than those observed in other NIH studies of HD patients. We will consider it feasible to include HBPM and ABPM in the full-scale study if we obtain 66% of these prescribed measurements. Caron et al. and Roth et al. demonstrated that assessment of adherence with study medications is accompanied by substantial error.^{24,25} Therefore, we do not employ pill counts. We assess adherence by asking about medication use at each study visit and by tracking refills of AHT medications.

Safety Monitoring

We conduct study visits weekly during the titration phase (time period from randomization until the BP goal is reached) and biweekly after achieving the BP target. At each visit, we review and assess symptoms that have occurred since the previous visit. The site Principal Investigator renders their opinion on whether a SAE is study-related. The Outcomes Committee adjudicates study relatedness independently. The DCC prepares monthly reports of adverse events (AEs) and SAEs across treatment arms for review by the DSMB. If the rate of intradialytic hypotension in the intensive arm is 20% higher than in the usual arm and if the rates of other AEs and SAEs in each arm do not exceed those in other NIH studies conducted in HD patients then it would appear safe to proceed with the full-scale study.

DISCUSSION

CVD is the leading cause of death among HD patients. The majority of HD patients are hypertensive and treatment of hypertension reduces CVD risk in the general population. Therefore, optimizing BP among HD patients may present an important opportunity to reduce the disparity in CVD rates between HD patients and the general population. Charra et al. reported that hypertension was associated with CVD mortality among HD patients.²⁶ Foley et al. reported that among HD patients each 10 mm Hg rise in mean arterial blood pressure was independently associated with LVH and dilated cardiomyopathy, but surprisingly, decreased mortality.²⁷

Stidley et al. reported that in an observational study with 16,959 patients baseline RDUSBPM <120 mm Hg were associated with increased mortality in the first two years of dialysis, whereas a RDUSBPM >150 mm Hg were associated with increased mortality among patients who survived 3 years.²⁸ In a secondary analysis of the HEMO study, pre-dialysis RDUSBP <120 mm Hg was associated with increased all-cause and CVD mortality.²⁹ Myers et al. reported that the increased mortality associated with low RDUSBPM occurred predominately among diabetic and elderly patients.³⁰ A portion of the benefit observed in the FHN study may be attributable to the reduction in BP in the daily HD arm.¹⁵

Two recent meta-analyses examined the impact of AHT drugs on cardiovascular events and mortality. Heerspink et al. assessed eight RCTs. Administration of AHT agents was associated with significant decreases in cardiovascular events, cardiovascular mortality and all-cause mortality although the mean decrease in SBP was only 4.5 mm Hg.³¹ Agarwal et al. assessed five RCTs. Administration of AHT drugs was associated with a decrease in CVD events.³² None of the trials included in these meta-analyses randomized patients to pre-specified BP targets. Whether the benefits seen in these studies were due to the BP lowering effects of the AHT or other actions cannot be ascertained.

Despite the paucity of RCT data and the results from observational trials, which suggest decreased mortality among HD patients with mild to moderate hypertension, current guidelines call for a pre-dialysis SBP <140 mm Hg. Observational studies are often hindered by limited internal validity and unidentified confounders. Therefore, it is not surprising that the results of observational studies in HD patients have often been refuted by RCTs.³³⁻³⁸ Challenges in conducting a RCT with two different BP targets include difficulty controlling BP in HD patients, disagreement about which BP measurements and levels to target, possible reluctance of patients and their physicians to accept randomization to selected targets, and safety concerns. The BID pilot will determine if these challenges are surmountable.

The BID pilot will answer the following questions: (1) Will patients, their families and health care providers respond favorably to participation? (2) What BP measurements should drive a full-scale study? (3) Will we achieve adequate separation in BP between the two arms? (4) Will the treatment algorithm employed in the pilot achieve the desired BP targets and how long will it take? (5) What percentage of participants will obtain the follow-up cardiac MRI? and (7) What will be the AE and SAE rates in each arm?

Since this is a pilot study, with feasibility and safety as the primary outcomes, it is not powered for hard endpoints. Ideally the full-scale study will be powered for all-cause mortality. To have 80% power at an $\alpha = 0.05$ to detect a 20% difference in mortality across study arms will require approximately 1000 participants in each arm. Identifying the financial resources necessary to conduct a full-scale study powered for all-cause mortality across study arms will likely require significant public-private partnerships. We may also

consider a composite end-point of all-cause mortality, non-fatal myocardial infarction and stroke for the full-scale study.

Changes in LVM, APWV, and HRQOL across study arms may be considered as secondary outcomes in the full scale trial. In the pilot we are obtaining preliminary data on changes in LVM across study arms. We are not aware of any full-length publications, which have reported on a RCT that assessed the impact of targeting two different levels of SBP on LVM in HD patients. Therefore, it is unclear whether there will be a significant difference in the changes in LVM across study arms. However, two studies have assessed the effect of frequent HD on LVM. In each study, frequent HD was accompanied by a reduction in SBP. Culleton et al. conducted a RCT, which compared frequent nocturnal HD to conventional HD.³⁹ The mean difference (95%CI) (frequent- conventional) in pre-dialysis SBP over the six-month intervention period was -11 (-24 to 2) mm Hg. The mean difference in the change in LVM (frequent- conventional) was -15.3 (-29.6 to -1.0)g. In the FHN study, the mean difference (frequent-conventional) in pre-dialysis SBP was -10.1(-14.3 to -6.0) mm Hg. The mean difference (frequent-conventional) in change in LVM was -13.8 (-21.8 to -5.8) g. Based on the results of these studies the BID Pilot has only ~60% power for a two-sided test at 5% alpha level for comparing the changes in LVM across treatment arms.

In summary, given the high prevalence of hypertension and the markedly increased CVD event and mortality rates among HD patients a RCT comparing intensive versus usual therapy of hypertension is warranted. The pilot will assess the safety and feasibility of such a trial and inform its design.

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Figure 1.
Organizational Structure of the BID Pilot Study

Table 1**Inclusion and Exclusion Criteria**

<p>Inclusion Criteria</p> <ol style="list-style-type: none"> 1. For entry into baseline period: two-week average RDUSBPM >155 mm Hg on no AHT medications or <155 mm Hg on 1 AHT medications 2. For randomization: two-week average SDUSBPM 155 mm Hg 3. Age 18 years 4. Thrice weekly HD for 90 days 5. Able to obtain and record weekly HBPM or has a partner willing to do this <p>Exclusion Criteria</p> <ol style="list-style-type: none"> 1. Two- week average, pre-dialysis mid-week RDUSBPM 180 mm Hg on maximal doses of 4 AHT agents 2. Inability to measure SBP in an upper arm 3. Intra or post-dialysis hypotension (RDUSBPM < 90 mm Hg) in past 2 weeks or requiring hospitalization, emergency room visit or the use of midodrine in the past month 4. 1 unscheduled dialysis treatments for congestive heart failure in past 3 months 5. Myocardial infarction, unstable angina, stroke or transient ischemic attack in past 3 months 6. Known history of aortic stenosis (aortic valve area < 1 cm²), > 70% carotid artery stenosis, abdominal aortic aneurysm > 5 cm in diameter or any thoracic aortic aneurysm 7. Arm circumference > 60 cm or < 16 cm 8. Life expectancy <1 year 9. Living donor, kidney transplant, or switch to peritoneal dialysis scheduled within the next year 10. Significant cognitive impairment 11. spKt/V 1.2 in the past 2 months 12. Active liver disease 13. Substance abuse in the past year 14. Contraindication to cardiac MRI at sites performing MRIs 15. Current or planned pregnancy 16. Unwillingness to consent to pregnancy test and use of two forms of contraception if of childbearing potential 17. Suspected poor adherence to study protocol 18. Incarcerated 19. Significant concern about the study expressed by participant's physician 20. Participation in another intervention study 21. Unable to speak or understand English, Spanish, Cantonese or Mandarin 22. Plan to relocate within a year

Table 2**Timing and Frequency of Blood Pressure Measurements**

Blood Pressure Measurement	Target Frequency
SDUSBPM	Pre-dialysis and before vascular access cannulation or connecting blood lines to catheter.
HBPM	Twice daily on the day following the mid-week dialysis treatment, weekly thereafter. Morning HBPM taken between 30 minutes post-awakening and noon; evening HBPM are also obtained.
ABPM	Once during the baseline period and then quarterly

Table 3**BID Study Drug Formulary**

Step	Drug Class	Drug	Dosages	Frequency
1	ACEi	Lisinopril	5-10-20-40 mg	Once daily
1A ^a	ARB	Losartan	25-50-100 mg	Once daily
2	β-Blocker	Metoprolol	25-50-100 mg	Twice daily
2A ^b	β-Blocker	Carvedilol	3.125-6.25-12.5-25 mg	Twice daily
2	Calcium Channel Blocker	Amlodipine	5-10 mg	Once daily
2	Peripheral Alpha Antagonist	Doxazosin	1-2-4-8 mg	Once daily
2	Central Alpha Agonist	Clonidine	0.1-0.2-0.3 mg	Two or three times daily
2	Vasodilator	Minoxidil	2.5-10 mg	Daily or twice daily
2	Vasodilator	Hydralazine	10-25-50 mg	Three or four times daily

^aLosartan is substituted in participants who are intolerant of ACEi due to cough, or angioedema.

^bThe choice of β- adrenergic-blocker is based on existing therapy.