Design of the Blood Pressure Goals in Dialysis Pilot Study

Ambreen Gul, MD, Dana Miskulin, MD, Jennifer Gassman, PhD, Antonia Harford, MD, Bruce Horowitz, MD, Joline Chen, MD, Susan Paine, MPH, Edward Bedrick, PhD, John W. Kusek, MD, Mark Unruh, MD, and Philip Zager, MD for the BID Pilot Study Investigators

Abstract: *Background:* Cardiovascular disease (CVD) is markedly increased among hemodialysis (HD) patients. Optimizing blood pressure (BP) 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 predialysis systolic BP (SBP) among HD patients is unknown. Current international guidelines, calling for a predialysis SBP < 140 mm Hg, are based on the opinion and extrapolation from the general population. Existing randomized controlled trials (RCTs) were small and did not include prespecified BP targets. *Methods:* The authors described the design of the Blood Pressure in Dialysis (BID) Study, a pilot, multicenter RCT where HD patients are randomized to either a target-standardized predialysis SBP of 110 to 140 mm Hg or 155 to 165 mm Hg. This is the first study to randomize HD patients to 2 different SBP targets. *Results:* Primary outcomes are feasibility and safety. Feasibility parameters include recruitment and retention rates, adherence with prescribed BP measurements and achievement and maintenance of selected BP targets. Safety parameters include rates of hypotension and other adverse and serious adverse events. The authors obtained preliminary data on changes in left ventricular mass, aortic pulse wave velocity, vascular access thromboses and health-related quality of life across study arms, which may be the secondary outcomes in the full-scale study. *Conclusions:* The data acquired in the pilot RCT will determine the feasibility and safety and inform the design of a full-scale trial, powered for hard outcomes, which may require 2000 participants.

Key Indexing Terms: Blood pressure; Cardiac MRI; Dialysis; Randomized controlled trial. **[Am J Med Sci 2014;347(2):125–130.]**

Hypertension is a major risk factor for cardiovascular disease (CVD) in the general population.[1,2] Hypertension may contribute to the increased risk of 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 BP (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 described the design of a pilot study of 2 SBP goals in HD patients. This study looks at longitudinal changes in 4 different types of BP measurements (BPM), predialysis routine dialysis unit measurements of SBP (RDUSBPM), predialysis standardized dialysis unit SBP (SDUSBPM), home BP measurements (HBPM) and ambulatory BP (ABPM) in HD patients. We are not aware of another RCT comparing 2 different SBP targets that uses magnetic resonance imaging (MRI) to assess changes in aortic pulse wave velocity (APWV) in HD patients.

Study Design

The Blood Pressure in Dialysis (BID) Study is an unblinded, multicenter, pilot RCT. Eligible HD patients are randomized in a 1:1 allocation to an SDUSBPM goal of 110 to 140 mm Hg or 155 to 165 mm Hg. We planed to achieve the assigned targets by each patient's postrandomization month and maintain it through postrandomization month 12. The organization of the study is shown in 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 1-year intervention period. We also assessed the differences in the changes from baseline to the end of the 1-year intervention in left ventricular mass (LVM), APWV, vascular access thromboses and heath-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 Healthcare 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 reviewed predialysis RDUSBPM and medical records to identify subjects meeting the eligibility criteria (Table 1). A 2-week averaged SDUSBPM ≥ 155 mm Hg is the SBP criterion for randomization. If the 2-week averaged SDUSBPM is < 155 mm Hg, antihypertensive medications (AHT) are back titrated.

From the Department of Medicine (AG, AH, BH, EB, PZ), University of New Mexico, Albuquerque, New Mexico; Department of Medicine (DM), Tufts University, Boston, Massachusetts; Department of Quantitative Health Sciences (JG), Cleveland Clinic Foundation, Cleveland, Ohio; Department of Medicine (JC), Boston University, Boston, Massachusetts; Dialysis Clinic, Inc (SP, PZ), Quality Management, Albuquerque, New Mexico; National Institutes of Health (JWK), NIDDK, Bethesda, Maryland; and Department of Medicine (MU), University of Pittsburgh, Pittsburgh, Pennsylvania.

Submitted July 26, 2012; accepted in revised form November 12, 2012.

Supported by Dialysis Clinic, Inc, and NIDDK: Grant number R01-DK083424-01.

Presented at the Western Regional Meeting, Carmel, CA, January 27, 2012.

A. Gul, D. Miskulin, J. Gassman, A. Harford, B. Horowitz, J. Chen, S. Paine, E. Bedrick, and J.W. Kusek have no conflicts of interest to disclose. M. Unruh disclosures: Baxter Healthcare Medical Advisory Board CRRT, 2009; Abbot, 2010; Sigma-Tau, 2010; UCB 2010, 2011; Mitsubishi, 2012; Investigator initiated grants from Baxter, Satellite and DCI in the past 3 years. P. Zager disclosures: DCI employee; Member, Medical Advisory Board of Amgen, Affymax.

The authors have no financial or other conflicts of interest to disclose.

Correspondence: Philip Zager, MD, Department of Medicine, University of New Mexico, 1500 Indian School Road NE, Albuquerque, NM 87102 (E-mail: pzag@unm.edu).

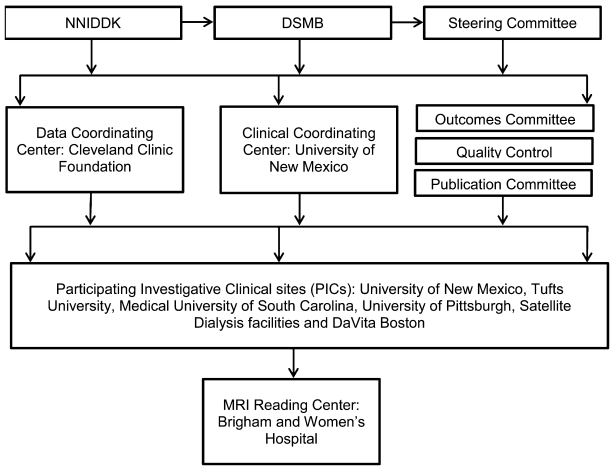

FIGURE 1. Organizational structure of the BID Pilot Study.

BP Measurements

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 interpatient variability.[8] In a cross-sectional study, the mean intraindividual difference between predialysis RDUSBPM and SDUSBPM was 14.2 mm Hg and the individual difference exceeded 10 mm Hg in 50% of the 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[11] demonstrated that the average of 12 RDUSBPM was as strong a predictor of left ventricular hypertrophy (LVH) as ABPM. Conversely, Agarwal et al[12] reported that RDUSBPM and SDUSBPM were significantly weaker than HBPM and ABPM as predictors of LVH and all-cause mortality.[13] ABPM monitoring can be cumbersome, disturb sleep patterns and be associated with reduced physical activity and poor adherence.[12] Because of uncertainty about patient adherence with HBPM and ABPM, SDUSBPM will guide therapy in the BID Pilot. We obtain HBPM and ABPM to assess patient and staff adherence with these measures. We assess the relationship of the absolute BP values and their intra-patient variability to cardiac parameters measured by MRI. These results will inform which measure will be used in the full-scale study.

Dialysis Unit BP Measurements

SDUSBPM is measured predialysis, in accordance with AHA guidelines after 5 minutes of rest. These measures are taken in all centers using the auto-inflating oscillometric LifeSource 767 PV or 789 devices (A&D Company, Limited for A&D Engineering, Inc, San Jose, CA) with the appropriate cuff attached. Participants do not eat, smoke, consume caffeine or engage in vigorous activity in the 30 minutes before the

TABLE 1. Inclusion and exclusion criteria

Inclusion criteria
For entry into baseline period: 2-week average RDUSBPM > 155 mm Hg on AHT medications or <155 mm Hg on ≥ 1 AHT medications
For randomization: 2-week average SDUSBPM ≥ 155 mm Hg
Age ≥ 18 years
Thrice weekly HD for ≥ 90 days
Able to obtain and record weekly HBPM or has a partner willing to do this
Exclusion criteria
Two-week average, predialysis midweek RDUSBPM ≥ 180 mm Hg on maximal doses of ≥ 4 AHT agents
Inability to measure SBP in an upper arm
Intra- or postdialysis hypotension (RDUSBPM < 90 mm Hg) in the past 2 weeks or requiring hospitalization, emergency room visit or the use of midodrine in the past month
≥ 1 unscheduled dialysis treatments for congestive heart failure in the past 3 months
Myocardial infarction, unstable angina, stroke or transient ischemic attack in the past 3 months
Known history of aortic stenosis (aortic valve area < 1 cm^2), >70% carotid artery stenosis, abdominal aortic aneurysm > 5 cm in diameter or any thoracic aortic aneurysm
Arm circumference > 60 cm or < 16 cm
Life expectancy < 1 year
Living donor, kidney transplant or switch to peritoneal dialysis scheduled within the next year
Significant cognitive impairment
spKt/V ≤ 1.2 in the past 2 months
Active liver disease
Substance abuse in the past year
Contraindication to cardiac MRI at sites performing MRIs
Current or planned pregnancy
Unwillingness to consent to pregnancy test and use of 2 forms of contraception if of childbearing potential
Suspected poor adherence to study protocol
Incarcerated
Significant concern about the study expressed by participant's physician
Participation in another intervention study
Unable to speak or understand English, Spanish, Cantonese or Mandarin
Plan to relocate within a year