BP in Dialysis: Results of a Pilot Study

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ABSTRACT

The optimal BP target for patients receiving hemodialysis is unknown. We randomized 126 hypertensive patients on hemodialysis to a standardized predialysis systolic BP of 110–140 mmHg (intensive arm) or 155–165 mmHg (standard arm). The primary objectives were to assess feasibility and safety and inform the design of a full-scale trial. A secondary objective was to assess changes in left ventricular mass. Median follow-up was 365 days. In the standard arm, the 2-week moving average systolic BP did not change significantly during the intervention period, but in the intensive arm, systolic BP decreased from 160 mmHg at baseline to 143 mmHg at 4.5 months. From months 4–12, the mean separation in systolic BP between arms was 12.9 mmHg. Four deaths occurred in the intensive arm and one death occurred in the standard arm. The incidence rate ratios for the intensive compared with the standard arm (95% confidence intervals) were 1.18 (0.40 to 3.33), 1.61 (0.87 to 2.97), and 3.09 (0.96 to 8.78) for major adverse cardiovascular events, hospitalizations, and vascular access thrombosis, respectively. The intensive and standard arms had similar median changes (95% confidence intervals) in left ventricular mass of −0.84 (−17.1 to 10.0) g and 1.4 (−11.6 to 10.4) g, respectively. Although we identified a possible safety signal, the small size and short duration of the trial prevent definitive conclusions. Considering the high risk for major adverse cardiovascular events in patients receiving hemodialysis, a full-scale trial is needed to assess potential benefits of intensive hypertension control in this population.

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The Kidney Disease Outcomes Quality Initiative guideline recommending a predialysis systolic BP (SBP) <140 mmHg in patients receiving hemodialysis (HD)[1] is on the basis of expert opinion.[2] Although hypertension control decreases mortality in the general population,[3] observational studies in patients on HD have found increased mortality among those with SBP≤140 mmHg.[4–9] Foley *et al.*[10] and the Frequent Hemodialysis Network (FHN) Study Group reported that a decrease in SBP was associated with a decrease in left ventricular mass (LVM).[11] However, reducing predialysis SBP may increase the frequency of intradialytic hypotension (IDH),[12,13] major adverse cardiovascular events (MACE),[14,15] and vascular access thromboses (VAT).[16]

In a meta-analysis of randomized, controlled trials (RCT) in patients receiving dialysis, antihypertensive therapy was associated with improved survival,

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although the pooled decline in SBP was only 5 mmHg.[17] In the Dry Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) Study, a 1 kg decrease in mean estimated dry weight at 8 weeks was accompanied by a mean 6.6 mmHg decline in SBP.[18] However, the short duration of the trial precluded assessing effects on clinical outcomes.

There is uncertainty regarding the optimal BP level and type of measurement. Predialysis SBP may be inferior to home BP measurements (HBPM) and ambulatory BP monitoring (ABPM) in predicting clinical outcomes.[19,20] However, the long-term adherence of patients on HD with requirements for repeated HBPM and ABPM is unknown.

Recent trials in high-risk patients, without ESRD, present strong evidence of equipoise. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, targeting an SBP<120 mmHg did not reduce MACE in patients with diabetes and was associated with increased hospitalization.[21] In contrast, in the Systolic Blood Pressure Intervention Trial (SPRINT), conducted in high-risk nondiabetic patients, including those with an eGFR of 20–60 ml/min per 1.73 m^2, intensive control of SBP reduced all-cause mortality and MACE.[22] ACCORD and SPRINT relied primarily upon measurements of clinic BP.

The primary objectives of the BP in Dialysis (BID) Pilot Study were to assess the feasibility and safety of treating hypertensive patients receiving HD to a standardized predialysis SBP of 110–140 mmHg (intensive arm) versus 155–165 mmHg (standard arm) and to inform the design of a full-scale RCT. Assessing changes in LVM was a secondary objective.

RESULTS

Participation Rates and Disposition

Approximately 45% of potentially eligible patients approached agreed to participate. A Consolidated Standards of Reporting Trials diagram depicts the flow of consented participants (Figure 1). We randomized 126 (45%) of the 281 participants who entered baseline, to intensive (n=62) and standard (n=64) treatment arms. The large number of dropouts during baseline reflected SBPs<155 mmHg despite back-titration of antihypertensive medications, frequent IDH, or voluntary withdrawal (Supplemental Table 2). Median follow-up was 365 days (10th and 90th percentiles, 291 and 392 days). There were four deaths in the intensive and one in the standard arm, two renal transplants in each arm, and missing cardiac magnetic resonance imaging (MRI) in six and seven participants in the standard and intensive arms, respectively. The intervention was stopped for safety concerns in one participant in the standard arm (ischemic stroke) and one in the intensive arm (repeated hospitalizations for chest pain and uncontrolled hypertension).

Study Participants

Baseline demographic and clinical characteristics of randomized participants were similar across treatment arms (Table 1).

Significance Statement

The SPRINT trial demonstrated benefit of intensive control of blood pressure (BP) in high-risk, non-dialysis patients, but the optimal BP in hemodialysis patients is uncertain due to the lack of randomized clinical trial (RCT) data. We performed a pilot RCT of intensive versus standard BP control to assess the feasibility and safety of a full-scale RCT. During months 4-12 the average difference in systolic BP across arms was 12.9 mm Hg. Although not powered for outcomes, we identified a potential safety signal: hospitalizations, vascular access thromboses, and intradialytic hypotension were more frequent in the intensive arm. These results support the need for a full-scale study to determine definitely the effects of intensive BP control on clinical outcomes in hemodialysis patients.

Mean age was 56.0±12.8 years, 46.8% were black, 54.1% had diabetes as cause of ESRD, 72.2% were dialyzed with an arteriovenous fistula, and the average treatment time was 218.7±27.8 minutes. Demographic and clinical characteristics of those randomized versus those enrolled but not randomized are shown (Supplemental Table 4). Age, race, and causes of ESRD were similar among randomized versus nonrandomized participants. Hispanics were more common among randomized participants.

Adherence with BP Measurements

Tables summarizing adherence with prescribed standardized dialysis unit BP measurements (SDUBPM) and HBPM are included in Supplemental Tables 5 and 7. We obtained ≥4 SDUBPM in 97%, 91%, 86%, and 75% of participants in months 1, 4, 8, and 12, respectively. However, in the same months, we obtained ≥1 HBPM in only 82%, 73%, 68%, and 62% and ≥4 HBPM in 36%, 33%, 25%, and 22%. We obtained ABPM in only 32%, 29%, 28%, and 58% of participants in quarters 1, 2, 3, and 4, respectively.

SBP

At baseline, 6, and 12 months, mean SBP in the intensive and standard arms was 159.7, 144.2, and 146.4 mmHg, and 159.9, 156.2, and 156.6 mmHg, respectively. Figure 2A shows the fitted values for 2-week moving averages of SDUBPM with 95% confidence intervals (95% CI), computed using a restricted cubic spline model. In the standard arm, the 2-week moving average SBP did not change significantly during the intervention period (horizontal line fits within the confidence band). In contrast, in the intensive arm the fitted 2-week average SBP decreased from 160 mmHg at baseline to 143 mmHg at 4.5 months. Separation in SBP between the arms was maintained from 2 months until the end of the study. Separation was greatest (14 mmHg) at 4.5 months. During months 4–12, mean separation in SBP between arms was 12.9 mmHg. The overall pattern of the fitted values for 2-week moving averages of SDUBPM and morning home SBP was similar (Figure 2B). Overall, the predialysis SBP was 6.1± 0.7 mmHg higher than the home SBP. We estimated within-subject SDs for SBP obtained from SDUBPM immediately

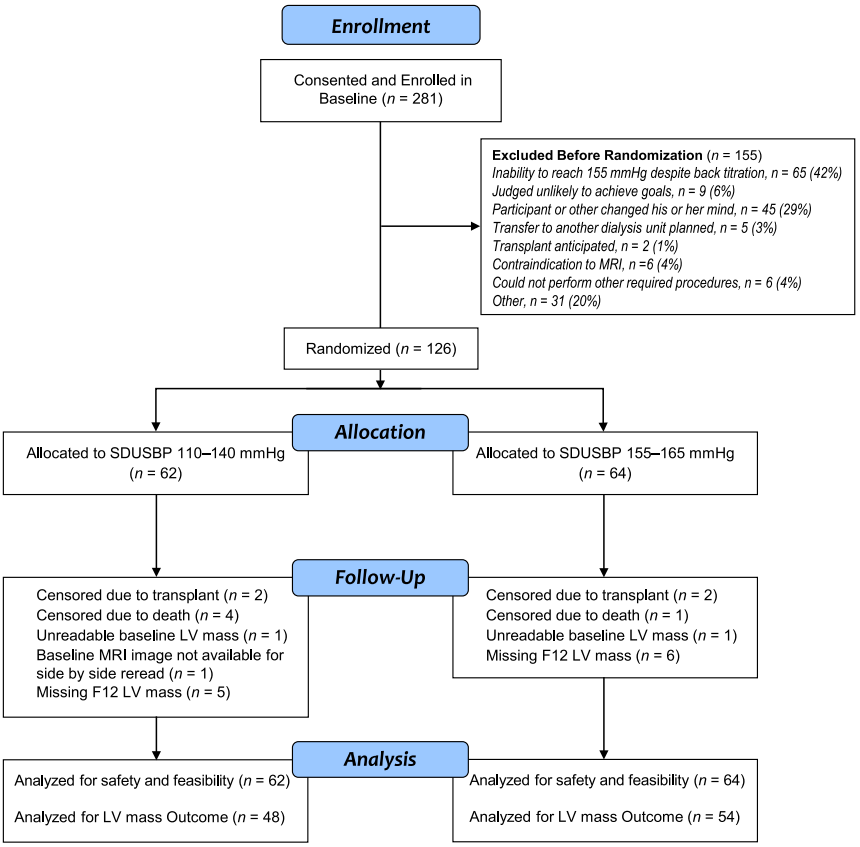


Figure 1. Consort diagram showing participant flow from enrollment to randomization, follow-up, and analysis. F12, month 12 post randomization; LV, left ventricular; SDUSBP, standardized dialysis unit systolic blood pressure.

before the midweek dialysis and HBPM taken the following morning using a linear mixed model in SAS 9.4. We obtained estimates of 14.3 and 16.9 mmHg for within-subject SDs for SBP obtained in the dialysis unit and at home, respectively, using a likelihood ratio test ($P<0.001$) as described by Rhorscheib *et al.*[23]

The mean number of antihypertensive medications, by month, in each arm is shown in Figure 2C. The number of antihypertensive medications was greater in the intensive versus standard arm at baseline (2.9 versus 2.4), 6 months (3.5 versus 2.5), and 12 months (3.5 versus 2.5). The percentage of participants who were prescribed angiotensin converting enzyme inhibitors or angiotensin receptor blockers was higher in the intensive versus standard treatment arms (Figure 2C).

Postdialysis Weight and Interdialytic Weight Gain by Treatment Arm

During the intervention, postdialysis weight, expressed as least square means and 95% CI, decreased by 1.05 (95% CI, −1.55 to −0.55; $P<0.001$) kg in the standard arm but increased by 1.13 (95% CI, 0.60 to 1.66; $P<0.001$) kg in the intensive arm. Interdialytic weight gain after a 2-day interval decreased by 0.20 (95% CI, −0.30 to −0.10; $P<0.001$) kg and by 0.25 (95% CI, −0.35 to −0.15; $P<0.001$) kg in the intensive and standard arms, respectively. After a 3-day interval, interdialytic weight gain decreased by 0.10 (95% CI, −0.23 to 0.04; $P=0.16$) kg and 0.19 (95% CI, −0.32 to −0.06; $P=0.003$) kg in the intensive and standard arms, respectively. There were no significant changes in treatment time in either arm.

Safety Outcomes

There were four deaths in the intensive arm: one acute myocardial infarction, one cardiac arrhythmia, one vascular access hemorrhage, and one lung cancer. There was one death in the standard arm which was attributed to a combination of stroke, acute myocardial infarction, and heart failure. The incidence rate ratios (IRR) were 1.18 (95% CI, 0.40 to 3.33; $P=0.78$); 1.61 (95% CI, 0.87 to 2.97; $P=0.13$); 3.09 (95% CI, 0.96 to 8.78; $P=0.06$); and 0.90 (95% CI, 0.51 to 1.58; $P=0.72$) for MACE, all-cause hospitalizations, VATs, and emergency room visits (Table 2). The hazard ratios (HR) for time to first and to recurrent events are shown (Table 2).

Intradialytic Events and Symptoms

The frequency of IDH requiring intervention was similar in the intensive versus standard arm (IRR, 1.29; 95% CI, 0.86 to 1.94; $P=0.22$). The IRR and HR for other intradialytic events are summarized in Table 3. The IRRs for any intradialytic event

Table 1. Baseline characteristics of participants

Characteristic	Intensive Treatment Arm (*n*=62) *n* (%) or mean±SD	Standard Treatment Arm (*n*=64) *n* (%) or mean±SD	*P* Value
Age, yr	56.7±14.5	55.3±10.8	0.55
Men	32 (51.6)	39 (60.9)	0.37
Race			0.85
Native American, Aboriginal Canadian/Alaskan	4 (6.5)	2 (3.1)	
Asian	4 (6.5)	4 (6.3)	
Black, African	30 (48.4)	29 (45.3)	
White	22 (35.5)	28 (43.8)	
More than one race, part Native American	1 (1.6)		
Unknown or not reported	1 (1.6)	1 (1.6)	
Hispanic ethnicity	21 (33.9)	23 (35.9)	0.85
Cause of ESRD			0.68
Diabetic nephropathy	30 (50.9)	36 (57.1)	
Hypertensive nephrosclerosis	22 (37.3)	17 (27.0)	
GN	4 (6.8)	6 (9.5)	
Other	3 (5.1)	4 (6.4)	
Vascular access			0.77
Arteriovenous graft	11 (17.7)	11 (17.2)	
Arteriovenous fistula	46 (74.2)	45 (70.3)	
Central venous catheter	5 (8.1)	8 (12.5)	
Years on dialysis (from most recent dialysis start)	3.1±2.4	3.5±2.8	0.39
BMI, kg/m^2	28.1±7.0	27.1±5.8	0.38
Last baseline 2 wk running mean SBP	161.1±9.8	160.5±11.9	0.76
Last baseline 2 wk running mean DBP	79.5±12.2	82.1±12.3	0.24
Treatment time, min	216.8±30.2	220.5±25.4	0.46
FACIT score	30.8±12.9	30.0±12.8	0.76
Charlson index	3.3±1.0	3.3±1.0	0.89
Number of antihypertensive medications	2.9±1.4	2.4±1.1	0.03
History of myocardial infarction	4 (6.5)	5 (7.8)	1.00
History of congestive heart failure	9 (14.5)	9 (14.1)	1.00
History of CVA	4 (6.5)	3 (4.7)	0.72
History of atrial fibrillation	2 (3.2)	1 (1.6)	0.62
LVH (*n*=102)	42 (87.5)	43 (79.6)	0.43

P values for race, cause of ESRD, and ateriovenous access types are from chi-squared test. BMI, body mass index; DBP, diastolic blood pressure; CVA, cerebrovascular accident.

did not differ significantly across treatment arms. However, the HR for recurring events of hypotension, cramps, and nausea/vomiting revealed significant increased risks in the intensive arm.

LVM

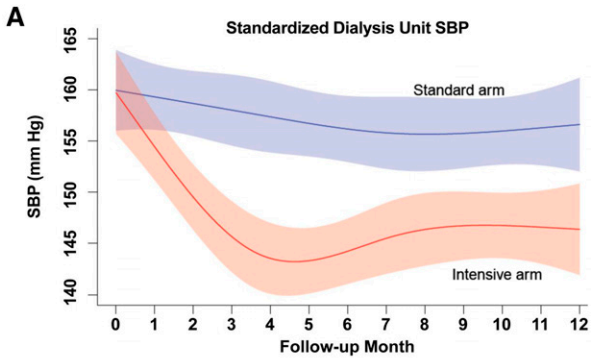
At baseline, 87.5% and 79.6% of participants in the intensive and standard arms, respectively, had left ventricular hypertrophy (LVH) by LVM.[24] In the intensive arm, median LVM, excluding papillary muscle, decreased from baseline 149.5 (95% CI, 115.0 to 184.3) g to 133.2 (95% CI, 110.2 to 168.7) g at month 12 (Table 4). In the standard arm, median LVM increased slightly from baseline 143.8 (95% CI, 120.4 to 176.8) g to month 12, 149.9 (95% CI, 126.8 to 176.0) g. The median differences from baseline to month 12 in the intensive arm −0.84 (95% CI, −17.1 to 10.0) g versus the standard arm 1.4 (95% CI −11.6 to 10.4) g were similar (*P*=0.43).

Health-Related Quality of Life

There were no differences in baseline values and changes in the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scores across treatment arms. Recovery times at baseline and follow-up were similar in each treatment arm (Supplemental Table 8). The physical and mental component scores, respectively, on the Short Form-36 (SF-36) did not differ across treatment arms at baseline or on the last administration (Supplemental Table 9).

DISCUSSION

The BID Pilot demonstrated the feasibility of recruiting and retaining hypertensive patients receiving HD in an RCT of intensive versus standard control of SBP. Similar to ACCORD[21] and SPRINT,[22] the achieved average SBP in the intensive arm was slightly above the target. However, we achieved a sustained ≥10 mmHg separation in both predialysis and morning home SBP, the magnitude required to detect a 20% relative reduction in MACE.[25] The magnitude of the separation in SBP across treatment arms was similar to that in previous



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Month	0	1	2	3	4	5	6	7	8	9	10	11	12
Number of participants with data													
Standard arm	64	64	61	60	60	58	58	57	54	52	51	50	50
Intensive arm	62	62	62	62	60	60	59	59	57	55	53	52	51
Mean number of antihypertensive medications													
Standard arm	2.4	2.5	2.6	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Intensive arm	2.9	3.2	3.3	3.5	3.5	3.4	3.5	3.4	3.5	3.5	3.5	3.5	3.5

Figure 2. Standardized dialysis unit and home SBP and mean number of antihypertensive medications. (A) Fitted values for 2-week moving averages of SBP measured in the dialysis unit. (B) Fitted values for 2-week moving averages of SBP measured at home. (C) Mean number of antihypertensive medications throughout the intervention period.

trials. The African American Study of Kidney Disease achieved an average (SD) BP 128/78 (12/8) mmHg in the intensive versus 141/85 (12/7) mmHg in the standard arm.[26,27] DRIP, an RCT of aggressive ultrafiltration versus usual care, achieved a 6.6 (95% CI, 12.2 to 1.0 mmHg; P=0.02) mmHg reduction in SBP at 8 weeks among patients randomized to aggressive ultrafiltration.[18] In the FHN Trial, the decrease in mean SBP from baseline to 12 months was 10.1 (95% CI, 6.0 to 14.3) mmHg greater in the six versus three times weekly HD arm.[10]

BID encouraged site investigators to challenge estimated dry weight as the initial step in reducing SBP. Because many participants were intolerant to or refused these challenges, changes in antihypertensive medications were mainly responsible for achieving separation in SBP across treatment arms. This is similar to the experience in an RCT of atenolol versus lisinopril in which mean postdialysis weight increased by 0.9 kg and decreased by 1.5 kg in the atenolol and lisinopril arms, respectively.[28] However, in DRIP there was a −1 (95% CI, −1.6 to −0.5) kg change in postdialysis weight at 8 weeks in the aggressive ultrafiltration arm, which was the sole intervention.[18] Because DRIP lasted only 8 weeks it did not test long-term feasibility of aggressive ultrafiltration.

Although volume is undoubtedly important, the pathogenesis of hypertension in patients on HD is multifactorial. A German study of 500 hypertensive patients receiving HD used bioimpedance to estimate extracellular volume. Less than 50% of hypertensive participants had evidence of volume expansion.[29] In a recent observational study of patients receiving HD treated in facilities operated by Fresenius Medical Care, sustained fluid overload was strongly associated with increased mortality across BP categories.[30] However, because the study was observational it did not establish causation. Several studies have shown that aggressive ultrafiltration is associated with increased frequency of IDH,[31] VAT,[16] loss of residual renal function,[32] and increased mortality.[33–35]

As in ACCORD[21] and SPRINT,[22] the rate of serious adverse events (SAEs) was higher in the intensive versus the standard treatment arm. BID identified a possible safety signal because deaths, all-cause hospitalizations, and VATs were more frequent in the intensive arm. However, there were no significant differences in the number of patients hospitalized or experiencing VATs. The frequency of MACE or emergency room (ER) visits, respectively, was similar across treatment arms. Overall, hospitalizations in BID were not more frequent than reported by the US Renal Data Systems (USRDS).[36] The frequency of IDH was higher in the intensive versus standard treatment arm. Nevertheless, the frequency of IDH in the intensive arm (3.7%) was lower than in the baseline period of the Hemodialysis (HEMO) study (11.3%),[13] a large United States dialysis provider organization (9.7%),[13] and the conventional (10.9%) and frequent (13.6%) arms of FHN.[10] VATs were more frequent in the intensive versus the standard arm. These results are consistent with data from a subset of HEMO participants, in which low predialysis SBP and frequent IDH were associated with an increase in VAT.[16] In BID, VATs were less common than in the control arm of contemporary prospective trials for arteriovenous grafts[37] and fistulas.[38] However, the increase in VATs in the intensive arm of BID and the daily arm of FHN speaks to the need to ascertain the risk-benefit ratios of these interventions in RCTs powered for all-cause mortality and MACE.

In BID, LVM tended to decrease in the intensive arm and increase in the standard arm but these differences did not attain statistical significance. Although we were underpowered for this outcome, it is possible that targeting a lower SBP may not reduce LVM in hypertensive patients receiving HD dialyzed thrice weekly. Nevertheless, multiple studies have shown that decreases in dialysis unit BP are associated with decreases in LVM.[10,11,39]

We chose predialysis SDUBPM rather than HBPM to guide therapy, in anticipation that adherence with HBPM would be low. Some investigators have postulated that HBPM and ABPM are superior to predialysis BP in predicting LVH.[19,20] However,

Table 2. Hospitalizations and VAT

Event	No. Events/No. Subjects Incidence Rate[a] per Patient Year (95% CI)		IRR (95% CI)	*P* Value	HR[b] of Time to First Event (95% CI)	*P* Value	HR[c] of Recurrent Events (95% CI)	*P* Value
	Intensive Arm (*n*=62)	Standard Arm (*n*=64)						
MACE[d]	11/10 0.20 (0.09 to 0.41)	10/6 0.17 (0.08 to 0.37)	1.18 (0.40 to 3.33)	0.78	1.76 (0.64 to 4.85)	0.27	0.89 (0.30 to 2.66)	0.84
Hospitalization	85/29 1.51 (0.99 to 2.30)	53/25 0.94 (0.60 to 1.46)	1.61 (0.87 to 2.97)	0.13	1.29 (0.76 to 2.21)	0.35	1.66 (1.18 to 2.34)	0.004
VAT	19/10 0.34 (0.18 to 0.66)	7/7 0.11 (0.05 to 0.28)	3.09 (0.96 to 8.78)	0.06	1.54 (0.59 to 4.04)	0.38	2.80 (1.18 to 6.66)	0.020
ER visit	50/30 0.89 (0.59 to 1.34)	55/27 0.99 (0.67 to 1.46)	0.90 (0.51 to 1.58)	0.72	1.24 (0.74 to 2.09)	0.42	0.94 (0.64 to 1.38)	0.74

[a]Calculated using negative binomial regression.
[b]Calculated using Cox proportional hazards regression.
[c]Calculated using Anderson–Gill method in Cox proportional hazards regression.
[d]MACE defined as fatal or nonfatal myocardial infarction, stroke, or hospitalization for congestive heart failure.

the majority of these reports compared only 2 weeks of predialysis BP, 1 week of HBPM, and a single 44-hour ABPM. Moreover, there was considerable overlap in the 95% CI of the area under the receiver operator characteristic curves for predialysis BP, HBPM, and ABPM.[19] Conion *et al.*[40] and Zoccali *et al.*[39] reported that multiple BP readings averaged over a month are as good as ABPM in predicting an increase in LVM.

Strengths and Limitations

BID has several important strengths. It was the first RCT to randomize patients receiving HD to different predialysis SBP targets. Participants were demographically diverse and treated in for-profit and not-for-profit facilities. BP measurements were made in accord with American Heart Association (AHA) guidelines. A National Institutes Health (NIH)–appointed Review Panel and a Data Safety Monitoring Board reviewed the study before its start. An experienced Outcomes Committee (A.S.L. and A.K.S.) adjudicated outcomes. The main limitations relate to the small size and short duration, which constrained statistical power and generalizability, and the lack of an objective tool for assessing volume. Although some may argue that the use of SDUBPM instead of HBPM or ABPM to drive therapy is a limitation,[19,20] the enhanced adherence with SDUBPM likely overrides this potential limitation. The mean age of participants (56.0 years) was slightly lower than that of prevalent patients in the USRDS 2016 Annual Data Report (59.4 years);[41–43] 25% were ≥65 years of age. We did not perform pill counts or HPLC of antihypertensive medication metabolites.[44,45]

Informing the Design of a Full-Scale Trial

In a full-scale trial, it may be necessary to protocolize challenges to postdialysis weights, including use of frequent small decrements;

Table 3. Intradialytic events

Events	No. Events/No. Subjects[a] per 100 Treatments (95% CI)		IRR (95% CI)	*P* Value	HR[b] of Time to First Event (95% CI)	*P* Value	HR[c] of Recurrent Events (95% CI)	*P* Value
	Intensive Arm (*n*=62)	Standard Arm (*n*=64)						
SBP<90 mmHg	332/39 3.67 (2.53 to 5.31)	264/45 2.69 (1.85 to 3.91)	1.36 (0.80 to 2.31)	0.25	0.88 (0.57 to 1.35)	0.56	1.30 (1.10 to 1.52)	0.002
Cramps	641/55 6.74 (5.05 to 8.96)	571/51 5.87 (4.42 to 7.82)	1.15 (0.77 to 1.72)	0.51	1.19 (0.81 to 1.75)	0.37	1.16 (1.04 to 1.30)	0.01
Nausea±vomiting	90/25 0.98 (0.61 to 1.57)	66/29 0.73 (0.44 to 1.17)	1.35 (0.70. 2.63)	0.37	0.89 (0.52 to 1.53)	0.68	1.41 (1.02 to 1.94)	0.04
Dizziness	110/24 1.15 (0.66 to 2.01)	126/23 1.31 (0.75 to 2.27)	0.88 (0.40 to 1.95)	0.76	1.00 (0.56 to 1.78)	>0.99	0.92 (0.71 to 1.19)	0.50
Dyspnea	27/12 0.28 (0.12 to 0.68)	56/11 0.66 (0.28 to 1.50)	0.44 (0.13 to 1.45)	0.18	1.13 (0.50 to 2.57)	0.77	0.50 (0.31 to 0.79)	0.003
Chest pain	11/7 0.12 (0.05 to 0.26)	9/7 0.09 (0.05 to 0.21)	1.27 (0.40 to 4.01)	0.69	1.06 (0.37 to 3.03)	0.91	1.26 (0.52 to 3.04)	0.61
Loss of consciousness	4/4 0.05 (0.02 to 0.12)	1/1 0.00 (0.00 to 0.07)	4.15 (0.46 to 37.12)	0.20	4.18 (0.47 to 37.43)	0.20	4.10 (0.46 to 36.64)	0.21
Seizure	2/1 0.02 (0.00 to 0.19)	1/1 0.00 (0.00 to 0.14)	2.05 (0.08 to 55.05)	0.67	1.05 (0.07 to 16.84)	0.97	2.08 (0.19 to 22.95)	0.55

Includes all events, regardless of whether an intervention was done. Referent group: Standard treatment arm.
[a]Calculated using negative binomial regression
[b]Calculated using Cox proportional hazards regression
[c]Calculated using Anderson–Gill method in Cox proportional hazards regression

Table 4. Effects of intensive versus standard SBP goal on LVM

Variable	Intensive Arm (*n*=48)	Standard Arm (*n*=54)	*P* Value of Differences Across Arms
Baseline median (IQR) LVM (g/m)	149.5 (115.0, 184.3)	143.8 (120.4, 176.8)	0.95
F12 median (IQR) LVM (g/m)	133.2 (110.2, 168.7)	149.9 (126.8, 176.0)	0.19
Median difference (IQR) (g/m^2) baseline minus month 12	−0.84 (−17.1, 10.0)	1.4 (−11.6, 10.4)	0.43

IQR, interquartile range; F12, study visit in month 12 post randomization.

repeated measurements of volume *via* a practical, accurate, and reliable method;[30] and participant agreement to adhere to dialysis prescriptions. Despite their putative advantages, use of HBPM or ABPM to drive therapy would require innovative solutions to ensure adequate adherence. Although SDUBPM added approximately 8 minutes to the treatment time, which some staff and participants found burdensome, adherence was excellent and indicates it could be used in a full-scale trial. Vascular access monitoring should be incorporated into a full-scale trial to minimize risk for VAT. The use of cooled dialysate may be considered to decrease the risk for IDH and VAT.

BID demonstrated the feasibility and safety of conducting a full-scale RCT to test the hypothesis that intensive SBP lowering in patients receiving HD reduces MACEs and all-cause mortality. However, the pilot study did identify a potential safety signal. Although the deaths in the intensive arm did not appear to be protocol related, all-cause hospitalizations, VAT, and IDH, analyzed as recurrent events, were increased in the intensive arm. Given the small size and short duration of BID, these findings represent a safety signal, not a definitive result. Given the high risk for adverse cardiovascular events in patients receiving HD and the potential benefits of intensive SBP lowering observed in SPRINT, conducting a large-scale trial is warranted.

CONCISE METHODS

The study protocol has been previously described in Gul *et al.*[46]

The Study Protocol is currently available at: http://qhsapps.ccf.org/bid/protocol/Protocol.pdf and will become available on the National Institute of Diabetes and Digestive and Kidney Diseases repository website.

Study Population

Each site's institutional review board approved the study. Our goal was to recruit 120 participants from five geographic hubs, which included dialysis units operated by Dialysis Clinic, Inc. (DCI), Centers for Dialysis Care, and DaVita. Eligibility criteria included ≥18 years of age, treatment with HD for ≥3 months, upper arm suitable for measuring BP, and a 2-week average predialysis SBP≥155 mmHg. Exclusion criteria included unscheduled dialysis treatments for congestive heart failure and IDH requiring hospitalization in the 3 months before enrollment.[46]

Baseline Period

Antihypertensive medications were sometimes reduced (back-titrated) to achieve a 2-week average predialysis SBP≥155 mmHg. Comorbidity was classified using the Charlson Index.[47] The FACIT[48] and the recovery question were administered.[49] LVM was measured using MRI. We used web-based randomization with random-sized blocks and stratification by geographic site to ensure unpredictable treatment allocation and balance within sites.

Study Visits

At each study visit, participants were asked if they had a recent hospitalization, ER visit, VAT, or IDH. VAT was defined by the inability to use the access for dialysis due to thrombosis with an urgent need for intervention to restore flow. IDH was defined as an intradialytic SBP<90 mmHg.

BP Control

In planning the study, we were aware of the putative superiority of HBPM and ABPM compared with predialysis BP for predicting outcomes including LVH.[19,20] However, the primary objectives of the BID pilot were to assess the safety, feasibility, and inform the design of a full-scale trial to determine optimal dialysis unit SBP. Also, there is considerable evidence that dialysis unit SBP can predict changes in LVM. Because we had significant concerns about adherence with HBPM and ABPM during a 1-year intervention, the BID investigators and DSMB decided that the possible slightly stronger predictive value of HBPM and ABPM versus SDUBPM would be offset by poorer adherence.

Standardized predialysis BP was measured in accord with AHA guidelines.[50] Although we used SDUBPM to drive therapy, the study protocol included morning and afternoon HBPM the day after each midweek dialysis[46] and (in four geographic hubs) quarterly ABPM.[46] We encouraged site investigators to challenge postdialysis weights as the initial step in attaining the assigned target SBP. This was followed by addition of antihypertensive agents. Blockade of the renin-angiotensin system was the preferred first-line antihypertensive drug therapy, unless there was an indication for a β-adrenergic blocker. The DCI pharmacy provided all study medications.

Assessing Outcomes

We reviewed discharge summaries and coded primary diagnoses using a study-specific checklist. The Outcomes Committee adjudicated all deaths, MACE, VATs, and a random sample of noncardiovascular SAEs. The NIH-appointed Data and Safety Monitoring Board reviewed all SAEs annually. Baseline and 12-month cardiac MRIs were read side-by-side, in blinded fashion, by a cardiologist using a standardized protocol, at Brigham and Women's Hospital (Supplemental Appendix 5). We assessed health-related quality of life by administering the FACIT, recovery question, and SF-36 at baseline and at the end of the intervention.

Statistical Analyses

Feasibility was assessed by number of participants randomized, separation in 2-week running average of predialysis SBP between arms, and participant retention. Prespecified safety outcomes included deaths, all-cause hospitalizations, MACE, VAT, and IDH. We calculated incidence rates with corresponding 95% CIs for all-cause hospitalizations, MACE, and ER visits. Incidence rates were calculated by negative binomial regression from the MASS[51] package in R[52] after using Akaike information criterion and Vuong's test from the PSCI[53] package to eliminate Poisson regression and zero-inflated versions of Poisson and negative binomial regression. We tested for differences across treatment arms by computing HR and corresponding 95% CI with proportional hazards regression for time to first event and for recurring events (Anderson–Gill model).

To assess the longitudinal trends of standardized SBP in each treatment arm we examined 2-week moving averages for each participant. We used a linear mixed model with autoregressive error structure to model trends in SBP moving averages throughout the study. Time was fit using restricted cubic splines to allow for nonlinear trends in the data.[54] To assess changes in LVM by arm, we specified a Wilcoxon–Mann–Whitney rank sum test before testing because the data were skewed. We recognized that the small size of the trial severely constrained our power to detect a difference between arms for change in LVM. We had only 80% power to detect a $\geq$21.5 g difference, which was almost twice the difference observed in the Daily Trial in FHN.[10] Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and R Core Team 2016.52.

For the SF-36 analysis, we compared between-group mean changes in scores from baseline to month 12 for the physical component summary scores and mental component summary scores using linear mixed effects models with unstructured covariance matrix incorporating baseline and 12-month scores for each metric. We adjusted for baseline score, clinical center, and the interactions of these factors with treatment time. ClinicalTrials.gov Identifier: NCT01421771.

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DISCLOSURES

None.

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