Timing of Antihypertensive Medications on Key Outcomes in Hemodialysis: A Cluster Randomized Trial

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Key Points
- Taking BP medications before hemodialysis was not noninferior to holding BP medications for the outcome of intradialytic hypotension.
- Taking BP medications before hemodialysis (rather than holding) reduced the occurrence of uncontrolled hypertension.
- Whether any benefit of holding BP medications on IDH is offset by potential harms related to higher predialysis BP remains to be seen.

Abstract
Background: We conducted this study to examine the effect of taking versus holding BP medications before hemodialysis on intradialytic hypotension (IDH).

Methods: In this cluster randomized trial, each dialysis unit was randomly designated as TAKE or HOLD units. Participants within a TAKE unit were instructed to take all BP medications as prescribed, whereas participants within a HOLD unit were instructed to hold medications dosed more than once daily before hemodialysis. The intervention lasted for 4 weeks. We hypothesized that TAKE would be noninferior to HOLD on the primary outcome of asymptomatic IDH, defined as \( \geq 30\% \) of sessions with nadir systolic BP \( < 90 \) mm Hg, and on the following secondary outcomes: uncontrolled hypertension (predialysis systolic BP \( > 160 \) mm Hg), failure to achieve dry weight, and shortened dialysis sessions.

Results: We randomized 10 dialysis units in a 1:1 ratio to TAKE or HOLD, which included 65 participants in TAKE and 66 participants in HOLD. We did not show that TAKE was noninferior to HOLD for the primary IDH outcome (mean unadjusted difference of 8%; 95% CI, −3% to 19%). TAKE was superior to HOLD for the outcome of uncontrolled hypertension (mean unadjusted difference of −15%, 95% CI, −28% to −1%). TAKE was noninferior to HOLD for the outcomes of failure to achieve dry weight and shortened dialysis sessions.

Conclusions: In this cluster randomized trial that randomized patients to either taking or holding BP medications before hemodialysis, a strategy of taking BP medications dosed more than once daily was not noninferior to holding BP medications for the primary outcome of IDH, but did reduce the occurrence of uncontrolled hypertension. Whether any potential benefit of holding BP medications on reducing IDH is offset by any potential harm related to higher predialysis BP remains to be seen.

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Introduction
High BP is one of the major modifiable risk factors for cardiovascular disease, and >90% of patients on hemodialysis have a high BP (1) requiring pharmacological treatment. Treatment of high BP in patients receiving hemodialysis can be limited by intradialytic hypotension (IDH), which affects an estimated 20%–30% of all dialysis sessions (2). IDH is variably defined as a decrease in BP during the hemodialysis procedure, with or without associated symptoms such as abdominal discomfort, nausea, or dizziness (3). Numerous studies have shown that IDH is associated with adverse events, including decreased quality of life, inadequate dialysis, and death (4–7).

Clinical practice guidelines state that taking BP medications the morning before a dialysis session can contribute to the occurrence of IDH (8), and many patients indicate that they purposely hold BP medications before dialysis (9–11). Yet the effect of BP medications on IDH is not clear, and the practice could lead to adverse events, such as tachyarrhythmias stemming from a missed beta-blocker doses or prolonged elevations in BP. For example, although administering more BP medications can reduce...
predialysis systolic BP, in at least two separate studies, more BP medications did not increase the frequency of IDH (12,13).

We conducted the Timing of Antihypertensive Medications on Key Outcomes in Hemodialysis (TAKE-HOLD) study to examine the effect of taking versus holding BP medications on IDH. To minimize crossover between treatment groups, we conducted a cluster randomized trial where participating dialysis units were randomly designated as TAKE or HOLD units. Study participants within a TAKE unit were instructed to take all BP medications as prescribed, whereas participants within a HOLD unit were instructed to hold BP medications dosed more than once daily on the morning of the hemodialysis session. We hypothesized that the TAKE strategy would be noninferior to the HOLD strategy on the primary outcome of asymptomatic IDH. We also examined the following secondary outcomes: uncontrolled hypertension, failure to achieve dry weight, and shortened dialysis sessions.

Materials and Methods

This study was approved by a Stanford Institutional Review Board panel (protocol 43790), was adherent to the Declaration of Helsinki, and was registered on ClinicalTrials.gov (NCT03327909) on January 11, 2017.

Selection and Randomization of the Hemodialysis Units

TAKE-HOLD was originally planned as a cluster randomized trial, wherein all patients within a participating unit would be instructed to either take or hold any BP medications dosed more than once per day on the morning of the hemodialysis session, depending on the randomized treatment group of the dialysis unit; individual patients within a dialysis unit would be allowed to opt out of the intervention for any reason. However, the Institutional Review Board required that we obtain permission from each treating nephrologist and individual participant consent (e.g., “opt in”) for inclusion in the study. Despite being unable to proceed with the opt-out approach, given our prior work showing that dialysis unit staff, covering physicians, or advanced practice providers frequently advise patients on whether to take or hold BP medications (11), we continued with a cluster randomized design to minimize crossover between the treatment groups.

From March 2018 to September 2018, we approached 252 patients identified for inclusion in the study. Despite being unable to proceed with the opt-out approach, given our prior work showing that dialysis unit staff, covering physicians, or advanced practice providers frequently advise patients on whether to take or hold BP medications (11), we continued with a cluster randomized design to minimize crossover between the treatment groups.

From March 2018 to September 2018, we approached 11 dialysis unit medical directors in the Northern California Bay Area for permission to participate in the trial; ten consented (Figure 1). We required that dialysis units have ≥30 patients who would meet the inclusion and exclusion criteria and excluded any units that had a planned unit-level intervention study within 90 days of TAKE-HOLD. Dialysis units were paired by location and size where possible, and randomized in blocks of two in a 1:1 ratio to the TAKE or HOLD group using a computerized random-number generator. Randomization of the dialysis units occurred after we obtained informed consent from each individual participant.

Selection of Individual Participants

We recruited individual participants from July 2018 to November 2019. To be considered for inclusion in the study, participants had to be ≥18 years old and on in-center, thrice weekly hemodialysis. Participants had to be taking at least one BP medication dosed more than once per day. Exclusion criteria included initiation of hemodialysis within the previous 90 days, a cardiovascular event in the previous 90 days, active infection requiring antibiotics, or any factors judged by the treatment team to limit adherence to the intervention (Supplemental Table 1). Among patients who were eligible but declined participation, the most common reason given was an unwillingness to be randomized to one of the two treatment groups, due to prior adverse experience with either taking or holding their BP medications before the hemodialysis treatment session.

Study Procedures

During a 2-week run-in period, we educated participating patients and providers of dialysis care about the upcoming intervention period. We encouraged providers to refrain from changing BP medications, dry weight, or the hemodialysis prescription, with the exception of the potassium bath during the 4-week intervention period, unless required for patient safety. We collected baseline demographics and comorbid conditions during the run-in period from the electronic health record and from participant interview in the dialysis center by a trained member of the study team. Race and Hispanic ethnicity were self-reported. We collected information on serum albumin (g/dl), hemoglobin (g/dl), and Kt/Vurea using the most recent value before the start of intervention period from the
electronic health record. Baseline dialysis session parameters including the BP parameters, treatment time (prescribed and delivered), dry weight, and ultrafiltration were defined as the average value from the 4 weeks before the 2-week run-in period. Intradialytic hypertension was defined as postdialysis systolic BP greater than the predialysis systolic BP by >10 mm Hg and postdialysis systolic BP >140 mm Hg (3).

The intervention period lasted a total of 4 weeks. During this time, all participants were instructed to take their once daily BP medications at night. The intervention, therefore, only applied to medications taken more than once per day. We chose to focus on medications dosed more than once per day because the shorter half-life of these medications would make them more likely to be affected by taking or holding them than medications with a longer half-life. For BP medications dosed more than once per day, participants in TAKE units were instructed to take all BP medications as prescribed, whereas participants in HOLD units were instructed to hold the dose of BP medications before the dialysis session on the morning of dialysis days. For participants in HOLD units, the decision about whether to take any BP medications that had been held was left to the discretion of the patient and/or provider. The following medications were considered dialyzable: benazepril, lisinopril, atenolol, metoprolol, isosorbide dinitrate, isosorbide mononitrate, and minoxidil (14). We assessed adherence to the study intervention during each week of the 4-week intervention period by administering a questionnaire in-person in the dialysis center, or by phone that asked whether the participant took once-daily BP medications in the evening, and whether BP medications dosed more than once daily were skipped before the dialysis session. We followed an intention-to-treat principle during the analysis phase. The study was not blinded. The study intervention was conducted serially for each pair of randomized dialysis units, and the final 4-week intervention period ended on December 14, 2019.

Outcomes

All BP measurements were taken in the dialysis unit as per routine clinical care. The primary outcome was the proportion of participants with ≥30% of dialysis sessions during the 4-week intervention period with asymptomatic IDH, defined as nadir systolic BP <90 mm Hg during the dialysis session (15).

We examined several secondary outcomes, defined as the proportion of participants with ≥30% of dialysis sessions during the 4-week intervention period with: (1) uncontrolled hypertension (i.e., predialysis systolic BP >160 mm Hg); (2) failure to achieve dry weight (i.e., postdialysis weight larger than the prescribed estimated dry weight); and (3) shortened dialysis session (i.e., delivered dialysis treatment time less than the prescribed dialysis treatment time). As a sensitivity analysis, we also used less stringent outcome definitions for failure to achieve dry weight (postdialysis weight greater than the prescribed dry weight by >0.5 kg), and for shortened hemodialysis session (delivered dialysis treatment time less than the prescribed treatment time by >5 minutes).

All outcomes were collected through usual clinical care and ascertained from the electronic health records.

Adverse Events

We asked the treating nephrologist, dialysis staff, and study participants to report emergency department visits, hospitalizations or death during the 4-week intervention period. We also asked for any reports of hypotension or worsening hypertension in the TAKE and HOLD groups, respectively. After completing the intervention in the first four dialysis units, we compared the occurrence of missed hemodialysis sessions, hospitalizations, or any other adverse events overall and by treatment group. No safety concerns were identified.

Statistical Analysis

For the primary outcome, we compared the proportion of patients with ≥30% of dialysis sessions with IDH in TAKE versus HOLD using a generalized linear model with binomial distribution and identity link and a generalized estimating equation approach with an independent correlation matrix to account for clustering by dialysis unit. We computed a 95% confidence interval (95% CI) for the difference in proportions of IDH in TAKE versus HOLD, and a priori decided we would conclude noninferiority of TAKE versus HOLD on the outcome of IDH if the upper end of the confidence interval of the difference in proportions was <10%. In other words, the study was designed to show the TAKE strategy would not result in >10% of participants having the primary outcome compared with the HOLD strategy. Previous trials in the hemodialysis population were designed on the basis of treatment effect estimates of a 20% reduction in outcomes (16,17). We therefore chose a relatively conservative 10% noninferiority margin for our study on the basis of these prior studies and clinical judgement for what would constitute an acceptable noninferiority threshold. The superiority threshold was set at 0%. An analogous statistical approach was used to assess for noninferiority and superiority for each of the secondary outcomes.

We performed a power calculation for the primary outcome. We followed formulas given for noninferiority trials comparing probabilities for two groups (18) and used an adjustment for the clustered design (Variance Inflation Factor) (19). We assumed a type I error of \( \alpha = 0.05 \), 80% power, an intracluster correlation of 0.01, and that a difference in the proportion of IDH between TAKE and HOLD group would be ≤10%. On the basis of these assumptions, and the assumption that we would recruit an average of 30 patients per dialysis unit, we estimated a required sample size of 144 patients per treatment group with five facilities randomized into each group, for an initial target sample size of 300 participants. However, due to lower than expected recruitment from each dialysis unit, we revised our estimate to assume that a difference in the proportion of IDH between TAKE and HOLD group would be ≤13%, which would require an average of 15 patients per dialysis unit, or 75 participants per treatment group for a total of 150 participants.

After the conclusion of the study, we noted some imbalances in baseline variables between the TAKE and HOLD
groups. We therefore conducted post hoc analyses for the primary and secondary outcomes that included an adjustment for baseline proportions with IDH, uncontrolled hypertension, failure to achieve dry weight and shortened dialysis sessions, respectively, and report these as adjusted analyses. We further conducted analyses for the outcomes of IDH and uncontrolled hypertension that included adjustments for the baseline variables of sex, other cardiac conditions, diabetes, needs assistance with ambulation, transfer or activities of daily living, and whether the participant took dialyzable BP medications.

We conducted all analyses using SAS Enterprise Guide Version 7.15 (Cary, NC).

Results

We recruited and analyzed 65 participants from the five dialysis units randomized to the TAKE intervention, and 66 participants from the five dialysis units randomized to the HOLD intervention (Figure 1). Participants in the two treatment groups were similar with respect to demographics, dialysis vintage, comorbid conditions, and baseline serum albumin, hemoglobin, and Kt/Vurea (Table 1). At baseline, a larger proportion of patients in the TAKE group had ≥30% of sessions with IDH and shortened dialysis sessions, whereas a larger proportion of patients in the HOLD group had ≥30% of sessions with uncontrolled hypertension and failure to achieve dry weight.

Participants were taking an average of 2.6 and 3.0 BP medications at baseline in the TAKE and HOLD groups, respectively (Table 2). Once-daily BP medications were used before the start of the trial in 72% of TAKE participants and 77% of HOLD participants. The most commonly used BP medication class was beta-blockers (85% TAKE, 88% HOLD), followed by angiotensin converting enzyme inhibitors or angiotensin receptor blockers (46% TAKE, 56% HOLD), and the calcium channel blocker amiodipine (45% TAKE, 64% HOLD). Nearly half of the study cohort were in both treatment groups reported using vasodilators.

At baseline, 36 out of 65 (55%) participants in the TAKE group reported taking BP medications before dialysis, whereas 18 out of 66 (27%) participants in the HOLD group reported holding one or more BP medications before the dialysis session. A majority of participants in both groups took one or more of their BP medications at night (83% and 89% in the TAKE and HOLD groups, respectively, Table 2).

During the 4-week intervention period, 90%, 92%, 92%, and 90% of participants in the TAKE group and 91%, 90%, 89%, and 85% of participants in the HOLD group were taking once daily medications at night during weeks 1, 2, 3, and 4 of the intervention, respectively, as specified in the protocol. For medications dosed more than once daily, 69%, 68%, 68% and 66% of participants in the TAKE group and 76%, 80%, 77%, and 76% of participants in the HOLD group reported adherence to the assigned intervention during weeks 1, 2, 3, and 4 of the intervention, respectively.

Primary Outcomes

During the 4-week intervention period, 19% of participants in TAKE and 11% of participants in HOLD had ≥30% of sessions with IDH, for a mean unadjusted difference of 8% (95% CI, −3% to 19%) and mean adjusted difference of 6% (95% CI, −2% to 14%; Figure 2). We were therefore unable to conclude that TAKE was noninferior to HOLD with regard to the primary outcome of IDH. The observed intraclass correlation was 0.02. Results were not materially changed after in post hoc analyses that included an adjustment for sex or other baseline variables (Supplemental Table 2).

Secondary Outcomes

During the 4-week intervention period, 39% of TAKE participants and 53% of HOLD had ≥30% of sessions with uncontrolled hypertension, for a mean unadjusted difference of −15% (95% CI, −28% to −1%) and a mean adjusted difference of −10% (95% CI, −18% to −2%). The TAKE strategy was therefore superior to HOLD with regard to uncontrolled hypertension. Results were not materially changed after in post hoc analyses that included an adjustment for sex or other baseline variables (Supplemental Table 2).

The proportion of patients with failure to achieve dry weight and shortened dialysis sessions during the 4-week interventions were similar in TAKE and HOLD. In adjusted analyses, we were able to conclude that TAKE was noninferior to HOLD for failure to achieve dry weight and shortened dialysis sessions (Figure 2). Results were not materially changed using the less stringent definitions for these outcomes (Supplemental Table 3).

Safety Outcomes

During the 4-week intervention, 1547 hemodialysis sessions were completed out of 1616 expected (96%). Among the 69 missed hemodialysis sessions, 25 were prearranged absences. The remaining 44 missed hemodialysis sessions occurred in 22 participants: 13 participants were listed as “no-shows” without reason (four in TAKE, nine in HOLD) and nine participants were hospitalized. Among the four TAKE (6%) participants hospitalized during the intervention period, two were due to pneumonia, one was due to fever, and one was due to a non-ST elevation myocardial infarction. Among the five HOLD participants (8%) hospitalized during the intervention period, two were due to fluid overload (one of whom transitioned to comfort care and died), one was due to a non-ST elevation myocardial infarction, one was due to hemodialysis access malfunction, and one was due to an elective transcatheter aortic valve replacement. None of the hospitalizations was attributed to the intervention. There were no other deaths during the intervention period.

Discussion

We conducted a cluster randomized trial that assigned participants within a dialysis unit to either take or hold BP medications, dosed more than once per day before the dialysis session. All participants were instructed to take BP medications dosed once daily at night. We did not show that a strategy of taking BP medications was noninferior to a strategy of holding BP medications for the primary outcome of IDH. However, taking BP medications as prescribed was superior to holding BP medications for the secondary outcome of uncontrolled hypertension, defined
Table 1. Baseline characteristics of the timing of antihypertensive medications on key outcomes in hemodialysis study dialysis units and participants

| Characteristics                                      | TAKE     | HOLD    |
|------------------------------------------------------|----------|---------|
| Dialysis units                                       | n=5      | n=5     |
| Cluster size, n                                       |          |         |
| <100 patients                                        | 3        | 3       |
| ≥100 patients                                        | 2        | 2       |
| Number of treating nephrologists, n                  |          |         |
| ≥10                                                  | 1        | 1       |
| 11–16                                                | 2        | 3       |
| 17–25                                                | 2        | 1       |
| Participants                                         | n=65     | n=66    |
| Demographics                                         |          |         |
| Age, y, mean (SD)                                    | 62.5 (13.8) | 60.7 (13.9) |
| Male, n (%)                                          | 43 (66)  | 39 (59) |
| Racial, n (%)                                        |          |         |
| White                                                | 29 (45)  | 39 (59) |
| Black                                                | 4 (6)    | 3 (5)   |
| Asian                                                | 18 (28)  | 16 (24) |
| Other/unknown                                        | 14 (22)  | 8 (12)  |
| Hispanic                                             | 31 (48)  | 38 (58) |
| Insurance status, n (%)                              |          |         |
| Medicare                                             | 34 (52)  | 41 (62) |
| Dual eligible                                        | 18 (28)  | 20 (30) |
| On disability                                        | 10 (15)  | 14 (21) |
| Unemployed                                            | 16 (25)  | 12 (18) |
| Vintage, y, median (IQR)                             | 2.8 (1.4, 4.3) | 2.5 (1.2, 5.5) |
| Cause of ESKD, n (%)                                 |          |         |
| Diabetes                                             | 41 (63)  | 37 (56) |
| Hypertension                                         | 10 (15)  | 15 (23) |
| Glomerulonephritis                                   | 3 (5)    | 2 (3)   |
| Other/unknown                                        | 11 (17)  | 12 (18) |
| Heart failure                                         | 13 (20)  | 17 (26) |
| Hypertension                                         | 61 (94)  | 61 (92) |
| Peripheral arterial disease/amputation               | 9 (14)   | 8 (12)  |
| Other cardiovascular condition                       | 10 (15)  | 19 (29) |
| Diabetes mellitus                                    | 51 (79)  | 45 (68) |
| Smoking history                                       | 24 (37)  | 25 (38) |
| Assistance with ambulation/transfer/ADLs             | 11 (17)  | 15 (23) |
| Laboratory data, g/dl, mean (SD)                     |          |         |
| Serum albumin                                        | 3.9 (0.4) | 3.9 (0.3) |
| Serum hemoglobin                                     | 10.5 (1.2) | 10.5 (1.2) |
| Dialysis adequacy, Kt/Vuera                          | 1.6 (0.2) | 1.5 (0.2) |
| Blood pressure, mm Hg, mean (SD)                     |          |         |
| Predialysis SBP                                       | 149 (19) | 151 (16) |
| Predialysis DBP                                       | 75 (12)  | 76 (11) |
| Postdialysis SBP                                      | 138 (20) | 142 (14) |
| Postdialysis DBP                                      | 70 (12)  | 71 (9)  |
| Sessions with intradialytic hypertension per patient, %, mean (SD) | 11.7 (17.5) | 16.2 (18.5) |
| Treatment time, minutes, mean (SD)                   |          |         |
| Prescribed                                            | 211 (27) | 208 (20) |
| Delivered                                             | 207 (28) | 204 (20) |
| Dry weight, kg, mean (SD)                             | 79.5 (23.8) | 77.0 (16.4) |
| Ultrafiltration, kg, mean (SD)                        | 2.1 (0.9) | 2.3 (0.8) |
| Ultrafiltration rate, ml/min/kg, mean (SD)            | 8.4 (3.9) | 9.2 (3.1) |
| IDH, % of dialysis sessions, median (IQR)             | 8.3 (0, 25.0) | 7.4 (0, 16.7) |
| Number of dialysis sessions, n, mean (SD)             | 11.8 (1.0) | 12.0 (1.1) |
| ≥30% of sessions with:                               |          |         |
| IDH, n (%)                                            | 13 (20)  | 11 (17) |
| Uncontrolled hypertension, n (%)                      | 27 (42)  | 35 (53) |
| Shortened dialysis session, n (%)                     | 56 (86)  | 43 (65) |
| Failure to achieve dry weight, n (%)                  | 46 (71)  | 59 (89) |

IQR, interquartile range; IDH, intradialytic hypotension, defined as nadir systolic blood pressure <90 mm Hg; ADLs, activities of daily living.
as predialysis systolic BP >160 mm Hg. For the secondary outcomes of failure to achieve dry weight and shortened dialysis sessions, taking BP medications as prescribed was noninferior to holding BP medications dosed more than once per day. A majority of participants adhered to the 4-week treatment intervention and we did not observe any other BP-unrelated safety concerns with either treatment arm.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guidelines on the management of cardiovascular disease in patients on hemodialysis state that “antihypertensive drugs should be given preferentially at night, because it may minimize IDH, which may occur when drugs are taken the morning before a dialysis session” (8). Although the guidelines make no mention of whether to hold antihypertensive

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### Table 2. Baseline blood pressure medication use in the Timing of Antihypertensive Medications on Key Outcomes in Hemodialysis study cohort

| Medication                                                                 | TAKE         | HOLD        | MEAN DIFFERENCE (95% CI) | SUPERIORITY THRESHOLD | NON-INFERIORITY THRESHOLD |
|---------------------------------------------------------------------------|--------------|-------------|--------------------------|-----------------------|--------------------------|
| n                                                                         | 65           | 66          |                          |                       |                          |
| Number of blood pressure medications, mean (SD)                         | 2.6 (1.1)    | 3.0 (1.2)   |                          |                       |                          |
| On ≥1 blood pressure medication dosed once daily                        | 47 (72)      | 51 (77)     |                          |                       |                          |
| Takes ≥1 blood pressure medication at night                              | 54 (83)      | 59 (89)     |                          |                       |                          |
| On ≥1 dialyzable blood pressure medication                              | 41 (63)      | 47 (71)     |                          |                       |                          |
| Angiotensin converting enzyme inhibitor/angiotensin receptor blocker     | 30 (46)      | 36 (56)     |                          |                       |                          |
| Dosed once daily                                                         | 25 (39)      | 28 (42)     |                          |                       |                          |
| Lisinopril                                                               | 12 (19)      | 13 (20)     |                          |                       |                          |
| Losartan                                                                 | 15 (23)      | 18 (28)     |                          |                       |                          |
| Beta-blocker                                                             | 55 (85)      | 56 (88)     |                          |                       |                          |
| Dosed once daily                                                         | 3 (5.0)      | 6 (9)       |                          |                       |                          |
| Metoprolol                                                               | 27 (42)      | 32 (50)     |                          |                       |                          |
| Carvedilol                                                               | 22 (34)      | 18 (28)     |                          |                       |                          |
| Labetalol                                                                | 4 (6)        | 6 (9)       |                          |                       |                          |
| Calcium channel blocker                                                  | 31 (48)      | 44 (67)     |                          |                       |                          |
| Dosed once daily                                                         | 28 (43)      | 37 (58)     |                          |                       |                          |
| Amlodipine                                                               | 29 (45)      | 41 (64)     |                          |                       |                          |
| Clonidine                                                                | 8 (12)       | 8 (13)      |                          |                       |                          |
| Vasodilators                                                             | 32 (49)      | 32 (50)     |                          |                       |                          |
| Hydralazine                                                              | 24 (37)      | 23 (36)     |                          |                       |                          |
| Isosorbide dinitrate or mononitrate                                      | 8 (12)       | 7 (11)      |                          |                       |                          |
| Alpha-blocker                                                            | 7 (11)       | 5 (8)       |                          |                       |                          |
| Minoxidil                                                                | 2 (3)        | 8 (13)      |                          |                       |                          |

All values are n (%) unless otherwise indicated.

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![Figure 2](image-url)

**Figure 2.** Effect of TAKE versus HOLD on the specified outcomes, defined as the proportion of participants with ≥30% of sessions with that outcome during the 4-week intervention period. Adjusted values include the baseline proportion of the specified outcomes in the models. 95% CI, 95% confidence interval.
medications, the practice is nonetheless common, with prior studies showing that 54%–85% of patients hold anti-hypertensive medications before dialysis (9,10). We had hypothesized that the TAKE group would be noninferior to the HOLD group with regard to IDH, on the basis of prior studies showing little effect of BP medications on the frequency of IDH. For example, in patients on hemodialysis with uncontrolled hypertension, administering more BP medications reduced predialysis systolic BP from 175 mm Hg to 154 mm Hg, but did not affect the frequency of IDH (12). In another study, 251 patients on hemodialysis were randomly assigned to receive amlodipine 10 mg versus placebo (13), and although the mean predialysis systolic BP was lower during follow-up in the amlodipine group, there again was no significant difference in the frequency of IDH between the groups (7% versus 13%, respectively, $P=0.21$). Physiologic studies suggest that IDH may be related to maladaptive hemodynamic responses to fluid removal during hemodialysis (20), including the inability to increase heart rate irrespective of beta-blocker or other BP medication use (21).

We did not find that the TAKE strategy was noninferior to the HOLD strategy for the primary outcome of ≥30% of sessions with IDH. In the TAKE group, we saw a slight decrease in the proportion of patients with ≥30% of sessions with IDH during the intervention period (19%) compared with baseline (20%). The larger change was in the HOLD group, where the proportion of patients with ≥30% of sessions with IDH decreased from 17% at baseline to 11% during the intervention. However, we found that the TAKE strategy was superior to the HOLD strategy with respect to uncontrolled hypertension, defined as predialysis systolic BP >160 mm Hg. Whether any potential benefit of holding BP medications on reducing IDH is offset by any potential harms related to having higher predialysis BP requires further study. The pilot Blood Pressure in Dialysis study randomized patients on hemodialysis to a standardized or intensive predialysis systolic BP target (achieved systolic BP approximately 156 mm Hg versus approximately 145 mm Hg, respectively), and found no difference in left ventricular mass, but more IDH and adverse cardiovascular events in the intensive BP-lowering group (22).

A large majority of participants in our study failed to achieve dry weight, regardless of the treatment group, and shortened their hemodialysis sessions, findings that persisted even when we used less-stringent definitions for these outcomes. Moreover, participants required an average of 2–3 BP medications, suggesting ongoing volume overload. These results highlight a potential area for practice improvement through more frequent reassessments of dry weight, enhanced efforts at patient education with regard to fluid and sodium intake, and other targeted patient education efforts.

Our study has several strengths, including its randomized treatment assignment and a patient population diverse by age, sex, racial and ethnicity, vintage, and primary cause of kidney failure. However, there are also several limitations to note. First, we did not meet our recruitment goal, and adherence rates to the study intervention were suboptimal. Challenges with low patient recruitment and adherence rates have been seen in other trials in patients receiving hemodialysis, and underscores the importance of continuing to work on capacity-building strategies aimed at promoting research readiness in this population (23). Some patient-recruitment barriers were related to regulatory processes, such as requiring explicit approval from each potential participant’s treating physician before approaching the patient, which could be improved in future trials by engaging earlier with these oversight or governing bodies. Other patient recruitment barriers can be improved by changing the expectations such that research is an expected part of the culture of the dialysis unit, whereas efforts to increase patient and provider understanding of study-specific protocol details could have improved protocol adherence. These issues, along with an observed intraclass correlation larger than we had estimated, diminished our statistical power. Second, our study had a short duration, which precluded our ability to examine the effect of the intervention on cardiovascular outcomes. Third, in maximizing the pragmatic nature of the trial, we relied on routine in-center BP measurements, which do not always correlate well with outcomes (24,25). Finally, despite the large proportion of patients of Asian race and Hispanic ethnicity, our sample had few Black participants, so the results may not be applicable to all dialysis programs.

In conclusion, we randomized patients on hemodialysis to alternative strategies of BP medication prescription (i.e., taking versus holding before dialysis). Although we did not show that the TAKE strategy was noninferior to the HOLD strategy on IDH, our results show that taking BP medications as prescribed reduces the occurrence of uncontrolled hypertension. Managing BP in patients requiring hemodialysis may hinge less on BP medications and more on nonpharmacologic interventions such as optimizing dry weight, and empowering patients to reduce salt and fluid intake and to reduce the frequency of foreshortened hemodialysis sessions.

Disclosures
G.M. Chertow reports serving on the Board of Directors for Satellite Healthcare, a nonprofit dialysis provider; reports serving as a consultant to Akebia, Argylex, AstraZeneca, Baxter, CloudCath, Cricket, Durect, Gilead, Miromatrix, Outset, Reata, Sanifit, and Vertex; and reports serving on data safety monitoring boards for Angion, Bayer, National Institute of Diabetes and Digestive and Kidney Diseases, and ReCor. T.I. Chang reports receiving funding from Janssen Pharmaceuticals to Stanford University for serving as a national leader for CREalDENCE; and reports serving as a consultant for AstraZeneca, Bayer, Fresenius Medical Care, Gilead, Janssen Pharmaceuticals, Novo Nordisk, and Tricida. All remaining authors have nothing to disclose.

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Author Contributions
T. Chang and G. Chertow conceptualized the study; T. Chang and E. Tatoian were responsible for the data curation; T. Chang, G. Chertow, and M. Montez-Rath were responsible for the formal analysis; T. Chang was responsible for the funding acquisition; T. Chang and G. Chertow were responsible for the investigation; T. Chang and M. Montez-Rath were responsible for the methodology; T. Chang and E. Tatoian were responsible for the project administration; T. Chang and G. Chertow provided supervision; T. Chang was responsible for the validation; T. Chang and M. Montez-Rath wrote the original draft; and T. Chang, G. Chertow, E. Tatoian, and M. Montez-Rath reviewed and edited the manuscript.

Supplemental Material
This article contains the following supplemental material online at http://kidney360.asnjournals.orglookup?suppl doi:10.34067/KID.0001922021/DCSupplemental.

Supplemental Table 1. Detailed facility- and patient-level inclusion and exclusion criteria for the TAKE-HOLD study.

Supplemental Table 2. Effect of TAKE versus HOLD on the specified outcomes, defined as the proportion of participants with ≥30% of sessions with that outcome during the 4-week intervention period. Adjusted values include the baseline proportion of the specified outcomes in the models.

Supplemental Table 3. Effect of TAKE versus HOLD on the specified outcomes, defined as the proportion of participants with ≥30% of sessions with that outcome during the 4-week intervention period. Adjusted values include the baseline proportion of the specified outcomes in the models.

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