Intensive home blood pressure lowering in advanced chronic kidney disease: a pilot randomized controlled trial

Study Protocol

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Study design

This pilot study is a non-blinded randomized controlled trial investigating the safety and feasibility of strict blood pressure control in patients with advanced CKD. Patients will be randomized in 2:1 ratio to intervention (home SBP target < 120 mmHg) or usual care (home SBP target 130-140 mmHg) until 75 patients are enrolled, and then subsequently patients will be randomized in 1:1 ratio to intervention or usual care. Antihypertensive medications will be titrated as needed to achieve target home SBPs over the course of 4 months and maintained thereafter until study closeout (see Figure 1). Biannual visits are conducted after month 12.

Study population

All patients are recruited from the University of California San Francisco nephrology clinics. Inclusion and exclusion criteria are as follows:

Inclusion criteria:

1. ≥ 18 years of age
2. English-speaking
3. Patients with advanced CKD who meet the eGFR criteria defined as either
    a. at least two eGFRs ≤30 mL/min/1.73m^2 in the last three months
    b. a prior diagnosis of CKD and at least one eGFR ≤30 mL/min/1.73m^2 in the last three months.
4. Presence of elevated BP, defined as receipt of one or more antihypertensive agents or an office SBP>140 mmHg at the time of the screening visit. If the participant is not on antihypertensive medications, they must have an average home SBP>130 mmHg during the first week of the study when baseline home BPs are ascertained.
5. Participants must have a mid-arm circumference between 22-37 cm and access to a smart phone or tablet in order to use the Bluetooth-enabled home BP device, QardioArm©.

Exclusion criteria:

Patients are excluded if they:

1. are planning to become pregnant or are currently pregnant
2. are marginally housed due to concerns regarding follow-up
3. are institutionalized or a prisoner
4. are actively participating in a different interventional trial that may affect blood pressure
5. are actively abusing illicit drugs and alcohol
6. have a history of poor compliance
7. take >5 antihypertensive medications (including diuretics) at maximum doses
8. have cognitive impairment and are unable to follow instructions regarding home BP measurement during screening visit

If patients meet all inclusions and exclusion criteria, we will check with their nephrology providers prior to approaching participants to ensure their candidacy in our study.

Baseline Visit

During the baseline visit, participant eligibility is confirmed, written consent is obtained, and demographic, co-morbidity, and laboratory data are collected. A brief physical examination is performed and three automated office BP readings in the seated position followed by two standing BP readings are recorded one minute apart after five minutes of quiet rest. At the baseline visit, enrollees are provided with a QardioArm© device and trained to use the device to take standardized home BP measurements.

Participants are asked to take home BPs for a one-week baseline period to ensure continued eligibility and compliance with our protocol prior to randomization, with a minimum of 6 readings required over the one-week period. Participants are also asked to complete 24-hour ambulatory blood pressure monitoring (ABPM) during their baseline period. Patients who refuse to undergo 24-hour ABPM are not excluded from study.

Randomization

Eligible patients who complete the one week of baseline home readings will be randomized to either a home SBP target of <120 mmHg (intervention group) or 130-140 mmHg (usual care group) in 2:1 ratio until 75 participants are enrolled, and participants will be subsequently randomized in 1:1 ratio thereafter. The rationale for the 2:1 ratio for the first 75 patients is to ensure that we initially capture enough safety data on participants randomized to intervention, but we plan to transition to 1:1 ratio randomization thereafter. We will conduct a sensitivity analysis comparing the effect during the 2:1 randomization phase of the trial and 1:1 phase to determine if there is an interaction between the intervention and the phase of the trial.

Once patients are screened and deemed eligible, study personnel will notify nephrologists of their patients' eligibility and obtain assent for patient participation in the trial prior to randomization. Stratified permuted-block randomization will be performed with stratification by diabetes status in order to ensure that patients with diabetes who have previously been excluded from many trials of intensive BP lowering (8–10) are represented in our pilot study. Investigators will be blinded to the ordering of the randomization blocks and their respective sizes. The generation of allocation sequence is performed by and only accessible to the study coordinator for assignment of participants to the intervention and not accessible to investigators. Patients are contacted via phone or secure messaging to begin active titration of their antihypertensive regimens to achieve their assigned target SBPs after randomization.

Home blood pressure monitor

QardioArm© is a wireless Bluetooth-enabled home BP monitor that is validated by the European Society of Hypertension Protocol and the American Heart Association (31) and has a strong direct linear correlation (r=.96) with the previously validated and widely accepted Omron M3© BP device (32). The device is compatible with most smartphones and allows for real-time

wireless transmission of BP readings through an online phone application. The device is also accompanied by a secure platform used by providers for BP data transmission, monitoring, download, and storage. All participants are provided a device at no cost, and Bluetooth linkage between the device and smartphone are setup by study personnel at the baseline visit.

Office BP readings during study visits

Office BPs are measured at the baseline, 2, 4, 8, and 12-month study visits (Figure 1), and every six months thereafter. Participants are seated quietly in a room with the study coordinator for 5 minutes before BPs are taken. Three measurements are taken one minute apart. Participants are then be asked to stand for two minutes and two standing BPs are recorded one minute apart. One study coordinator will be present during all office BP measurements.

Intervention

Blood Pressure Targets

We have chosen to target home SBP, as opposed to mean arterial pressure (MAP) or diastolic BP (DBP) based primarily on the CV and mortality benefits seen recently in SPRINT (8) and data that suggest that SBP is a stronger predictor of ESKD risk and CV disease than DBP or MAP (24,33,34). Our usual care group will be treated to home SBP targets of 130-140 mmHg (equivalent to office SBP of 135-145 mmHg) because this was the range of BPs that screened patients had at baseline enrollment under routine care. During routine clinical care, any non-study provider can titrate antihypertensive agents as per their preference outside of the study protocol based on the clinic BP readings and other data available to them, and such titrations are noted and will be accepted by the study team. Home BP readings are made readily available to non-study providers upon request, and all nephrology clinic providers are alerted of patient enrollment in the study and the assigned BP target following randomization.

Home blood pressure readings

Participants are asked to measure their BPs at home on any three days of the week. For each day, participants take 3 readings in the morning and 3 in the evening. Participants are instructed to rest for 5 minutes before taking readings and sit quietly for 1 minute in between readings. Weekly home BP averages are calculated from the most recent 18 readings in a given week. Antihypertensive medications will be titrated by study investigators based on the average of the most recent 18 home BP measurements received, with a minimum of 6 required readings per week to be considered sufficient for any changes to medications. An insufficient number of measurements will prompt contact with the participant to increase the number of readings.

Antihypertensive Therapy Titration Intervention

Antihypertensive medications are titrated during the first 4 months to achieve target home SBP levels in both the intervention and usual care groups if home BP readings are not already within the target range. The antihypertensive therapy titration intervention will be individualized according to each patient's medical history, current medication regimen, and medication preference as specified by their nephrologist. Participants' referring nephrologist will be informed of their participation at the time of enrollment and asked to indicate which BP agents they would prefer to withdraw or add if SBP is outside of target according to their own practice patterns. Doses of current antihypertensive agents may be preferentially increased or decreased first depending on patient's home BP readings relative to their target SBP. This will be the first-line approach to avoid introduction of multiple new medications if doses of current medications are not yet optimized. New agents may be prescribed or discontinued after careful consideration of patient's medical history and nephrologist's input. Combination drugs will be acceptable but only used if suggested by the participant's nephrologist, as there may be cost barriers to the use of combination drugs. Although every antihypertensive treatment regimen will

likely differ for each participant, the suggested order of antihypertensive agent titration (if the nephrologist does not indicate a specific preference) will be angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEi) as first-line therapy, followed by (in order of preference) diuretics, calcium-channel blockers, beta-blockers, vasodilators/nitrates, sympatholytics, alpha-blockers, and potassium-sparing diuretics. See Figure 2 for the antihypertensive medication titration protocol.

We will permit up to a 30% increase in serum creatinine level after ACEi/ARB initiation or uptitration of dosages of other antihypertensive medications, in accordance with traditional guidelines and published literature (35,36). For patients who experience >30% increase in serum creatinine, the ACEi/ARB dose or other antihypertensive medication will be reduced, with plans for a repeat serum creatinine within 2 weeks. If the serum creatinine continues to be elevated, then the ACEi/ARB will be discontinued. We will also respect the opinion of the patient's nephrologist on this issue. If a nephrologist is concerned about any rise in serum creatinine, we will reduce or discontinue the drug. We will then proceed with the next suggested class of antihypertensive agents to help achieve the target blood pressure.

During the first 8 months of the study, participants will be contacted every other week by study coordinators to note any adverse events including dizziness, falls, syncope, hospitalizations, emergency room visits, acute kidney injury, CV events, or allergic reactions, as well as adherence to medication regimen and medication side effects such as diuresis, impotence, cough, lack of energy and sleepiness, lightheadedness on standing, or headaches.

Laboratory Tests

Basic metabolic panel and urine chemistry laboratory tests are obtained at baseline and at months 1, 2, 4, 8, 12, and every six months thereafter but timed as closely to clinical laboratory tests as possible (to avoid additional burden on participants) in a pragmatic approach. Labs are closely monitored by study investigators and medications titrated

accordingly to ensure the safety of all participants. Additional laboratory testing is performed as needed.

Follow-Up Timeline

The timeline of study visits during the one-year of follow-up is outlined in Figure 1. Participants are instructed to take weekly home BP readings for the first 4 months of the study, or until target SBP levels are achieved for two consecutive weeks. Once participants reach target SBP levels, home BP readings can be taken on a monthly basis over a one-week period each month. If participants maintain their target SBP levels after 8 months, home BP readings can be taken every two months thereafter. Participants will maintain their respective SBP target levels for the remainder of the study after month 8. If mean weekly SBP readings are > 4 mmHg outside the target range, antihypertensive therapy titration is resumed weekly until target SBP levels are achieved again for two consecutive weeks.

Participants are seen in person at Months 2, 4, 8, and 12, and every 6 months thereafter, but visits will be timed as close to their clinical visits as possible to avoid additional burden on participants in a pragmatic approach. In-person follow-up visits consist of a brief physical exam, office BP readings which will be obtained and used to calibrate the QardioArm© device to ensure accuracy of its readings, and laboratory testing. Patients will be contacted throughout the study via phone or secure text messages depending on patient preference. Adherence to antihypertensive therapy treatment will be assessed by administering a questionnaire during every in-person visit and follow-up phone call to ask participants if they are taking antihypertensive medications as prescribed and if they missed any doses since last follow-up. Adverse events (including emergency room visits or hospitalizations) and onset of ESKD, defined as initiation of chronic dialysis or receipt of kidney transplant, are also ascertained during follow-up. Participants will be followed indefinitely unless they choose to disenroll from the study or are lost to follow-up.

Outcomes measures

The primary outcome will be feasibility of achieving at least a 6 mmHg separation between intensive BP control and usual BP control arms at month 8. A secondary outcome will be the difference in BP between the two treatment strategies at study closeout. Adherence to home BP monitoring will be measured by the number of weeks participants successfully complete the minimum number of home readings.

Safety of our intervention will also be a secondary outcome and will be determined by a composite of adverse events including hyperkalemia (K ≥ 6.0 meq/L), self-reported falls, syncope, or acute kidney injury (AKI) requiring emergency room visit or hospitalizations. Discharge summaries from emergency room visits and hospitalizations in patient health records will be reviewed and events adjudicated by two study investigators. In addition, onset of ESKD will not be a censoring event; patients will be encouraged to continue to check home BPs following transplant or dialysis, but no study-driven active titration of antihypertensive agents will occur after ESKD onset.

Statistical analysis

Safety outcomes, or rates of adverse events, will be tallied using simple proportions and descriptive statistics. Intention-to-treat analysis will be performed. Stratified analyses by diabetes status will be performed given the lack of robust trial data to support intensive BP lowering in patients with diabetes. We will also test for differences in the composite rates of hospitalizations, emergency room visits, and hyperkalemia in the two arms. We will explore differences in the rates of ESKD or cardiovascular events and determine if there is any effect modification of the intervention by level of proteinuria or by diabetes. For patients lost to follow-up, we plan to use chained multiple imputation to perform analyses.

Sample size rationale

Randomizing 96 participants to strict vs usual BP control will provide 80% power (with 2-sided α of 0.05) to detect a 6-mmHg difference in SBP (with SD difference of 10 mmHg) between the two arms at month 8. Anticipating approximately 25% dropout, we plan to enroll 120 participants. An effect size of similar magnitude has been reported previously in tele-monitoring feedback from pharmacists in adult home BP monitoring trials (37).

List of Abbreviations

BP- blood pressure

CKD- chronic kidney disease

CV- cardiovascular

SBP- systolic blood pressure

ESKD- end-stage kidney disease

SPRINT- Systolic Blood Pressure Intervention Trial

eGFR- estimated glomerular filtration rate

MDRD- Modification of Diet in Renal Disease

RAAS- renin-angiotensin-aldosterone system

AKI- acute kidney injury

BMP- basic metabolic panel

UPCR- urine protein creatinine ratio

ABPM- ambulatory blood pressure monitoring

DBP- diastolic blood pressure

MAP- mean arterial pressure

ARB- angiotensin receptor blockers

ACE- angiotensin-converting enzyme

This protocol has been published:

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