Study Title: Screen-and-treat Program for Chronic Kidney Disease- High Risk Persons

NCT#: NCT02059408

Document Date: 11/4/2019

Additional Study Information

Adapted from original IRB application, last approved July 10, 2019

Summary: We propose a pragmatic, cluster-randomized clinical trial to evaluate the effectiveness and feasibility of a CKD screening program followed by education and incrementally intensified treatment strategies to improve BP management among non-diabetic, hypertensive adults with screen-detected CKD.

Study Design: Pilot, pragmatic, three-arm cluster-randomized trial

Intervention Arm #1: triple-marker screening for CKD followed by education for the patient and the primary care provider (Screen-Educate)

Intervention arm #2: addition of an option for pharmacist co-management (Screen-Educate plus Pharmacist)

Usual Care: No Intervention

Setting: Primary care practices at the San Francisco Veterans Affairs Medical Center.

Unit of Randomization: provider team

Additional Information

Participants

Inclusion Criteria:
The entire primary care medical practice at SFVAMC will be considered. Randomization will occur at the team level. Within each team, individual patients will be considered eligible for CKD screening by this protocol and inclusion in our trial if they have hypertension without concomitant diabetes, and no prior recorded diagnosis of CKD. HTN will be defined as SBP >140 or DBP >90 mmHg at more than two encounters (any encounter) within the previous 3 years or a documented diagnosis of HTN (listed in problem list or ICD-9 code). Diagnosed CKD will be defined as a documentation of CKD in the problem list or ICD-9 code or on-going nephrology follow up. We define diagnosed CKD without consideration of eGFRcreat or ACR in the laboratory section of the medical record, since work from our group and others has shown that awareness and recognition of CKD is extremely low, even among persons with documented reduced eGFR or albuminuria. Persons will be required to have seen their physician at least one time within the past 18 months.

Exclusion Criteria:
Kidney transplant recipients, known pregnant women, and individuals with an eGFR < 15 ml/min/1. 73 m^2 will be excluded from this study as they likely need specialty care for uncontrolled hypertension. Persons aged >80 will be excluded because data on aggressive BP lowering in this population are less clear and adverse effects associated with aggressive BP control have been well documented. We will exclude persons with NYHA class III or IV heart failure, known ejection fraction < 25%, or documented allergy to ACE/ARB. Other exclusion criteria relate to the required ability to communicate with clinical providers: impaired cognition or severe mental illness; expected life expectancy < 6 months. Patients will be excluded if the PCP informs the study coordinator that the patient should not be screened for CKD.

Additional Details:
Study Design: We propose a pragmatic, cluster-randomized clinical trial to evaluate the effectiveness and feasibility of a CKD screening program followed by education and incrementally intensified treatment strategies to improve BP management among non-diabetic, hypertensive adults with screen-detected CKD.

Primary care practices will be randomized into three groups: **usual care**, **screen and educate** and

screen-educate and intensify strategies. The **screen and educate** strategy takes advantage of the electronic medical record and established multi-disciplinary primary care teams in VA clinics to identify non-diabetic Veterans with hypertension who do not have a diagnosis of CKD. The study coordinator will order the screening tests on behalf of the primary care provider, after PCP consent has been obtained. In the information sheet, participants will be informed that tests are being ordered if they do not opt out. The nurse may alert the patient that they have orders to go to the laboratory prior to the PCP visit, as they already do in routine care. The PCP will receive the results of the triple marker. In addition, the study coordinator will summarize the results and provide standard, guideline concordant education and recommendations for CKD management, if applicable, in the form of a standardized "research note". This research note is entered into the medical record and it is co-signed by the PCP. This note serves as the provider education, and it will encourage the provider to counsel patients on their CKD related risks as outlined in this note. Patients will also receive a letter with the results, along with patient education materials. These materials have been designed and are used nationwide by the National Kidney Disease Evaluation Program (NKDEP).

The screen, educate and intensify treatment strategy will move a step further beyond screen-and-educate alone. Providers will be contacted notifying them of their patients with the highest risk for CKD via laboratory results, and reminding them of the option to refer patients to a clinical pharmacist-led BP management program. The intensified blood pressure management strategy (i.e. the Screening + Education + Clinical pharmacist outlined above) currently exists as part of the available treatment options for patients with hypertension, but will be refined to include CKD related considerations. A primary care clinical pharmacist, who is already an active member of the primary care team at the VA, will receive a referral for patients with the highest risk CKD, as defined by the CKD panel ($eGFR_{creat-cys}$ <6 0 ml/min/1.73m^2 and ACR 30 mg/g) from the physician in the intervention group (screen + educate + pharmacy option). The pharmacist will schedule a series of appointments with Veterans identified as having highest risk CKD to achieve sustained BP control and ensure use of ACE/ARB. The pharmacist would follow treatment algorithms recommended by the 2012 KDIGO international CKD guidelines, and designed by a team of internists and nephrologists.

Outcomes:

Primary Outcome Measure: Change in blood pressure [Time Frame: 12 months]: Change in blood pressure from enrollment to the end of the 12-month follow up period as a continuous outcome

Secondary Outcome Measures: ACE/ARB prescription by a clinician [Time Frame: 12 months]
Percent of persons with controlled blood pressure, defined as less than 140/90 at 2 consecutive visits.
Other Outcome Measures: Testing time, Testing Cost, Feasibility and Implementation Measures

Statistical Analysis Summary:

For patient-level variables, we will assess co-morbid conditions (diabetes, hypertension, cardiovascular disease, heart failure), medication use, blood pressure levels, laboratory data (eGFR, albuminuria) from the electronic medical record. National VA data will serve as our data source along with Pharmacy Benefits Management data. We will use this as a baseline data.

We will determine the proportion of persons who have CKD among those screened and calculate a number needed to screen (NNS) per CKD case detected. CKD is defined as $eGFR_{creat/cys}$ < 60 ml/min/1.73m^2 or ACR ≥ 30 mg/g, as per guidelines. We will estimate NNS across subgroups (age ><65, gender, presence of CVD). We will also estimate the NNS for eGFR and ACR separately.

We will begin by performing initial comparisons of patient characteristics among eligible patients in the usual care vs. screen-and-educate provider arms. These include age distribution, BP levels, and other baseline variables detailed above. We will also compare PCP characteristics such as years of training and average panel size. Baseline balance between the arms will be assessed with logit link

generalized estimating equation (GEE) models for categorical variables and linear GEE models for continuous variables. We will control for characteristics that might influence outcomes but differ significantly at baseline between trial arms in subsequent analyses of primary and secondary outcomes.

Our primary clinical outcome is change in BP from study enrollment to end of follow up. We will compare the usual care vs. screen-and-educate provider arms among all eligible hypertensives because CKD status will remain unknown within the usual care group. We will also compare the binary variable (proportion of persons with achieved sustained BP control) in the two arms as defined above. Change in BP from baseline to end of follow-up will be compared at the patient level. Multivariable regression analyses will utilize generalized estimating equations (GEE) to account for the cluster randomization. In this study, hypertensive patients (the units of analysis) are nested within nurse-led teams (the unit of randomization) and are not independent. We will compare different structures for the within-cluster correlation matrix (e. g., autoregressive, exchangeable, or unstructured) using the quasi-likelihood information criterion (QIC) to ensure estimation efficiency. Continuous outcomes including change from baseline in SBP and DBP will be analyzed with an identity link and normal distribution. Binary outcomes including BP control will be analyzed with a logit link and a binomial distribution. The final multivariable-adjusted models will be built separately for each outcome using a backward stepwise regression with a p-value of 0.05 or less for entry and retention of covariates. We will also report the unadjusted and adjusted intraclass correlation coefficient (ICC) to assist in the planning of future cluster randomized controlled trials. Additionally, among patients randomized to the screen-and-educate provider arm, we will also compare utilization of ACE/ARB at baseline and at the end of the trial and among patients with ACR ≥ 30 mg/g, using paired *t* test or Wilcoxon signed rank test, depending on the distribution of the outcome. We will compare BP control among all persons with screen detected CKD in the provider screen-educate-intensify arm vs. screen-and-educate. As we are interested in understanding *the additional benefit* of the pharmacy intervention in the highest risk group, we will perform analyses comparing the clinical outcomes in the subset of patients with highest risk CKD in the screen-and-educate provider vs. the screen-educate-intensify arms.