Clinical Outcomes Among High-Risk Primary Care Patients With Diabetic Kidney Disease

Methodological Challenges and Results From the STOP-DKD Study

Hayden B. Bosworth, PhD,†‡§‖ Uptal D. Patel, MD,¶# Allison A. Lewinski, PhD,*§ Clemontina A. Davenport, PhD,** Jane Pendergast, PhD,** Megan Oakes, MS,* Matthew J. Crowley, MD,†††† Leah L. Zullig, PhD, MPH,*† Sejal Patel, BPharm,‡ Jivan Moaddeb, PharmD,‡‡ Julie Miller, BS,* Shauna Malone,* Huiman Barnhart, PhD,** and Clarissa J. Diamantidis, MD, MHS*‡¶*

Background/Objective: Slowing the progression of diabetic kidney disease (DKD) is critical. We conducted a randomized controlled trial to target risk factors for DKD progression.

Methods: We evaluated the effect of a pharmacist-led intervention focused on supporting healthy behaviors, medication management, and self-monitoring on decline in estimated glomerular filtration rate (eGFR) for 36 months compared with an educational control.

Results: We randomized 138 individuals to the intervention group and 143 to control. At baseline, mean (SD) eGFR was 80.7 (21.7) mL/min/1.73m^2, 56% of participants had chronic kidney disease and a history of uncontrolled hypertension with a baseline SBP of 134.3 mm Hg. The mean (SD) decline in eGFR by cystatin C from baseline to 36 months was 5.0 (19.6) and 5.9 (18.6) mL/min/1.73m^2 for the control and intervention groups, respectively, with no significant between-group difference ($P = 0.75$).

Conclusions: We did not observe a significant difference in clinical outcomes by study arm. However, we showed that individuals with DKD will engage in a pharmacist-led intervention. The potential explanations for a lack of change in DKD risk factors can be attributed to 5 broad issues, challenges: (1) associated with enrolling patients with low eGFR and poor BP control; (2) implementing the intervention; (3) limited duration during which to observe any clinical benefit from the intervention; (4) potential co-intervention or contamination; and (5) low statistical power.

Key Words: diabetes, diabetic kidney disease, telehealth, hypertension

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From the *Department of Population Health Sciences, Duke University, Durham, NC; †Center of Innovation to Accelerate Discovery and Practice Transformation (ADAPT), Durham Veterans Affairs Health Care System, Durham, NC; ‡Division of General Internal Medicine, Duke University School of Medicine, Durham, NC; §School of Nursing, Duke University, Durham, NC; ‖Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC; ¶Division of Nephrology, Duke University School of Medicine, Durham, NC; #Gilead Sciences, Inc., Foster City, CA; **Department of Biostatistics and Bioinformatics, Durham, NC; ††Division of Endocrinology, Durham, NC; and ‡‡Center for Applied Genomics and Precision Medicine, Duke University, Durham, NC.

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Correspondence to: Department of Population Health Sciences, Duke University Medical Center Hayden B. Bosworth, PhD, 411 West Chapel Hill Street, Suite 600, Durham, NC 27701. E-mail: hayden.bosworth@duke.edu.

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Diabetic kidney disease (DKD) is a major public health problem that affects approximately one third of individuals with diabetes mellitus.[1] DKD is a growing global health concern and is associated with major health complications and increased health costs.[2] Black, Hispanic, and Asian individuals are at higher risk for DKD and subsequently poorer outcomes than White patients due to genetic, social, and environmental factors.[3–5]

A fundamental DKD treatment goal is to slow kidney function decline. To do so, individuals with DKD may be prescribed complex medical treatments and daily self-care activities. Yet, adherence to these treatments and self-care activities are suboptimal.[4] A need exists for ef-

fective, patient-centered interventions to slow the progression of DKD.

One way to address the progression of DKD is by using a comprehensive, lifestyle- and medication management-based approach to achieving early control of risk factors like blood pressure, glucose, and lipids.[5,6] Yet, few studies have examined the benefits of addressing multiple behaviors and complex pharmacological treatment simultaneously using interventionists trained to deliver both patient-centered medical and lifestyle management (eg, clinical pharmacy specialists).[7–9] Furthermore, most existing interventions have been tested within homogenous patient cohorts, limiting generalizability to the racially and ethnically diverse DKD population.

OBJECTIVE

The primary aim of this randomized controlled trial was to evaluate whether patients with DKD and uncontrolled hypertension who received a comprehensive, multifactorial telehealth intervention would have a smaller decrease in kidney function after 36 months compared with an educational control group. Secondary aims involved evaluating changes in blood pressure, blood glucose, and urinary albumin excretion relative to control.

METHODS

The Simultaneous Risk Factor Control Using Telehealth to Slow Progression of Diabetic Kidney Disease (STOP-DKD) (clinical trial.gov NCT01829256) evaluated a pharmacist-led telehealth intervention designed to reduce kidney function decline compared with an educational control group among patients with DKD.[10] The Duke University Institutional Review Board approved all study procedures and protocols.

Inclusion and Exclusion Criteria

Eligible patients were ascertained through electronic health data within the Duke University Health System (DUHS). Electronic screening took place monthly for patients who, during the preceding 36 months, met the eligibility criteria described in Table 1.

Randomization

Eligible patients were randomized 1:1 to the intervention or education control group. Patient randomization was stratified by estimated glomerular filtration rate (eGFR) and race, in which eGFR was dichotomized as 45–60 mL/min/1.73m^2 versus >60 and race was dichotomized as self-reported Black versus non-Black. Statisticians performed the entire study randomization before enrollment using blocked randomization with random blocks of size 2 or 4 to ensure balance between groups over the recruitment period. Randomization assignments created using the Strata software (Stata 15 software, StataCorp 2017). and participant group assignment was automatically generated at the baseline visit.

Treatment Groups

Education Control Group

Patients randomized to both the intervention and education control groups received management of DKD at the discretion of their providers. At baseline, the educational control group received information describing optimal management strategies for kidney disease developed by the National Kidney Disease Education Project (NKDEP).[13] This information included generic information on what DKD is, ways to manage DKD including lifestyle information. Material also included information on optimal blood pressure and glucose values.

Multifactorial Intervention

The intervention included similar information provided to those in the education control, plus module-based information tailored to each individual. Key risk factors such as hypertension, diabetes, and smoking were addressed monthly via telephone, including evaluation of medications,

TABLE 1. Eligibility Criteria

Inclusion criteria	Exclusion criteria
1. Adults aged ≥ 18 and ≤ 75 y 2. ≥ 2 primary care visits in 3 prior years 3. diagnosis of type 2 diabetes (ICD-9 codes 250.x0, 250.x2) 4. ≥ 2 serum creatinine values available in the 3 prior years, separated by at least 3 mo 5. eGFR greater than 45 mL/min/1.73 m^2 on most recent creatinine, estimated by calculating an eGFR using the 4-variable Modification of Diet in Renal Disease Study equation[11] 6. Evidence of diabetic nephropathy (ie, any of: presence of macroalbuminuria; history of microalbuminuria before ACE inhibitor or ARB therapy; previous documentation of diabetic retinopathy or laser therapy[12]; if only microalbuminuria and no diabetic retinopathy, then urinalysis without hematuria, and no other renal etiologies [ie, glomerulonephritis, polycystic kidney disease, membranous nephropathy, renal artery stenosis]) 7. Poorly controlled hypertension (ie, 2 SBP $\geq$ 140 and/or DBP $\geq$ 90 for 1 y) 8. Prescribed hypertension and diabetes medications	1. No telephone access 2. Not proficient in English 3. Residents of a long-term care facility or home healthcare patients 4. impaired hearing, speech, or vision; were participating in another clinical trial 5. Planning to leave the area within 36 mo 6. Pancreatic insufficiency or diabetes secondary to pancreatitis 7. Currently misusing alcohol (>14 alcoholic beverages weekly) 8. Diagnosis of nondiabetic kidney disease 9. Active malignancy 10. Life-threatening illness.

ARB indicates angiotensin receptor blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

health behaviors, and health knowledge around these risk factors. The activation frequency of each module varied based on clinical indicators (one telephone encounter covered multiple modules); some modules were activated at every encounter when the intervention was activated (medication adherence/update, side effects, and pill refill), whereas others were activated every 6 months (disease knowledge/risk perception, patient-physician communication, and health behaviors [smoking, activity/exercise, diet]). When needed, medication change recommendations were made based on evidence-based protocols communicated to the participant's PCP via the electronic health record.[10]

Intervention contacts were delivered via telephone by one of two pharmacists monthly for three years. All patients in the intervention group received a home blood pressure (BP) monitor (Omron Model HEM-790IT) and were requested to provide ≥ 3 values for at least 1 week before each monthly medication management call session. Patients were asked to provide $\geq$ 3 blood sugar values for at least 1 week before each session. If individuals did not provide enough values, the pharmacists encouraged them to take them for the next monthly call. If more than 3 values, the pharmacist took the last 3 values.

Primary Outcome

The primary outcome was eGFR using the CKD-EPI cystatin-C equation (https://www.kidney.org/content/ckd-epi-cystatin-c-equation-2012) measured annually for 3 years. Creatinine-based eGFR from the electronic health record was used for eligibility; however, cystatin C based eGFR has been observed to have the least bias in extremes of kidney function and was measured at study visits.[14]

Secondary Outcomes

SBP was operationalized as an average of 3 measures at 1-minute intervals after individuals rested for 5 minutes measured with a validated electronic BP cuff (Omron Model HEM-907XL).[15,16] Hemoglobin A1c was measured using standard, calibrated HPLC methods. Urinary albumin-to-creatinine ratio (ACR) was assessed by single first morning void urine sample measured with calibrated turbidimetric methods. All secondary measures were obtained at baseline, 12, 24, and 36 months.

Statistical Analyses

The study was designed to detect a −5 mL/min/1.73m^2 difference in the mean change in eGFR from baseline to 36 months between intervention and education control groups. The power calculations for the primary outcome assume a baseline eGFR standard deviation of 14 mm Hg, a within-person correlation of 0.7, and a 10% drop-out rate. Under these assumptions, the target sample size of 300 (150 in each arm) has 95.6% power, and the actual sample size of 280 had 85% power using a two-sided 0.05 level t test under the same assumptions.

The average change in eGFR from baseline to visit 3 in each study group was compared using a two-sample t test per study protocol. In a secondary analysis, a multivariable linear mixed model with a random intercept for participant was used to compare those in the intervention to those in educational control group on changes in the trajectories of eGFR over the course of the study. The fixed effects in this model were an indicator variable for the intervention study group, indicator variables for each follow-up study visit, and interaction terms between intervention group and follow-up visits. Overall joint tests and contrasts of the estimated parameters were used to assess the differences between study groups on trajectories over time and on overall average eGFR. The random participant-level accounted for within-person correlation over time and variability from person-to-person on unmeasured covariates.

Similarly, t tests and mixed models were used to compare study groups in terms of the secondary outcomes: eGFR measured by the CKD-EPI creatinine equation (https://www.kidney.org/content/ckd-epi-cystatin-c-equation-2012), SBP, hemoglobin A1C, and log-transformed ACR. In sensitivity analyses, we compared mean change using two-sample nonparametric Mann-Whitney tests and performed multiple imputation to determine if results were sensitive to either the normality assumption or missing data (assuming data were missing at random).[17] We also fit constrained mixed models assuming a common baseline outcome value across the two study groups.[18,19] Of note, statistical analyses did not account for study group differences because the study groups were randomized; any differences present would be due to random chance. We did not account for type of health center in the modeling because randomization was blocked by clinic. Similarly, the effect of the type of clinic would be similar across the two study arms due to randomization. As such, any differences between clinic effects and type of clinic would be solely due to random chance.

RESULTS

Enrollment and Retention

We identified 3894 potentially eligible individuals; however, 1402 were ineligible after chart review and 1698 individuals were potentially eligible but were unable to be contacted. Enrollment concluded at 281 individuals based on time limitations; 138 were randomized to the intervention group and 143 to the educational control group. Overall, 74% and 78% of participants in the educational control and intervention group completed their 3-year visit, respectively (Fig. 1).

Participant Demographic and Clinical Characteristics

The mean (SD) age of participants was 61.9 (8.8) years, 52% were male, and 56% were Black. (Table 2). The mean (SD) baseline eGFR was 80.7 (21.7) mL/min/1.73m^2 and half (56%) had chronic kidney disease (CKD) defined as eGFR <60 or ACR ≥ 30 mg/g. Of those with CKD, only 11% self-reported having CKD. Despite meeting our inclusion criteria for elevated BP based on EHR records, nearly two-thirds (63%) of enrolled patients had controlled BP $<140/90$ at their baseline study visit, with a mean (SD) SBP and DBP of 134.3 (19.5) and 76.3 (12.4) mm Hg, respectively.

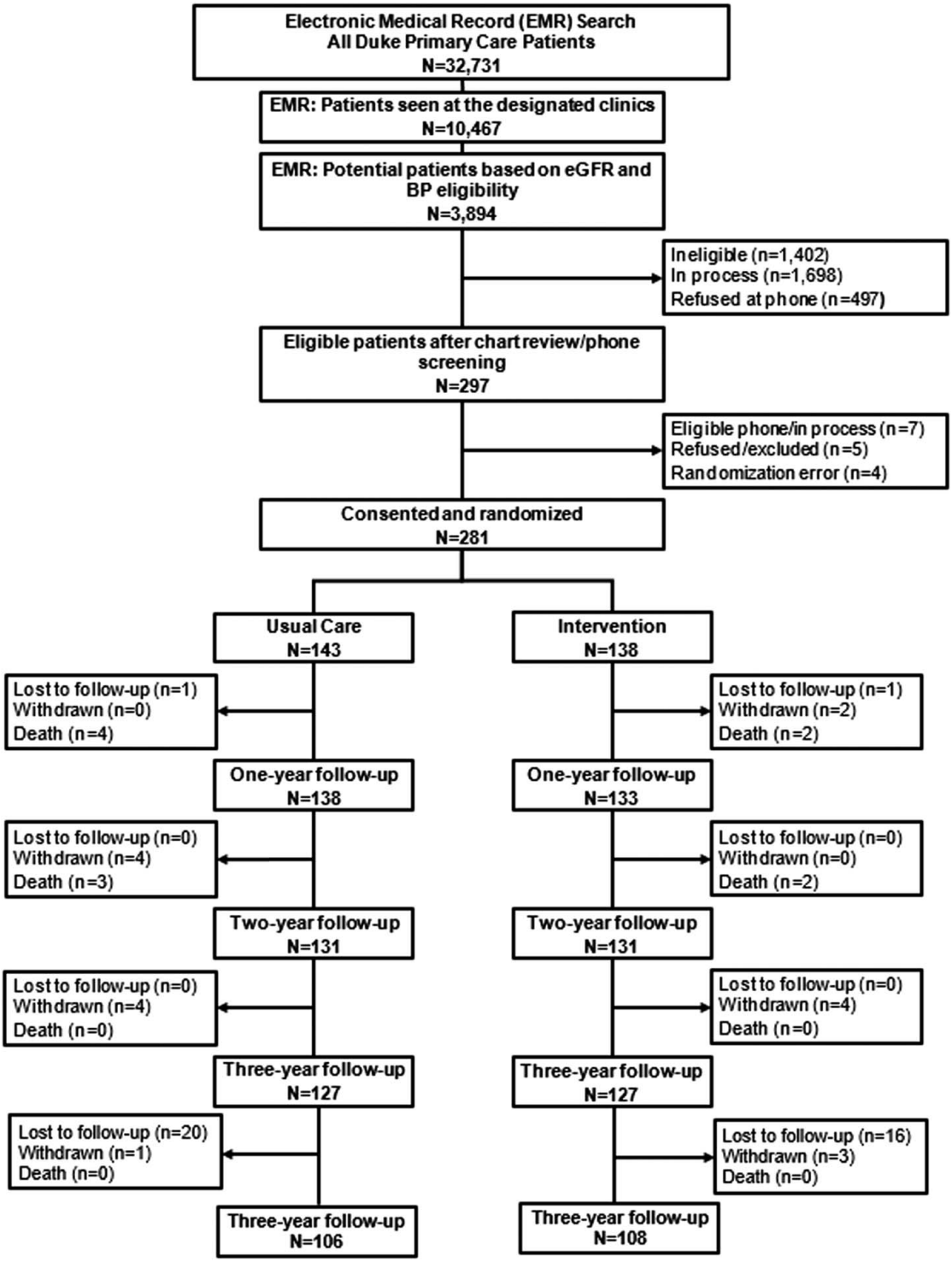

FIGURE 1. Consort Diagram.

Primary Outcome: eGFR by Cystatin-C

Among the 195 participants with data, the mean (SD) decline in eGFR by cystatin-C from baseline to visit 3 was 5.0 (19.6) and 5.9 (18.6) mL/min/1.73m^2 for educational care and intervention group, respectively, with no significant difference between the 2 groups ($P = 0.75$) (Table 3). Both study groups had lower eGFR at each follow-up visit compared with baseline (Table 4, Supplemental Figures, Supplemental Digital Content 1, http://links.lww.com/MLR/C870).

TABLE 2. Baseline Demographics and Clinical Characteristics of Participants

	Overall	Control	Intervention
n	**281**	**143**	**138**
Age, y, mean (SD)	61.89 (8.83)	61.33 (9.36)	62.47 (8.25)
Sex			
Female	136 (48.4)	75 (52.45)	61 (44.2)
Male	145 (51.6)	68 (47.55)	77 (55.8)
Race			
Non-Hispanic white	116 (41.28)	60 (41.96)	56 (40.58)
Non-Hispanic black	156 (55.52)	79 (55.24)	77 (55.8)
Asian	2 (0.71)	0 (0)	2 (1.45)
American Indian/Alaska Native	1 (0.36)	1 (0.7)	0 (0)
Other/Hispanic	6 (2.14)	3 (2.1)	3 (2.17)
Education			
1st to 8th grade	4 (1.42)	2 (1.4)	2 (1.45)
9th to 11th grade	24 (8.54)	14 (9.79)	10 (7.25)
12th grade or GED	62 (22.06)	34 (23.78)	28 (20.29)
Associates degree (AA or AS)	22 (7.83)	11 (7.69)	11 (7.97)
College 1 to 3 y	72 (25.62)	34 (23.78)	38 (27.54)
College graduate	95 (33.81)	46 (32.17)	49 (35.51)
Missing	2 (0.71)	2 (1.4)	0 (0)
Household income			
Less than $15,000	33 (11.74)	15 (10.49)	18 (13.04)
$15,000–$29,999	49 (17.44)	27 (18.88)	22 (15.94)
$30,000–$59,999	77 (27.4)	37 (25.87)	40 (28.99)
$60,000–$89,999	59 (21)	32 (22.38)	27 (19.57)
$90,000 or more	53 (18.86)	25 (17.48)	28 (20.29)
Do not know	6 (2.14)	4 (2.8)	2 (1.45)
Refused	2 (0.71)	1 (0.7)	1 (0.72)
Missing	2 (0.71)	2 (1.4)	0 (0)
Tobacco use in the past 12 mo			
No	233 (82.92)	120 (83.92)	113 (81.88)
Yes	44 (15.66)	21 (14.69)	23 (16.67)
Missing	4 (1.42)	2 (1.4)	2 (1.45)
Self-reported medical history			
Hypertension			
No	22 (7.83)	13 (9.09)	9 (6.52)
Yes	256 (91.1)	127 (88.81)	129 (93.48)
Do not know	1 (0.36)	1 (0.7)	0 (0)
Missing	2 (0.71)	2 (1.4)	0 (0)
Cardiovascular disease*			
No	237 (84.34)	118 (82.52)	119 (86.23)
Yes	44 (15.66)	25 (17.48)	19 (13.77)
Chronic kidney disease†			
No	137 (87.82)	68 (83.95)	69 (92.0)
Yes	17 (10.9)	11 (13.5)	6 (8.0)
Do not know	1 (0.64)	1 (1.23)	0 (0)
Missing	1 (0.64)	1 (1.23)	0 (0)
High cholesterol			
No	84 (29.89)	42 (29.37)	42 (30.43)
Yes	187 (66.55)	92 (64.34)	95 (68.84)
Do not know	6 (2.14)	6 (4.2)	0 (0)
Missing	4 (1.42)	3 (2.1)	1 (0.72)
Blood pressure (BP) variables, mm Hg, mean (SD)			
Systolic BP (n = 279)	134.33 (19.46)	133.55 (22.34)	135.14 (16.05)
Diastolic BP (n = 279)	76.31 (13.53)	75.98 (14.95)	76.65 (11.96)
Mean arterial pressure (n = 279)	71.33 (12.38)	71.07 (12.07)	71.6 (12.74)
BP ≥ 140/90			
No	176 (62.63)	93 (65.03)	83 (60.14)
Yes	103 (36.65)	48 (33.57)	55 (39.86)
Missing	2 (0.71)	2 (1.4)	0 (0)
BMI, kg/m^2 (n = 279), mean (SD)	35.66 (7.87)	36.15 (8.45)	35.16 (7.23)
Hemoglobin A1c, % (n = 280), mean (SD)	7.97 (1.8)	7.98 (1.84)	7.96 (1.77)
eGFR, mL/min/1.73m^2, mean (SD)	80.7 (21.69)	80.09 (23.11)	81.33 (20.17)
eGFR categories			
0–44	15 (5.34)	9 (6.29)	6 (4.35)
45–59	35 (12.46)	20 (13.99)	15 (10.87)
60–89	133 (47.33)	68 (47.55)	65 (47.1)
≥90	98 (34.88)	46 (32.17)	52 (37.68)
Urinary ACR, mg/g (n = 271), median [IQR]	30 [10–125]	30 [11–120]	30 [9–131]
Urinary ACR categories			
0–29	136 (48.4)	69 (48.25)	67 (48.55)
30–299	100 (35.59)	52 (36.36)	48 (34.78)
≥300	35 (12.46)	16 (11.19)	19 (13.77)
Missing	10 (3.56)	6 (4.2)	4 (2.9)

*Not self-report; ascertained from the electronic medical record.

†Among the 156 participants with chronic kidney disease (eGFR < 60 mL/min/1.73m2) or urinary ACR ≥ 30 mg/g.

ACR indicates albumin-to-creatinine ratio; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate.

Secondary Outcomes

Those in the intervention group had a greater mean decline in SBP and hemoglobin A1C than those in the educational control group (7.4 vs. 3.6 mm Hg and 0.34% vs. 0.25%, respectively), but these differences were not statistically significant ($P = 0.28$ and 0.63, respectively). Both study groups had an increase in mean log-transformed ACR at visit 3, with the intervention group having a numerically smaller increase than the educational control group (0.14 vs. 0.22, $P = 0.63$) (Table 3).

Intervention Fidelity and Provider Adherence

Of the 138 participants randomized to the intervention group, 51 (37%) completed all 36 pharmacist encounters. Participants had median (IQR) of 32.5 (19.25–36) completed encounters and 3 (1–6) expired encounters. The median (IQR) adherence defined as completed over total encounters was 91% (80.5%–97.1%). Of 176 treatment recommendations made by study pharmacists (among 59 participants), 107 (61%) were accepted by PCPs. In addition, we noted that the number of recommendations made by the 2 pharmacists was not correlated with PCP acceptance.

TABLE 3. Mean (SD) Change from Baseline to Visit 3 for Primary and Secondary Outcomes

	Usual Care	Intervention	Difference (95% CI)	*P*
eGFR by cystatin-C	4.98 (19.59)	5.93 (18.61)	0.952 (−6.752, 4.848)	0.746
eGFR by creatinine	8.75 (17.69)	8.83 (14.89)	0.077 (−4.703, 4.549)	0.974
SBP	3.55 (26.35)	7.35 (22.26)	3.799 (−10.643, 3.045)	0.275
A1C	0.25 (1.29)	0.34 (1.47)	0.095 (−0.482, 0.293)	0.631
log(ACR)	−0.22 (1.07)	−0.14 (1.18)	0.079 (−0.403, 0.244)	0.63

ACR indicates albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

DISCUSSION

Despite its use of comprehensive, lifestyle- and medication management-based approaches to slow DKD progression, this pharmacist-based intervention did not significantly improve eGFR, hemoglobin A1C, or SBP relative to a control group receiving an education control. However, there were trends toward greater improvement in SBP and hemoglobin A1C with the intervention, with declines of 7.4 mm Hg and 0.34% at 36 months in the intervention group versus 3.6 mm Hg and 0.25% in the control group. In addition, we observed significant declines of SBP among non-Black individuals in the intervention group and overall significant declines in SBP among Black individuals for the first 2 years.[20]

The potential explanations for a lack of change in DKD risk factors and eGFR can be attributed to 5 broad issues: (1) challenges associated with enrolling patients with low eGFR and poor BP control, (2) challenges with implementing the intervention, (3) a limited duration during which to observe any clinical benefit from the intervention, (4) potential co-intervention/contamination, and (5) low statistical power.

Our first challenge was enrolling patients with low eGFR and poor BP control from an academic primary care setting. The risk factors at baseline assessments were better controlled than expected. We had to change the study protocol because of a lack of individuals who met the initial eGFR criteria GFR >45 mL/min/1.73 m^2 but <90 mL/min/1.73 m^2 and had to loosen the inclusion criteria and remove the <90 requirement.[10] In addition, the mean baseline BP was 134/76 with only 36% at baseline with poor BP control, despite us identifying individuals who were poorly controlled over the last 12 months via electronic medical records. We have documented the challenges of relying on the electronic medical records to identify individuals with poor BP control;[21] variability in routine clinic BP measurement has been increasingly recognized.[22] The baseline standard deviation for baseline SBP and DBP was higher than expected at 19 and 22 mmHg, respectively. Thus, lower than expected rates of poorly controlled hypertension and lower rates of eGFR decline overall, diminished the potential for intervention benefit.

Our second challenge was integrating pharmacists into clinical care. Although some clinics were accepting of the use of pharmacists, the study protocol had to be adapted because the trial's 2 clinical pharmacists were not licensed to practice in the clinics and could not independently make medication changes. Instead, the pharmacists had to make recommendations via secure messaging to individual providers for PCP approval, but adoption of these recommendations was limited.[23] Thus, the impact of pharmacists' recommendations on medication management was limited. Pharmacists had access to patients' home-monitored BP values, but PCPs did not necessarily have the ability to view these data on which pharmacist recommendations were based. Finally, the impact of the intervention may have been greater if pharmacists were able to intervene when there was a need (eg, high home BP values) versus a set monthly scheduled intervention call independent of whether an individual needed support or not.

Third, although the STOP-DKD intervention was 36 months, it may have been an inadequate length of time to follow individuals to detect clinically meaningful differences. The STENO 2 trial which shared similarities with our own, took 13.3 years to show beneficial effects.[24] In the end, time may not have been as important as baseline risk for progression. The progression rates of ~5–5.9 mL/min/1.73m^2 for 36 months indicates annualized progression

TABLE 4. Estimated Change from Baseline in SBP at each Visit for each Racial Group

	Control [95% CI]	Intervention [95% CI]	Difference, Intervention – Control [95% CI]	3-way interaction [95% CI]; *P*
12 Mo				
Non-Black	2.98 (−2.22, 8.18)	−5.14 (−10.38, 0.1)	−8.12 (−15.51, −0.74)	10.09 (0.19, 19.98), 0.046
Black	−6.3 (−10.99, −1.6)	−4.33 (−8.95, 0.28)	1.97 (−4.62, 8.55)	
24 Mo				
Non-Black	2.7 (−2.57, 7.96)	−11.82 (−17.36, −6.29)	−14.52 (−22.16, −6.88)	15.64 (5.37, 25.92), 0.003
Black	−7.69 (−12.6, −2.79)	−6.57 (−11.38, −1.76)	1.12 (−5.74, 7.99)	
36 mo				
Non-Black	−0.92 (−6.41, 4.57)	−13.21 (−18.75, −7.68)	−12.29 (−20.09, −4.5)	17.57 (6.97, 28.18), 0.001
Black	−7.78 (−12.9, −2.66)	−2.5 (−7.53, 2.54)	5.28 (−1.9, 12.46)	

rates of ~1.7–2 mL/min/1.73m^2 per year. Although double the age-related decline of ~1 mL/min/1.73m^2 per year, this is short of the −3 to 5 mL/min/1.73m^2 year that characterizes those with rapid declines in eGFR, the intended target population.

Fourth was the potential for co-interventions/contamination. There existed a medication reconciliation program which available to both groups; it was difficult to determine which participants had participated in the program. This type of contamination was unavoidable and often reflects what may increasingly occur in healthcare systems. A potential unintended consequence of this cross contamination is increasing burden on patients given the potential of overwhelming patients with duplicative communications.

Finally, our study may not have been powered adequately as the observed missing data rate, SD for SBP, and the SDs of eGFR were larger than assumed in the original sample size calculation. Nonetheless, our findings may be consistent with a recent meta-analysis of 3 randomized clinical trials examining multidisciplinary management compared with standard usual care for eGFR which showed a tendency to favor standard care (relative risk −3.30, at 95% CI −6.55, −0.05, $P = 0.05$).[4] Whether baseline risk of progression in these other studies was a factor is not clear.

CONCLUSIONS

This study demonstrated that individuals with moderate DKD would engage in a telehealth-based intervention. However, the impact of pharmacists may have been greater if they were better integrated and coordinated with physicians to ensure medication recommendations were more likely to be followed and have clincal impact. Finnaly, future studies of this nature should consider the real-world clinical environemnt and be activated only when there are clinical indications to ensure valuable clinical resources are used more effectively.

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