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Association of Physician Care With Mortality in Kidney Early Evaluation Program (KEEP) Participants

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Background: People with or at high risk of chronic kidney disease (CKD) are at increased risk of premature morbidity and mortality. We sought to examine the effect of care provided by a primary care physician (PCP) on survival for all participants in the National Kidney Foundation's Kidney Early Evaluation Program (KEEP) and the effect of care provided by a nephrologist on survival for KEEP participants with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.

Methods: Provision of care by a PCP (n = 138,331) or nephrologist (n = 10,797) was defined using self-report of seeing that provider within the past year. Survival was ascertained by linking KEEP data to the Social Security Administration Death Master File. Multivariable Cox proportional hazards models examining the relationship between primary care and nephrologist provider status adjusted for age, sex, race, smoking status, education, health insurance, diabetes, cardiovascular disease, hypertension, cancer, albuminuria, body mass index, baseline eGFR, and hemoglobin level, with nephrology models further adjusting for calcium, phosphorus, and parathyroid hormone levels.

Results: Of all participants, 70.9% (98,050 of 138,331) reported receiving PCP care; older age and female sex were associated with this care. During a median follow-up of 4.2 years, 4,836 deaths occurred. After multivariable adjustment, receiving PCP care and mortality were not associated (HR, 0.94; 95% CI, 0.86-1.03; $P = 0.2$). Of participants with eGFR <60 mL/min/1.73 m^2, 10.1% (1,095 of 10,797) reported receiving nephrology care; younger age and male sex were associated with receipt of nephrology care. During a mean follow-up of 2.2 years, 558 deaths occurred. After multivariable adjustment, nephrologist care was not associated with mortality (HR, 1.01; 95% CI, 0.75-1.36; $P = 0.9$). These associations were not modified by other specialist care (endocrinologist or cardiologist).

Conclusions: For all KEEP participants, neither PCP nor nephrology care was associated with improved survival. These results highlight the need to explore the connection between access to health care and outcomes in persons at high risk of or with CKD.

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INDEX WORDS: Chronic kidney disease; mortality; nephrologist; primary care physician (PCP); survival.

The prevalence of chronic kidney disease (CKD) is increasing,[1] and CKD is associated with increased mortality.[2] Most studies suggest that early and more frequent nephrology care is associated with improved outcomes both before and after initiation of renal replacement therapy.[3-5] Therefore, measures that encourage referral to a nephrologist might be expected to result in improved outcomes. Additionally, the prevalence of cardiovascular disease appears to be higher in people at high risk of CKD than in the general population, even in the absence of CKD.[6] Given the heightened risk in the CKD population, participants in the Kidney Early Evaluation Program (KEEP) may also benefit from care from a primary care physician (PCP).[7,8]

Thus, we sought to examine the effect of physician care from a PCP or nephrologist in KEEP participants. The KEEP population provides an ideal opportunity

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to study physician care and outcomes in a population at high risk of and enriched with CKD.

METHODS

Study Participants

KEEP methods have been described previously.[7,8] Participants are eligible for screening if they are 18 years or older and have a personal history of diabetes or hypertension or a first-degree relative with kidney disease, diabetes, or hypertension. People with a history of dialysis or kidney transplant are excluded. For the PCP analysis, the KEEP database from January 1, 2000, through December 11, 2010, was examined; a total of 138,331 participants were included in this analysis. For the nephrologist analysis, the KEEP database from November 1, 2005, through December 11, 2010, was examined; a total of 10,797 participants were included in this analysis. The last date of follow-up was December 31, 2010. All-cause mortality data were determined by linking KEEP participants to the Social Security Administration Death Master File.[9] Examination of KEEP data was approved by the Human Subjects Committee of the Minneapolis Medical Research Foundation (HSR 03-2262), Minneapolis, MN, and this protocol was approved by the Human Research Protection Office at Washington University (ID 201106346), St. Louis, MO.

Patient Characteristics

Age, sex, race, education level, health insurance coverage, tobacco use, and timing of last physician visit were defined by self-report. As part of the screening, KEEP participants respond to 2 questions: (1) When were you last examined by a physician? and (2) What physician(s) or other health care provider(s) were you seeing? Only 1 response was recorded for the first question even if the participant reported seeing multiple physicians. Participants were considered to have a PCP if they were examined by a physician within the previous year and reported having an internist or family physician; participants who did not meet this criterion were considered not to have a PCP. Participants with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 were considered to have a nephrologist if they were examined by a physician in the past year and reported having a nephrologist; participants with eGFR <60 mL/min/1.73 m^2 who did not meet this criterion were considered not to have a nephrologist. Participants were considered to have a specialist if they were examined by a physician in the past year and that physician was a cardiologist or endocrinologist; participants who did not meet this criterion were considered not have a specialist. Participants were considered to have another health care provider if they had been examined by a provider in the past year and that provider was an endocrinologist, obstetrician/gynecologist, gerontologist, nurse practitioner, physician assistant, or nephrologist (for PCP analysis)/PCP (for nephrologist analysis). Diabetes was defined as self-reported history of hyperglycemia or diabetes mellitus or use of glucose-lowering medications. Cardiovascular disease was defined as self-reported history of heart angina, heart attack, heart bypass surgery, heart angioplasty, stroke, heart failure, abnormal heart rhythm, or coronary heart disease. Hypertension was defined as self-reported history of hypertension or use of antihypertensive medication. Blood pressure, height, and weight were measured by trained personnel. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared.

Laboratory Data

Calcium, phosphorus, and intact parathyroid hormone (iPTH) were measured as previously described[7,8] only in participants with eGFR <60 mL/min/1.73 m^2.[10] Specifically, iPTH was analyzed using Immulite 2000 (Siemens Medical Solutions Diagnostics, www.usa.siemens.com), a 2-site chemiluminescent enzyme-labeled immunometric assay. Serum creatinine was measured and calibrated to the Cleveland Clinic Research Laboratory, as previously described.[11] GFR was estimated using the CKD Epidemiology Collaboration (CKD-EPI) equation.[12] Microalbuminuria was defined as a spot urine albumin-creatinine ratio ≥ 30 mg/g. Hemoglobin levels were measured from samples sent to a central laboratory.

Statistical Methods

Univariate associations were compared for KEEP participants with and without a PCP and with and without a nephrologist using *t* test for continuous variables and χ^2 test for categorical variables. Multivariable logistic regression was used to examine independent effects of demographic and clinical characteristics on having a PCP or nephrologist. iPTH data were found to be skewed and were natural log–transformed when used in multivariate analyses. Subsequently, Cox regression was used to evaluate the association of having a physician (PCP or nephrologist) and mortality. An initial model was unadjusted. A second model was adjusted for age, sex, and race. A third model was adjusted for age, sex, race, smoking status, alcohol intake, high school education (yes/no), health insurance (yes/no), diabetes (yes/no), cardiovascular disease (yes/no), hypertension (yes/no), cancer (yes/no), albuminuria (yes/no), BMI, baseline eGFR, and hemoglobin level. In participants with eGFR <60 mL/min/1.73 m^2, the third model was adjusted additionally for calcium, phosphorus, and iPTH levels. Multiplicative interaction terms were used to assess for effect modification of care by a specialist or other health care provider. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 138,331 participants were included in the PCP analysis; 98,050 (70.9%) met the definition of having a PCP. In participants with eGFR <60 mL/min/1.73 m^2, 10,797 were included in the nephrologist analysis; 1,095 (10.1%) met the definition of having a nephrologist.

Baseline characteristics of all KEEP participants with and without a PCP are listed in Table 1. Participants with a PCP were older and more likely to be women, white, and not current smokers. They also were more likely to have at least a high school education, health insurance, and comorbid conditions, such as diabetes, cardiovascular disease, cancer, hypertension, or albuminuria. Hemoglobin and eGFR were lower in participants with a PCP; systolic blood pressure and BMI were higher. On multivariate analysis, older age, female sex, white race, high school education, health insurance coverage, diabetes, cardiovascular disease, cancer, and hypertension were associated positively with having a PCP. Albuminuria and current smoking status were associated negatively (Table 2). Higher BMI, lower eGFR, and lower hemoglobin level also were associated with having a PCP.

Table 1 also lists baseline characteristics of KEEP participants with eGFR <60 mL/min/1.73 m^2 with and without a nephrologist. Participants with a nephrologist were younger, more likely to be men, and

Table 1. KEEP Participant Demographic Characteristics

Characteristic	Primary Care Physician[a]			Nephrologist[b]		
	No	Yes	*P*	No	Yes	*P*
No.	40,281	98,050		9,702	1,095	
Age (y)	49.2 ± 15.1	57.7 ± 14.9	<0.001	71.0 ± 10.7	68.4 ± 12.1	<0.001
Men	36.6	29.9	<0.001	31.5	41.0	<0.001
Race			<0.001			0.2
White	41.5	51.9		68.9	66.7	
African American	33.1	32.9		21.8	22.7	
Other	25.4	15.2		9.2	10.6	
Smoker			<0.001			0.002
Never	61.0	60.8		60.3	54.6	
Former	24.0	29.9		34.6	39.7	
Current	15.0	9.2		5.0	5.7	
High school education	82.1	86.4	<0.001	82.9	85.3	<0.05
Health insurance	59.8	88.1	<0.001	91.2	92.6	0.1
Comorbid conditions						
Diabetes	21.0	33.7	<0.001	45.2	52.6	<0.001
CVD	14.4	23.5	<0.001	42.8	50.1	<0.001
Cancer	6.8	12.0	<0.001	20.6	24.2	0.007
Hypertension	41.5	63.2	<0.001	84.2	90.8	<0.001
Albuminuria	10.9	12.0	<0.001	21.8	40.9	<0.001
Physical measurements						
Systolic BP (mm Hg)	131.4 ± 20.2	134.1 ± 19.5	<0.001	137.5 ± 20.4	137.1 ± 19.9	0.5
BMI (kg/m^2)	29.7 ± 6.8	30.5 ± 6.9	<0.001	30.1 ± 6.3	30.5 ± 6.7	0.02
Laboratory measurements						
eGFR (mL/min/1.73 m^2)	91.0 ± 22.3	81.9 ± 22.5	<0.001	48.3 ± 9.2	39.6 ± 12.6	<0.001
Hemoglobin (g/dL)	13.9 ± 1.5	13.6 ± 1.4	<0.001	13.3 ± 1.5	12.8 ± 1.6	<0.001
Calcium (mg/dL)	NA	NA		9.7 ± 0.5	9.6 ± 0.6	<0.001
Phosphorus (mg/dL)	NA	NA		3.7 ± 0.6	3.8 ± 0.7	<0.001
iPTH (pg/mL)	NA	NA		81.2 ± 64.1	112.0 ± 118.5	<0.001

Note: Data are presented as mean ± standard deviation for continuous variables and percentage for categorical variables. Conversion factors for units: eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667; glucose in mg/dL to mmol/L, ×0.05551; hemoglobin in g/dL to g/L, ×10; calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229. No conversion necessary for PTH in pg/mL and ng/L.

Abbreviations: BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; KEEP, Kidney Early Evaluation Program; NA, not applicable.

[a]All participants.

[b]Participants with eGFR <60 mL/min/1.73 m^2.

more likely to have been smokers. They were more likely to have at least a high school education and comorbid conditions, such as diabetes, cardiovascular disease, hypertension, cancer, or albuminuria. Race and health insurance coverage were similar for participants with and without a nephrologist. eGFR and hemoglobin levels were lower in participants with eGFR <60 mL/min/1.73 m^2 with a nephrologist and iPTH levels were higher. On multivariate analysis, younger age, male sex, high school education, health insurance coverage, cancer, hypertension, and albuminuria were associated positively with having a nephrologist (Table 3). Phosphorus level and eGFR were associated negatively.

In all KEEP participants, 4,836 deaths occurred during a median follow-up of 4.2 years. In KEEP participants with eGFR <60 mL/min/1.73 m^2, 558 deaths occurred during a median follow-up of 2.2 years. On unadjusted analysis, risk of death was higher for participants with a PCP or nephrologist than for those without a physician (Table 4). After adjustment for age, sex, and race, the association between having a PCP and increased mortality was no longer present. The association between having a nephrologist and increased mortality persisted after adjustment for age, sex, and race. In fully adjusted models, the association between having a nephrologist and increased mortality was no longer present.

In the primary care analysis, there was no effect modification for specialist ($P = 0.4$) or other health care provider ($P = 0.6$) care in the past year. In the nephrologist analysis, there was no effect modifica-

Table 2. Multivariate Logistic Regression ORs of Having a Primary Care Physician

	OR (95% CI)	P
Age (/5 y)	1.10 (1.09-1.11)	<0.001
Men (vs women)	0.76 (0.73-0.79)	<0.001
Race		
White	1.00 (reference)	
African American	0.92 (0.88-0.95)	<0.001
Other	0.82 (0.79-0.86)	<0.001
Smoker		
Never	1.00 (reference)	
Former	1.04 (1.00-1.08)	0.04
Current	0.87 (0.83-0.92)	<0.001
High school education (yes vs no)	1.19 (1.14-1.25)	<0.001
Health insurance (yes vs no)	3.83 (3.70-3.97)	<0.001
Comorbid conditions		
Diabetes (yes vs no)	1.47 (1.42-1.53)	<0.001
CVD (yes vs no)	1.20 (1.15-1.25)	<0.001
Cancer (yes vs no)	1.11 (1.05-1.18)	<0.001
Hypertension (yes vs no)	1.67 (1.62-1.73)	<0.001
Albuminuria (yes vs no)	0.90 (0.86-0.95)	<0.001
BMI (/5 kg/m^2)	1.06 (1.05-1.07)	<0.001
Laboratory measurements		
eGFR (/1-SD increase)[a]	0.96 (0.94-0.98)	<0.001
Hemoglobin (/1-g/dL increase)	0.97 (0.95-0.98)	<0.001

Note: Based on all KEEP participants; n = 104,523; missing values for covariates excluded.

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; KEEP, Kidney Early Evaluation Program; OR, odds ratio; SD, standard deviation.

[a]eGFR/22.8 (SD of eGFR).

tion for specialist ($P = 0.4$) or other health care provider ($P = 0.6$) care in the past year.

DISCUSSION

This study addresses: (1) whether having a PCP was associated with improved survival in all KEEP participants and (2) whether having a nephrologist was associated with improved survival in KEEP participants with eGFR <60 mL/min/1.73 m^2. On unadjusted analysis, KEEP participants with a PCP or nephrologist were associated with a higher risk of death. Despite more comorbid conditions in KEEP participants who had a PCP, the association between having a PCP and increased mortality was lost only after adjustment for age, sex, and race. Conversely, in KEEP participants with eGFR <60 mL/min/1.73 m^2, the association between nephrology care and increased mortality persisted after adjustment for age, sex, and race, but disappeared in the fully adjusted model. Thus, the increased mortality associated with nephrology care likely was due to more medical illness and comorbid conditions in this group. These associations were similar for participants with and without a specialist (cardiologist or endocrinologist), suggesting that specialist care in participants without a PCP or nephrologist did not bias results to the null. Although our results do not support the view that physician care overall improves outcomes in patients with or at risk of CKD, several factors may have influenced the negative findings in these analyses.

Prior studies suggested that more frequent care[5,13] is associated with improved survival. KEEP did not record the frequency of physician visits and thus we were unable to examine whether this affected our results. Other factors, such as distance to the physician's office[14,15] and waiting times to see health care providers,[16] also were not recorded and could have affected our results. Prior studies have suggested that early nephrology referral is associated with improved outcomes in patients with CKD initiating dialysis

Table 3. Multivariate Logistic Regression ORs of Having a Nephrologist

	OR (95% CI)	P
Age (/5 y)	0.82 (0.79-0.86)	<0.001
Men (vs women)	1.43 (1.20-1.70)	<0.001
Race		
White	1.00 (reference)	
African American	0.99 (0.82-1.21)	0.9
Other	1.08 (0.83-1.39)	0.6
Smoker		
Never	1.00 (reference)	
Former	1.15 (0.98-1.34)	0.09
Current	0.89 (0.63-1.24)	0.5
High school education (yes vs no)	1.29 (1.04-1.59)	0.02
Health insurance (yes vs no)	2.37 (1.73-3.22)	<0.001
Comorbid conditions		
Diabetes (yes vs no)	1.12 (0.96-1.31)	0.2
CVD (yes vs no)	1.14 (0.98-1.33)	0.08
Cancer (yes vs no)	1.32 (1.11-1.58)	0.002
Hypertension (yes vs no)	1.48 (1.16-1.89)	0.002
Albuminuria (yes vs no)	1.31 (1.11-1.55)	0.002
BMI (/5 kg/m^2)	0.99 (0.93-1.05)	0.8
Laboratory measurements		
eGFR (/1-SD increase)[a]	0.48 (0.45-0.52)	<0.001
Calcium (/1-mg/dL increase)	1.01 (0.86-1.19)	0.9
Phosphorus (/1-mg/dL increase)	0.88 (0.78-0.998)	<0.05
iPTH (/1-SD increase)[b]	1.02 (0.95-1.10)	0.6
Hemoglobin (/1-g/dL increase)	0.96 (0.91-1.01)	0.1

Note: Based on KEEP participants with eGFR <60 mL/min/1.73 m^2; n = 8,992; missing values for covariates excluded.

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; KEEP, Kidney Early Evaluation Program; OR, odds ratio; SD, standard deviation.

[a]eGFR/10 (SD of eGFR).

[b]iPTH/0.68 (SD of iPTH).

Table 4. Mortality Risk for KEEP Participants Having Seen a Primary Care Physician or Nephrologist Within the Last Year

	Primary Care Physician vs Not[a]	*P*	Nephrologist vs Not[b]	*P*
Model 1[c]	1.56 (1.46-1.67)	<0.001	1.42 (1.10-1.82)	0.006
Model 2[d]	0.98 (0.91-1.05)	0.5	1.52 (1.18-1.95)	0.001
Model 3[e]	0.94 (0.86-1.03)	0.2	1.01 (0.75-1.36)	0.9

Note: Values given are hazard ratio (95% confidence interval).

Abbreviations: eGFR, estimated glomerular filtration rate; KEEP, Kidney Early Evaluation Program.

[a]All participants.

[b]Participants with eGFR <60 mL/min/1.73 m^2.

[c]Unadjusted.

[d]Adjusted for age, sex, and race.

[e]Adjusted age, sex, race, smoking status, high school education (yes/no), health insurance (yes/no), diabetes (yes/no), cardiovascular disease (yes/no), hypertension (yes/no), cancer (yes/no), albuminuria (yes/no), body mass index, baseline eGFR, and hemoglobin level; and calcium, phosphorus, and intact parathyroid hormone levels in the nephrologist/no nephrologist analysis for participants with eGFR <60 mL/min/1.73 m^2.

therapy. Our study did not examine the effect of survival in relation to dialysis therapy initiation. Furthermore, although these studies found greater risk associated with late nephrology referral, a recent study of elderly patients with CKD initiating dialysis therapy found minimal improvement in survival over time despite increasing trends toward early referral.[17]

In addition, participants may have been misclassified as having a PCP or nephrologist. Participants reported when they were last examined by a physician and the types of physicians or health care providers they saw, but did not report the time since seeing each provider. Therefore, participants may have been classified as having a nephrologist or PCP if they had not seen such providers but another health care provider in the last year. However, formal testing of effect modification was not significant, suggesting that associations were similar regardless of whether participants had seen another health care provider in the past year and that misclassification may not have had an important role in this study.

Use of the CKD-EPI equation to estimate GFR may have potentially affected our results. Prior studies in KEEP have found a decreased prevalence of eGFR <60 mL/min/1.73 m^2 using the CKD-EPI equation compared with the Modification of Diet in Renal Disease (MDRD) Study[18] equation, and participants reclassified to higher eGFR levels were found to be generally healthier and younger.[9] Conversely, participants reclassified to lower eGFR levels (previously classified as 60-89 mL/min/1.73 m^2 by the MDRD Study equation) had more comorbid illness.[9] The greater comorbidity in reclassified participants may have mitigated the benefits of having a nephrologist seen in prior studies. We may have observed a difference in outcomes if the CKD population under study were stratified further beyond eGFR <60 mL/min/1.73 m^2, for example, eGFR of 45-60, 30-45, 15-30, and <15 mL/min/1.73 m^2. However, our population is too small to empower such analyses.

It also is possible that KEEP participants who seek screening for CKD represent a group with limited access to health care despite reporting being under physician care. Lack of frequent and readily available care may have led KEEP participants to seek screening given their known high risk of CKD. Thus, despite having a physician, lack of access to that physician or the care provided, leading to a need to seek screening, may have confounded the association between physician care and mortality in KEEP. Furthermore, KEEP participants are at high risk of CKD and have an increased prevalence of cardiovascular disease.[6] Lack of access to health care in such a high-risk population also may have confounded this association. Thus, being both a KEEP participant and under a physician's care presents 2 sources of confounding by indication, which may be the best explanation for our findings.

Finally, it is possible that a lack of survival benefit might reflect a success of the KEEP screening. Any abnormalities detected during the screening may have resulted in appropriate referrals to a PCP or nephrologist. Thus, any survival benefit from care at the time of screening may have been negated by subsequent care by an appropriate physician.

Strengths of this study include the large sample size and availability of important measures. However, in addition to issues previously discussed, the study is limited in several ways. First, the duration of follow-up was relatively short and the long-term benefits of physician care could not be assessed. Second, physician involvement in care may change over time, particularly if the KEEP screening process is successful. Using data obtained at baseline without time-varying covariates thus is an additional limitation. Third, most of our data were based on patient recall and thus are subject to bias, although this should be nondifferential and bias toward the null. Finally, this study was nonrandomized, and unmeasured confounding may exist despite multivariate adjustments. Despite these limitations, we believe that results of this study help address an important question and can generate hypotheses for future studies.

In conclusion, we found that in KEEP participants, PCP and nephrologist care was not associated with survival. These results may appear to suggest that physician access does not improve overall outcomes in patients with or at risk of CKD. However, we believe that the data instead highlight potential av-

enues for improving the connection between access and outcomes. These include more frequent physician visits, greater attention to nontraditional risk factors, and continued assessment of patients regarding trends in laboratory and comorbidity parameters.

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