Who Is Tested for Diabetic Kidney Disease and Who Initiates Treatment?

The Translating Research Into Action for Diabetes (TRIAD) study

SUSAN L. JOHNSON, MD, MS[1]
EDWARD F. TIERNEY, MPH[2]
KINGSLEY U. ONYEMERE, MD, MPH[1]
CHIEN-WEN TSENG, MD, MPH[3]
MONICA M. SAFFORD, MD[4]
ANDREW J. KARTER, PHD[5]
ASSIAMIRA FERRARA, MD, PHD[5]
O. KENRICK DURU, MD[6]
ARLEEN F. BROWN, MD, PHD[6]
K.M. VENKAT NARAYAN, MD, MSC, MBA, MRCP[2]
THEODORE J. THOMPSON, MS[2]
WILLIAM H. HERMAN, MD, MPH[1]

OBJECTIVE — We examined factors associated with screening for albuminuria and initiation of ACE inhibitor or angiotensin receptor blocker (ARB) treatment in diabetic patients.

RESEARCH DESIGN AND METHODS — We conducted surveys and medical record reviews for 5,378 patients participating in a study of diabetes care in managed care at baseline (2000–2001) and follow-up (2002–2003). Factors associated with testing for albuminuria were examined in cross-sectional analysis at baseline. Factors associated with initiating ACE inhibitor/ARB therapy were determined prospectively.

RESULTS — At baseline, 52% of patients not receiving ACE inhibitor/ARB therapy and without known diabetic kidney disease (DKD) were screened for albuminuria. Patients ≥65 years of age, those with higher HbA_{1c}, those with cardiovascular disease (CVD), and those without hyperlipidemia were less likely to be screened. Of the patients with positive screening tests, 47% began ACE inhibitor/ARB therapy. Initiation of therapy was associated with positive screening test results, BMI ≥25 kg/m^2, treatment with insulin or oral antidiabetic agents, peripheral neuropathy, systolic blood pressure ≥140 mmHg, and CVD. Of the patients receiving ACE inhibitor/ARB therapy or with known DKD, 63% were tested for albuminuria.

CONCLUSIONS — Screening for albuminuria was inadequate, especially in older patients or those with competing medical concerns. The value of screening could be increased if more patients with positive screening tests initiated ACE inhibitor/ARB therapy. The efficiency of screening could be improved by limiting screening to diabetic patients not receiving ACE inhibitor/ARB therapy and without known DKD.

Diabetes Care 29:1733–1738, 2006

From the [1]Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, Michigan; the [2]Division of Diabetes Translation, Centers for Disease Control and Prevention, Atlanta, Georgia; the [3]Pacific Health Research Institute, Honolulu, Hawaii; the [4]Department of Internal Medicine, Division of General Internal Medicine, University of Medicine and Dentistry of New Jersey, Newark, New Jersey; the [5]Division of Research, Kaiser Permanente, Oakland, California; and the [6]Department of Medicine, Division of General Internal Medicine and Health Services Research, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California.

Address correspondence and reprint requests to William H. Herman, MD, MPH, University of Michigan Health System, 1500 East Medical Center Dr., 3920 Taubman Center, Ann Arbor, MI 48109-0354. E-mail: wherman@umich.edu.

Received for publication 31 January 2006 and accepted in revised form 20 April 2006.

Abbreviations: ARB, angiotensin receptor blocker; CVD, cardiovascular disease; DKD, diabetic kidney disease; ESRD, end-stage renal disease; SBP, systolic blood pressure; TRIAD, Translating Research Into Action for Diabetes.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-0260

Diabetic nephropathy will develop in up to one-third of patients with diabetes (1). Diabetes is the leading cause of end-stage renal disease (ESRD) in the U.S. In 2001, ~43,000 Americans began treatment for ESRD due to diabetic nephropathy (2). In 2002, $1.9 billion in U.S. health care expenditures were attributable to renal complications of diabetes (3). The development and progression of diabetic nephropathy can be slowed by controlling glucose and blood pressure levels (4). Treatment with ACE inhibitors and angiotensin receptor blockers (ARBs) has been shown to delay progression of diabetic kidney disease (DKD) beyond their effect on blood pressure (5–10).

Patients with DKD should be identified and treated early (11). In 1992, the American Diabetes Association first recommended annual screening for microalbuminuria (11); however, adherence rates have been suboptimal (12–14). In addition, little is known about the extent to which screening for microalbuminuria influences treatment with ACE inhibitors/ARBs (15).

In this report, we present a cross-sectional analysis of patient and provider characteristics associated with testing for microalbuminuria. We examined both a population appropriate for screening, those not known to have DKD and not using ACE inhibitor/ARB therapy, and a population not appropriate for screening, those with known DKD or already using ACE inhibitor/ARB therapy. In addition, we present a longitudinal analysis of factors associated with initiating ACE inhibitor/ARB treatment in patients not receiving ACE inhibitor/ARB treatment at baseline.

RESEARCH DESIGN AND METHODS

— The Translating Research Into Action for Diabetes (TRIAD) study has been described previously (16). Six centers collaborate with 10 health plans and 68 provider groups that serve ~180,000 patients with diabetes. Patients aged ≥18 years were sampled. Institutional review boards at each participating site approved the study.

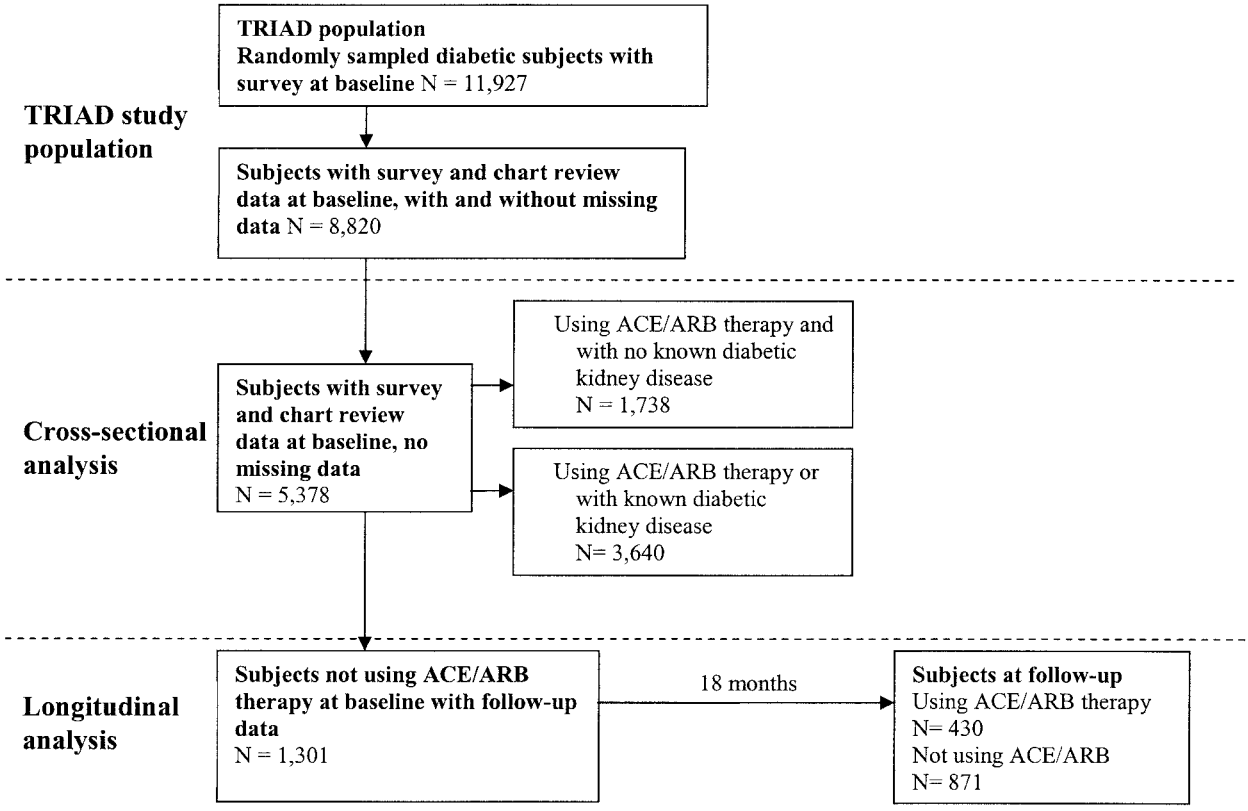

Figure 1— *Study populations for the cross-sectional analysis of baseline factors associated with receiving screening tests at baseline and for the longitudinal analysis of baseline factors associated with initiation of ACE inhibitor/ARB therapy in the 18 months following baseline.*

The study population is described in Fig. 1. In 2000–2001, 11,927 subjects completed a baseline survey administered by telephone or in written format. The cooperation rate, defined as the proportion of contacted eligible subjects who agreed to complete the survey, was 91%. The Council of American Survey Research Organizations response rate, calculated by including those we were unable to contact and assuming they had the same rate of eligibility as those contacted, was 69% (17). Of these patients, 8,820 (74%) also had a medical record review. Centrally trained reviewers abstracted medical records using standardized data collection instruments for the 18 months before the survey date. Two reviewers independently reviewed 5% of the records. Inter-rater reliability (κ) for microalbuminuria screening and ACE inhibitor/ARB use at baseline was 0.86 and 0.93, respectively.

For our analyses, we used subjects who had complete survey and medical record review data for ACE inhibitor/ARB use, history of microalbuminuria or nephropathy, screening status, diabetes treatment, diabetic retinopathy, systolic blood pressure (SBP), hypertension, hyperlipidemia, cardiovascular disease (CVD), serum creatinine, and physician type (n = 5,378). Missing values for age, sex, race and ethnicity, BMI, duration of diabetes, and smoking status from the patient survey and HbA_{1c} (A1C) from the medical record review were imputed using single imputation. Imputed variables had <10% missing data. The study population (n = 5,378) had demographic characteristics similar to the 11,927 patients with survey data at baseline and the 8,820 with both survey and medical record review data at baseline but with some missing medical record data (data not shown).

Cross-sectional analysis of baseline factors associated with microabuminuria screening/testing

We examined factors associated with screening in subjects who would clearly benefit from screening, that is, those not receiving ACE inhibitor/ARB therapy and without DKD at baseline (n = 1,738) (Fig. 1). In addition, we examined factors associated with testing in those receiving ACE inhibitor/ARB therapy or with known DKD (n = 3,640) (Fig. 1).

Longitudinal analysis of baseline factors associated with ACE inhibitor/ARB initiation

We examined factors associated with the initiation of ACE inhibitor/ARB therapy prospectively in the population not receiving ACE inhibitors/ARBs at baseline who had complete baseline and follow-up data (n = 1,301) (Fig. 1). Follow-up surveys and medical record reviews were conducted ~18 month after the baseline survey (2002–2003). The cooperation rate for the follow-up survey was 98%, and the Council of American Survey Research Organizations response rate was 80%.

Statistical methods

Patients were defined as having a screening test if the results of a urine microalbumin-to-creatinine ratio, urine protein-to-creatinine ratio, urine microalbumin, quantitative urine protein, or a semiquantitative urine albumin (Micral; Roche Diagnostics, Indianapolis, IN) were recorded in the medical record or if a urine dipstick was performed and showed protein ≥30 mg/dl (1+ or greater). Among tested patients, microalbuminuria was defined as a microalbumin-to-creatinine

Table 1—*Characteristics of study populations*

	TRIAD study population	Cross-sectional analysis		Longitudinal analysis
	Patients with a survey and chart review data at baseline, no missing data	Patients not using ACE/ARB therapy at baseline and no known DKD	Patients using ACE/ARB therapy at baseline or with known DKD	Patients not using ACE/ARB therapy at baseline with follow-up data
n	5,378	1,738	3,640	1,301
Age (years)	61.6 ± 12.6	60.3 ± 13.5	62.3 ± 12.1	59.5 ± 13.1
Sex (male)	2,461 (45.8)	772 (44.4)	1,689 (46.4)	618 (47.5)
Race/ethnicity				
White/non-Hispanic	2,381 (44.3)	826 (47.5)	1,555 (42.7)	639 (49.1)
American Indian/Alaskan	186 (3.5)	73 (4.1)	113 (3.1)	55 (4.2)
Asian/Pacific Islander	852 (15.8)	232 (13.4)	620 (17.0)	214 (16.5)
Black	753 (14.0)	209 (12.0)	544 (15.0)	144 (11.1)
Hispanic	876 (16.3)	326 (18.8)	550 (15.1)	184 (14.1)
Other	330 (6.1)	72 (4.1)	258 (7.1)	65 (5.0)
BMI (kg/m^2)	31.2 ± 7.2	30.4 ± 6.9	31.5 ± 7.3	30.4 ± 7.0
Diabetes duration (years)	9.6 (4.8–16.8)	8.3 (4.1–14.7)	10.2 (5.2–17.7)	8.3 (4.0–15.2)
Treatment				
Oral ± insulin	3,996 (74.3)	1,279 (73.6)	2,717 (74.6)	934 (71.8)
Insulin	1,004 (18.7)	309 (17.8)	695 (19.1)	243 (18.7)
Diet only	378 (7.0)	150 (8.6)	228 (6.3)	124 (9.5)
Visits	7.4 ± 4.9	6.7 ± 4.7	7.8 ± 5.0	6.4 ± 4.5
A1C (%)	7.6 ± 1.8	7.7 ± 1.9	7.6 ± 1.8	7.7 ± 1.8
SBP (mmHg)	136.0 ± 18.8	133 ± 16.9	137.7 ± 19.4	132.7 ± 17.3
Serum creatinine (mg/dl)	0.9 (0.8–1.1)	0.9 (0.7–1.0)	1.0 (0.8–1.2)	0.9 (0.8–1.1)
Diabetic retinopathy	1,038 (19.3)	223 (12.8)	815 (22.4)	206 (15.8)
Peripheral neuropathy	1,033 (19.2)	242 (13.9)	791 (21.7)	218 (16.8)
Hypertension	3,980 (74.0)	809 (46.6)	3,171 (87.1)	655 (50.4)
Hyperlipidemia	3,046 (56.6)	820 (47.2)	2,226 (61.2)	655 (50.4)
Smoking	1,582 (29.4)	450 (25.9)	1,132 (31.1)	377 (29.0)
CVD	1,832 (34.1)	429 (24.7)	1,403 (38.5)	316 (24.3)
Microalbuminuria or nephropathy	1,329 (24.7)	—	1,329 (36.5)	178 (13.7)
Screened	3,190 (59.3)	891 (51.3)	2,299 (63.2)	762 (58.6)
Physician type				
Endocrinology	299 (5.6)	89 (5.1)	210 (5.8)	77 (5.9)
Family medicine	2,707 (50.3)	916 (52.7)	1,791 (49.2)	602 (46.3)
Other/unknown	211 (3.9)	59 (3.4)	152 (4.2)	48 (3.7)
Internal medicine	2,161 (40.2)	674 (38.8)	1,487 (40.9)	574 (44.1)
ACE/ARB use	3,356 (62.4)	—	3,356 (92.2)	—

Data are means ± SD, median (interquartile range), or *n* (%).

ratio 30–299 mg/g, protein-to-creatinine ratio 50–499 mg/g, microalbumin 30–299 μg/ml or 30–299 mg/24 h, protein 50–499 μg/ml or 50–499 mg/24 h, or a Micral test result ≥50 mg/l (19). Diabetic nephropathy was defined as microalbumin-to-creatinine ratio ≥300 mg/g, protein-to-creatinine ratio ≥500 mg/g, microalbumin ≥300 μg/ml or ≥300 mg/24 h, protein ≥500 μg/ml or ≥500 mg/24 h, or a dipstick urine protein ≥30 mg/dl (1+ or greater) (18).

In the cross-sectional analyses, we assessed factors associated with being screened for microalbuminuria in the 18 months before the baseline survey. We included known risk factors for the development and progression of DKD (1,19) and other factors we believed were important (Table 1). Continuous variables were changed to three-level categorical variables in order to capture nonlinear relationships. History of CVD was defined as any history of stroke, myocardial infarction, angioplasty, bypass, or congestive heart failure. Interaction terms were not significant in initial models and were not included in the analysis.

In the longitudinal analysis of ACE inhibitor/ARB initiation, we examined associations between baseline factors and the likelihood of initiating an ACE inhibitor/ARB in the 18 months between baseline and follow-up. For this analysis, we used the same independent variables as in the screening model, except history of hypertension because SBP was more strongly associated with ACE inhibitor/ARB initiation. We also added a variable for screening results at baseline (screened and normal, screened and determined to have microalbuminuria or nephropathy, or not screened). We compared those receiving ACE inhibitor/ARB therapy at follow-up but not at baseline ($n = 430$) with those who were not receiving ACE inhibitor/ARB therapy at follow-up or at baseline ($n = 871$).

We performed hierarchical logistic regression using a penalized quasi-likelihood estimation method with ran-

Table 2—*Risk factors associated with tests for albuminuria being administered in the population not on ACE/ARB therapy and with no history of DKD and the population using ACE/ARB therapy at baseline or with a history of DKD*

Population	Conditional prediction	*P* value
Patients not on ACE/ARB therapy and with no DKD		
Age (years)		<0.0001
65	0.32 (0.17–0.52)	
45–64	0.44 (0.26–0.64)	
<45	0.47 (0.27–0.68)	
Physician type		0.026
Endocrinology	0.58 (0.35–0.79)	
Family medicine	0.39 (0.22–0.59)	
Other/unknown	0.42 (0.21–0.66)	
Internal medicine	0.37 (0.21–0.57)	
A1C (%)		0.031
8.1	0.37 (0.21–0.58)	
6.7–8.0	0.36 (0.20–0.57)	
<6.7	0.44 (0.26–0.64)	
Hyperlipidemia		0.047
Yes	0.46 (0.26–0.66)	
No	0.38 (0.21–0.58)	
CVD		0.026
Yes	0.34 (0.18–0.55)	
No	0.41 (0.23–0.61)	
Patients on ACE/ARB therapy or with DKD		
Age (years)		0.0004
65	0.45 (0.30–0.61)	
45–64	0.52 (0.36–0.67)	
<45	0.58 (0.41–0.74)	
Sex		0.034
Female	0.48 (0.32–0.63)	
Male	0.52 (0.36–0.67)	
Renal disease		<0.0001
Nephropathy	0.62 (0.46–0.76)	
Microalbuminuria	0.64 (0.47–0.78)	
No renal disease	0.44 (0.29–0.60)	
Peripheral neuropathy		0.033
Yes	0.53 (0.37–0.69)	
No	0.48 (0.33–0.64)	
Hyperlipidemia		0.043
Yes	0.51 (0.36–0.66)	
No	0.47 (0.32–0.63)	
CVD		0.005
Yes	0.46 (0.31–0.62)	
No	0.52 (0.36–0.67)	

Data are conditional prediction expressed as probability (95% CI). *P* value is the type 3 test for fixed effects.

dom intercepts for health plans to account for the clustered study design and correlation among participant characteristics within health plans, using SAS Proc Mixed procedure, version 9.1, and the Glimmix Macro. We used backward elimination and present the conditional probabilities and *P* values where the type 3 tests of fixed effects had a probability ≤0.05. SAS calculates the conditional probability by holding the covariates at their mean.

RESULTS — The overall study population was racially diverse, obese, and most often treated with oral antidiabetic agents (Table 1). Sixty-three percent of diabetic patients were treated with an ACE inhibitor/ARB at baseline. Seventy-four percent of patients had hypertension (Table 1), and 75% of them were treated with an ACE inhibitor/ARB. Twenty-six percent of patients had no history of hypertension, and 28% of them were treated with an ACE inhibitor/ARB. Overall, 59% of patients were screened for microalbuminuria (Table 1).

Cross-sectional analysis of baseline factors associated with microalbuminuria screening/testing

The baseline demographic characteristics of those not treated with an ACE inhibitor/ARB and with no history of DKD are shown in Table 1. Approximately half of these patients were screened, 25% of whom had results consistent with microalbuminuria or nephropathy. Younger age was associated with screening (Table 2). The conditional prediction indicates that 47% of those aged <45 years, but only 32% of those aged ≥65 years, were screened. Those with higher A1C levels and with CVD were less likely to be screened. Patients with hyperlipidemia or receiving their diabetes care from an endocrinologist were more likely to be screened.

Tests for microalbuminuria or proteinuria were administered to 63% of patients who were receiving ACE inhibitor/ARB therapy or who had known DKD (Table 1). Table 2 shows the factors associated with testing in this population. Testing was performed more often in male patients, those with hyperlipidemia or peripheral neuropathy, and those with histories of nephropathy or microalbuminuria. These tests were administered less often in patients aged ≥65 years and those with CVD.

Longitudinal analysis of baseline factors associated with ACE inhibitor/ARB initiation

The population not using ACE inhibitor/ARB therapy at baseline (n = 1,301) was younger, more likely to be white, and had a shorter diabetes duration. They were less likely to have diabetes complications or comorbid conditions (Table 1). A positive screening test for microalbuminuria or nephropathy was associated with initiation of an ACE or ARB in the 18 months between baseline and follow-up (Table 3). However, based on the conditional probability, only 47% of patients with a positive screening result began ACE inhibitor/ARB treatment. Being obese compared with normal weight, having an SBP ≥140 mmHg compared with an SBP of ≤120 mmHg, being treated with insulin and oral agents or insulin alone compared with diet therapy, having a history of peripheral neuropathy, and having a history of CVD were associated with beginning ACE inhibitor/ARB treatment (Table 3).

Table 3—*Risk factors associated with starting an ACE/ARB treatment in the population not on ACE/ARB treatment at baseline*

Variable	Conditional prediction	*P* value
BMI (kg/m^2)		0.003
30	0.41 (0.35–0.48)	
25–29	0.36 (0.29–0.43)	
<25	0.28 (0.21–0.36)	
SBP (mmHg)		0.0001
140	0.44 (0.37–0.52)	
120–139	0.34 (0.28–0.41)	
<120	0.27 (0.20–0.36)	
Treatment		0.027
Oral ± insulin	0.38 (0.32–0.44)	
Insulin	0.41 (0.33–0.50)	
Diet only	0.26 (0.18–0.36)	
Peripheral neuropathy		0.041
Yes	0.44 (0.35–0.53)	
No	0.36 (0.30–0.42)	
CVD risk		0.0001
Yes	0.46 (0.38–0.54)	
No	0.34 (0.28–0.40)	
Screening results		0.002
Microalbumin/nephropathy	0.47 (0.39–0.56)	
Negative	0.34 (0.27–0.41)	
Not done	0.34 (0.28–0.41)	

Data are conditional prediction expressed as probability (95% CI). *P* value is the test for type 3 fixed effects.

CONCLUSIONS — In a large, diverse, managed-care population with diabetes, nearly two-thirds of patients (63%) were using ACE inhibitor/ARB therapy. A large portion of patients were untreated and still at risk for DKD and would benefit from screening and subsequent ACE inhibitor/ARB treatment. However, only about half (51%) of such patients were screened (Table 1), and of those screened and found to have positive screening results, fewer than one-half (47%) were placed on ACE inhibitor/ARB therapy (Table 3). In fact, testing was more prevalent (63%) in the population already taking ACE inhibitor/ARB therapy or with known DKD (Table 1).

Among those not taking ACE inhibitor/ARB therapy at baseline and without known DKD, older patients was much less likely to be screened (Table 2). Although management of DKD has not been studied extensively in older adults, the recommendations of the American Geriatrics Society are consistent with the American Diabetes Association recommendations for annual screening (11,20). In the U.S., the life expectancy of a 65 year old is up to 18 years (21), and trials of ACE inhibitor/ARB treatment show beneficial effects within a few years (7–10). Clinical trials have found ACE inhibitor/ARB treatment to be well tolerated in older patients (22,23). We found no significant differences by age in the initiation of ACE inhibitor/ARB treatment, suggesting that increasing screening rates is crucial to improve renal outcomes for older individuals with diabetes. Screening occurred less often in patients with higher A1C levels, CVD, and those receiving their diabetes care from general internists or family physicians, perhaps because of competing medical concerns. Because both hyperglycemia and cardiovascular risk factors are also risk factors for progression to ESRD, this is an unfortunate occurrence (1,19).

A large proportion of testing was done in patients using ACE inhibitor/ARB therapy or with known DKD. A previous study showed that those using ACE inhibitor/ARB therapy received tests for proteinuria at the same rate as those not receiving therapy (24). The American Diabetes Association suggests that ongoing surveillance for disease progression or response to therapy may be appropriate but that prospective trials have not shown a benefit (25). Until trials show clear benefits to ongoing testing, testing for microalbuninuria in those on ACE inhibitor/ARB treatments and with known disease may represent an inefficient use of resources. The estimated glomerular filtration rate is a means of following renal function that does have clear implications for intervention (24).

As expected, initiation of ACE inhibitor/ARB treatment was associated with hypertension and cardiovascular risk and disease. We found that a positive screening test was also associated with initiation of ACE inhibitor/ARB therapy. Although this is encouraging, in this group with so much to gain from initiation of therapy, only 47% began treatment. Our observed rate of treatment (62 vs. 25%) and our rate of initiation of treatment for those with positive screening tests (47 vs. 40%) were better than those observed in a small study in a nonmanaged care family practice population (24). Little is known about specific barriers to ACE inhibitor/ARB initiation. A study at one TRIAD site found that those with albuminuria alone had lower rates of ACE inhibitor/ARB use than those with hypertension or hypertension and albuminuria (26). Patient-level barriers to ACE inhibitor/ARB initiation may include cost, side effects, lack of perception of health benefits, poor communication with providers, or complexity of medical regimens (27). Provider-level barriers may include lack of time or the complexity of disease management (27).

There are limitations to our study. We studied only those patients with complete survey and chart review data. The demographic characteristics of the populations with and without missing data were similar, and the sample size remained large. While data on ACE inhibitor/ARB use were obtained at two points in time, the reasons(s) for ACE inhibitor/ARB initiation could not be determined. Some patients receiving ACE inhibitor/ARB treatment at baseline may have been appropriately placed on therapy in response to screening in the 18 months before baseline and would not have been included in our analysis. However, we limit the degree of this bias by considering only the last screening test and last information regarding medication use in the 18-month period before the baseline assessment. Finally, our data may overestimate the number of patients who should be started on ACE inhibitor/ARB therapy because we did not take into account those who may have had repeat testing that did not confirm DKD. Similarly, a number of those found to have normoalbuminuria may have been false negatives. The population not on ACE inhibitor/ARB therapy

at baseline may also have included a higher proportion of patients with contraindications to ACE inhibitor/ARB therapy. Finally, our results may not be generalizable to settings other than managed care, where patients may be screened at lower rates.

In summary, we found that nearly two-thirds (62%) of diabetic patients in this large managed-care population were using ACE inhibitor/ARB therapy. Nevertheless, screening was not occurring as frequently as it should, particularly in those aged >65 years or with competing medical issues. Although screening was associated with initiation of ACE inhibitor/ARB therapy, far too few of the patients with positive screening tests were started on ACE inhibitor/ARB therapy. This may be particularly true for those without other indications for therapy, including hypertension and CVD. We also identified a number of areas that may represent inefficient use of resources. There are no guidelines for microalbumiuria testing in patients receiving ACE inhibitor/ARB therapy or with known DKD. Clear and unambiguous guidelines for such testing are needed. Finally, if patients are screened, found to have DKD, and not put on therapy, the initial screening wastes health care resources. Our measure of quality of care should not simply reflect the screening rate. It must also address whether screening leads to appropriate intervention.

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