Indications for and Utilization of ACE Inhibitors in Older Individuals with Diabetes

Findings from the National Health and Nutrition Examination Survey 1999 to 2002

Allison B. Rosen, MD, MPH, ScD[1,2,3]

[1]Division of General Medicine, University of Michigan Health Systems, Ann Arbor, MI, USA; [2]Department of Health Management and Policy, University of Michigan School of Public Health, Ann Arbor, MI, USA; [3]Center for Practice Management and Outcomes Research, Ann Arbor Veterans Affairs Medical Center, Ann Arbor, MI, USA.

BACKGROUND: Angiotensin-converting enzyme inhibitors (ACE) and angiotensin receptor blockers (ARB) improve cardiovascular outcomes in high-risk individuals with diabetes. Despite the marked benefit, it is unknown what percentage of patients with diabetes would benefit from and what percentage actually receive this preventive therapy.

OBJECTIVES: To examine the proportion of older diabetic patients with indications for ACE or ARB (ACE/ARB). To generate national estimates of ACE/ARB use.

DESIGN AND PARTICIPANTS: Survey of 742 individuals $\geq$ 55 years (representing 8.02 million U.S. adults) self-reporting diabetes in the 1999 to 2002 National Health and Nutrition Examination Survey.

MEASUREMENTS: Prevalence of guideline indications (albuminuria, cardiovascular disease, hypertension) and other cardiac risk factors (hyperlipidemia, smoking) with potential benefit from ACE/ARB. Prevalence of ACE/ARB use overall and by clinical indication.

RESULTS: Ninety-two percent had guideline indications for ACE/ARB. Including additional cardiac risk factors, the entire (100%) U.S. noninstitutionalized older population with diabetes had indications for ACE/ARB. Overall, 43% of the population received ACE/ARB. Hypertension was associated with higher rates of ACE/ARB use, while albuminuria and cardiovascular disease were not. As the number of indications increased, rates of use increased, however, the maximum prevalence of use was only 53% in individuals with 4 or more indications for ACE/ARB.

CONCLUSIONS: ACE/ARB is indicated in virtually all older individuals with diabetes; yet, national rates of use are disturbingly low and key risk factors (albuminuria and cardiovascular disease) are being missed. To improve quality of diabetes care nationally, use of ACE/ARB therapy by ALL older diabetics may be a desirable addition to diabetes performance measurement sets.

KEY WORDS: diabetes; ACE inhibitors; angiotensin receptor blockers; secondary prevention; renal disease; cardiovascular disease; quality of care; performance measures.
DOI: 10.1111/j.1525-1497.2006.00351.x
J GEN INTERN MED 2006; 21:315–319.

The worsening "epidemic" of diabetes in the United States[1,2] makes the use of effective secondary prevention critical to reducing excess morbidity, mortality, and costs. The elderly bear a disproportionate burden of diabetes with up to 18% of older individuals having diagnosed disease.[1,3,4] Angiotensin-converting enzyme inhibitors (ACE) and angiotensin receptor blockers (ARB) have been shown to prevent both cardiac and renal end-organ damage in diabetes.[5–21] Despite the marked morbidity and mortality benefits of these agents, no nationally representative studies have examined what percentage of older patients with diabetes would benefit from and what percentage actually receive this important preventive therapy. Therefore, the objectives of this study were to examine the proportion of older diabetic patients with clinical indications for ACE or ARB (ACE/ARB) therapy, and to generate national estimates of ACE/ARB use.

METHODS

Study Sample

The National Health and Nutrition Examination Survey (NHANES), a nationally representative cross-sectional survey of the U.S. noninstitutionalized civilian population, uses a complex, multistage, probability sample design, with oversampling of the elderly to allow for improved prevalence estimation of health indicators in this group. Beginning in 1999, NHANES became a continuous survey with data released in 2-year increments. The current study is based on the first 4 years (1999 to 2002) of the continuous NHANES.

We selected all respondents aged 55 years or older who responded "yes" to the question, "other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?" Age 55 was used as a cutoff because recent trials of the cardiovascular benefits of ACE inhibitors limited inclusion to individuals with diabetes $\geq$ 55 years.[13,14]

Indications for ACE/ARB Therapy

Several national guidelines recommend ACE inhibitors or ARBs for individuals with diabetes and select additional risk factors, including albuminuria, cardiovascular disease, congestive heart failure, and hypertension.[22–25] We grouped individuals with any one (or more) of these risk factors as having "guideline indications" for ACE/ARB. In addition to guideline indications, we explored two additional cardiac risk factors, hyperlipidemia and smoking, both of which have been used as inclusion criteria in trials demonstrating cardiovascular benefit from ACE or ARB[13,14] in individuals with diabetes. Analyses were performed with and without the inclusion of these two additional risk factors as indications for ACE/ARB.

Albuminuria. Albuminuria (including microalbuminuria or macroalbuminuria) was considered present if a respondent's urinary albumin to creatinine ratio was $\geq$ 30 mg/g or urine albumin concentration was $\geq$ 30 mg/L on a random, untimed urine specimen obtained at the NHANES Mobile Examination Center.

The authors have no conflicts of interest to report.

Address correspondence and requests for reprints to Dr. Rosen: Division of General Medicine, University of Michigan Health Systems, 300 North Ingalls, Suite 7E10, Ann Arbor, MI 48109 (e-mail: abrosen@umich.edu).

Manuscript received July 5, 2005
Initial editorial decision August 31, 2005
Final acceptance November 3, 2005

Cardiovascular Disease. Cardiovascular disease was considered present if a respondent self-reported a prior physician diagnosis of congestive heart failure, coronary artery disease, angina pectoris, myocardial infarction, or stroke.

Hypertension. Individuals were classified as hypertensive if they reported a prior physician diagnosis of hypertension, or had a mean systolic blood pressure ≥ 130 mmHg or a mean diastolic blood pressure ≥ 85 mmHg on examination. Over 90% of respondents had 3 or more measurements for averaging, and the 130/85 threshold was based on JNC VI recommendations for individuals with diabetes.[26]

Other Indications. Smoking status was based on self-reported current or past smoking history. Hyperlipidemia was considered present if a respondent self-reported a prior physician diagnosis of high cholesterol or they had an LDL cholesterol >130 mg/dL on fasting laboratory measurement.

Prescription Medications in NHANES

National Health and Nutrition Examination Survey respondents were asked during their in-home interview to present the containers of all prescription medications taken in the past month and to report any additional medications used for which containers were not available. All medication names were entered (during the home interview) by a trained interviewer into a handheld computer and matched to an annually updated comprehensive database of all prescription (and some nonprescription) drugs available in the U.S. market. Over 92% of medications had an exact match during the home interview. The remaining 8% of medications were manually reviewed later at the National Center for Health Statistics (NCHS). NCHS quality control activities, such as translation of medication names into English, correction of transcription errors, and removal of nonprescription dietary supplements from the prescription medication files resulted in less than 1% of medications listed as unknown.[27,28]

Respondents could have up to 20 medications recorded although none had all 20 medication fields filled. While NHANES uses the Federal Drug Administration's (FDA) National Drug Code (NDC) database to map medications to therapeutic classes, the FDA withdrew its support of this system (pending review and update) in the beginning of 2005. Therefore, for the current study, the first author (a trained physician researcher) reviewed the names of all medications used by this study's sample to identify ACE inhibitors and ARBs. A second review was performed by the same author 1 week later, and ACE/ARB use was successfully categorized in 99% of cases. The one discrepant record was reviewed and corrected by another physician.

Use of ACE/ARB Therapy

An individual was classified as on therapy if any of their medications included an ACE or ARB. Contraindications to treatment were considered rare because most individuals not tolerating an ACE can receive an ARB with a low likelihood of side effects.[29,30]

Statistical Analyses

We estimated the prevalence of risk factors that were indications for ACE/ARB. Within the overall population and in subgroups with differing clinical indications, we estimated national rates of ACE/ARB use. Comparisons were assessed using unpaired t-tests for continuous variables and Wald χ^2 tests for categorical variables. Logistic regression was used to determine the predictors of ACE/ARB use. Potential predictive variables included age, gender, race (non-Hispanic white, non-Hispanic black, Hispanic, other), and the presence or absence of each of the clinical indications for ACE/ARB. Bivariate odds ratios (ORs) for being on an ACE/ARB were calculated for each predictive variable. Multivariable logistic regression was performed using stepwise selection with the 3 guideline indications for ACE/ARB (hypertension, albuminuria, cardiovascular disease) kept in the model regardless of statistical significance to reflect their clinical significance as indicators to initiate ACE/ARB.

United States population estimates were obtained using NHANES sampling weights that account for the unequal probabilities of selection, nonresponse, and oversampling; standard errors were estimated using Taylor series linearization as recommended for the NHANES 1999 to 2002 survey data.[31] Analyses were performed using SAS-callable SUDAAN, version 8.0 (Research Triangle Institute, NC).

RESULTS

The study sample included 742 respondents, representing a population of 8.02 million U.S. adults 55 years or older with diabetes. Fifty-seven percent were between 55 and 69 years, 38% between 70 and 84 years, and 5% over 85 years. Half (54%) were female, and 28% comprised ethnic minority groups: 13% Hispanic, 15% non-Hispanic black.

Ninety-two percent had at least one guideline indication for ACE/ARB use. Including other cardiac risk factors as indications, 100% had an indication for ACE/ARB. Fourteen percent of the population had one indication, 37% 2 indications, 33% 3 indications, and 16% had 4 or more indications for ACE/ARB. The prevalence of each risk factor is given in Table 1.

Overall, 43% of the population was on an ACE or ARB. As the number of indications for ACE/ARB increased from 0 to 5, ACE/ARB use increased from 0% to 53%, respectively (P=.009 for trend). Rates of ACE/ARB use associated with each indication are reported in Table 1. On bivariate analyses, none of the demographic characteristics were associated with ACE/ARB use, and the only clinical indication significantly associated with increased ACE/ARB use was the presence of hypertension (Table 1). On multivariable modeling, hypertension remained the only significant predictor of increased ACE/ARB use (adjusted OR 3.36, 95% confidence interval [CI] 1.59, 7.12). Preexisting cardiovascular disease tended to be associated with higher rates of ACE/ARB use (adjusted OR 1.55; 95% CI 0.98, 2.46), while albuminuria was not associated with ACE/ARB use (adjusted OR 1.22; 95% CI 0.79, 1.89).

DISCUSSION

In a national sample of older individuals with diabetes, between 92% and 100% of patients had important clinical indications for ACE/ARB. Among these patients, ACE/ARB use was low, with an overall rate of 43%. While ACE/ARB use increased with increasing number of clinical indications, the highest rates of use (53% in individuals with diabetes and 4

Table 1. Indications for and Treatment with ACE/ARB

Risk Factors	Prevalence (%)	Rates of ACE/ARB Use for Each Indication		
		With Indication (%)	Without Indication (%)	OR (95% CI)
Guideline-based*				
Cardiovascular disease	34.5	50.5	39.8	1.54 (0.95, 2.50)
Albuminuria	41.1	46.8	43.2	1.08 (0.68, 1.71)
Hypertension	82.8	48.1	21.0	3.41 (1.81, 6.41)
Other cardiovascular*				
Hyperlipidemia	72.9	43.6	43.2	1.01 (0.60, 1.71)
Current smoker	24.0	43.2	43.5	0.84 (0.45, 1.56)
Number of indications†				
One	15.9	35.7	–	–
Two	39.2	38.9		
Three	30.4	51.6		
Four or more	12.8	53.4		

Risk factors are not mutually exclusive.
†P =.009 *for trend.*
ACE,angiotensin-converting enzyme; ARB, angiotensin receptor blockers; OR, odds ratio; CI, confidence interval.

or more additional indications for treatment) remained disturbingly low. Further, in patients with risk factors indicating clear mortality benefit from ACE/ARB, while hypertension was associated with higher rates of ACE/ARB use, albuminuria and preexisting cardiovascular disease were not, suggesting a major quality problem.

To our knowledge, this is the first nationally representative study to ask what proportion of older patients with diabetes would benefit from renin-angiotensin system blockade. As in past studies, we found that cardiovascular disease risk factors (including renal dysfunction) are highly prevalent in individuals with diabetes.[32] Expanding on prior studies, we document that nationally, the vast majority (92% to 100%) of older individuals with diabetes have clinical indications for ACE/ARB therapy.

This is also the first study to examine national rates of ACE/ARB use with data collected after guidelines started recommending ACE or ARB[22–24] for high-risk clinical subgroups with diabetes. In NHANES III, 13% of diabetics $\geq$ 40 years were on an ACE/ARB[33]; however, these data were collected between 1988 and 1994, a time before much of the evidence for ACE/ARB in diabetes existed. Smaller single-institution or state-based studies found rates of use ranging from 40% to 45% depending on the setting and clinical risk of the population.[34–37] One recent study in a large managed care plan found rates of ACE/ARB use between 54% and 74% in diabetic patients with hypertension or albuminuria, suggesting that it is possible to increase rates of use.[38] In contrast to the current community-based study, that study lacked information on preexisting cardiovascular disease (a key indication for ACE/ARB) and was limited to an employed, fully insured population enrolled in a health plan that had quality improvement tools in place specifically designed to increase ACE/ARB use in enrollees with diabetes. In the current study, despite nearly universal indication for treatment, only 43% of older diabetics received ACE/ARB and, in the highest risk groups (those with 4 or more indications), the likelihood of being on an ACE/ARB (53%) was not much higher than the toss of a coin.

A critical finding of the current study is the absence of significantly higher rates of ACE/ARB use in the setting of albuminuria or preexisting cardiovascular disease, both of which markedly increase cardiovascular risk in individuals with diabetes.[21,39–42] Despite clear guideline indications for ACE/ARB in diabetic patients with albuminuria or cardiovascular disease,[22–25] our results suggest that the presence of these risk factors may not be prompting physicians to initiate ACE/ARB therapy, indicating an important quality gap.

These findings may have important implications for improving the quality of diabetes care in the United States. Indications for therapy are highly prevalent (nearly universal), rates of receipt of therapy are disturbingly low, and key indications for ACE/ARB are being missed. Our current approach to determining candidacy for ACE/ARB therapy is to measure risk factors and treat accordingly. However, we have suboptimal rates of screening for some risk factors (only 41% of diabetic patients enrolled in HEDIS-reporting health plans in 2000 were screened for microalbuminuria[43]) and, in turn, suboptimal rates of appropriate treatment when risk factors are identified. If we are underdiagnosing risk factors and then undertreating those with diagnosed risk factors, the effectively treated population is just a fraction of the population that would benefit from treatment. Given that indications for ACE/ARB therapy are so prevalent in this population, it may be time to simplify our treatment algorithms by expanding indications for ACE/ARB to include *all* older individuals with diabetes regardless of their measured risk factors.

This study had some limitations. The NHANES 1999 to 2002 survey had a small sample size, which likely contributed to the lack of cardiovascular disease as a statistically significant predictor of ACE/ARB use. However, even if sample sizes increased (CIs tightened) such that we found a "statistically significant" difference in ACE/ARB use among those with and without cardiovascular disease, the quality problem remains unchanged: only half of diabetic patients with cardiovascular disease are on this life-saving therapy. In large part, our measures of risk factors and ACE/ARB use were based on self-report. Because we were unable to ascertain histories of adverse reactions to ACE, we could not exclude all individuals with contraindications to treatment. However, we would expect any bias to be small because our end point was a composite of ACE or ARB use and absolute contraindications to ARBs in those not tolerating ACE are rare (angioedema or refractory hyperkalemia occurs in $<$2%).[44,45] Finally, the current study explored the prevalence of indications for and treatment with

ACE/ARB during a time period (1999 to 2002) in which the evidence base for their use in diabetes was still being developed. While the current evidence base is substantially stronger, guidelines for ACE use in diabetic patients with hypertension (1997), albuminuria (1995), and congestive heart failure (1994) were in place well before this survey was initiated.[22–24]

CONCLUSION

Renin-angiotensin system blockade in individuals with diabetes is associated with decreases in cardiovascular events and renal failure. This analysis demonstrates that in 1999 to 2002, the entire (100%) noninstitutionalized U.S. population over the age of 55 with diagnosed diabetes would have benefited from ACE/ARB; yet, only 43% received it. Despite guideline indications, it appears that neither albuminuria nor cardiovascular disease are prompting increased rates of ACE/ARB use. To further increase ACE/ARB use and improve cardiovascular outcomes, it may be desirable to create a measure of ACE/ARB use for *ALL* older individuals with diabetes for inclusion in future diabetes performance measurement sets.

The author would like to thank Roger Davis, PhD, for statistical advice, as well as Norman Hollenberg, MD, and Rodney Hayward, MD, for their thoughtful comments on an earlier version of this manuscript.

Funding and Financial Support: At the initiation of this work, Dr. Rosen was supported by an AHRQ Health Services Research Fellowship at the Harvard School of Public Health, grant number 5 T32 HS00020-16.

REFERENCES

1. **Mokdad AH, Ford ES, Bowman BA, et al.** Diabetes trends in the US: 1990–1998. Diab Care. 2000;23:1278–83.
2. **Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP.** The continuing epidemics of obesity and diabetes in the United States. JAMA. 2001;286:1195–200.
3. **Medicare Current Beneficiary Survey.** Self-reported health conditions and risk factors of Medicare beneficiaries, by age and gender, 2000. Available at: http://www.cms.hhs.gov/MCBS/CMSsrc/2000/sec2.pdf. Accessed April 12, 2004.
4. **Bertoni AG, Krop JS, Anderson GF, Brancati FL.** Diabetes-related morbidity and mortality in a national sample of U.S. elders. Diab Care. 2002;25:471–5.
5. **Lewis EJ, Hunsicker LG, Bain RP, Rohde RD.** The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med. 1993;329:1456–62.
6. **Ravid M, Lang R, Rachmani R, Lishner M.** Long-term renoprotective effect of angiotensin-converting-enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. Arch Intern Med. 1996;156:286–9.
7. **Ravid M, Brosh D, Levi Z, Bar-Dayan Y, Ravid D, Rachmani R.** Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. Ann Intern Med. 1998;128:982–8.
8. **Viberti G, Mogensen CE, Groop LC, Pauls JF.** Effect of Captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. JAMA. 1994;271:275–9.
9. **Kvetny J, Gregersen G, Pedersen RS.** Randomized placebo-controlled trial of perindopril in normotensive, normoalbuminuric patients with type 1 diabetes mellitus. Q J Med. 2001;94:89–94.
10. **Ahmad J, Siddiqui MA, Ahamd H.** Effective postponement of diabetic nephropathy with enalapril in normotensive type 2 diabetic patients with microalbuminuria. Diab Care. 1997;20:1576–81.
11. **ACE Inhibitors in Diabetic Nephropathy Trialist Group.** Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. Ann Intern Med. 2001;134:370–9.
12. **Haider A, Oh P, Peloso PM.** An evidence-based review of ACE inhibitors in incipient diabetic nephropathy. Can J Clin Pharmacol. 2000;7:115–9.
13. **Heart Outcomes Prevention Evaluation (HOPE) Study Investigators.** Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000;342:145–53.
14. **Heart Outcomes Prevention Evaluation (HOPE) Study Investigators.** Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet. 2000;355:253–9.
15. **Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A for the CAPPP Study Group.** Reduced cardiovascular morbidity and mortality in hypertiensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/[beta]-blocker-based treatment regimen: a subanalysis of the Captopril prevention project. Diab Care. 2001;24:2091–6.
16. **Brenner BM, Cooper ME, de Zeeuw D, et al.** Effect of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861–9.
17. **Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA.** Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with neuropathy due to type 2 diabetes. N Engl J Med. 2001;345:851–60.
18. **Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Amer P.** Irbesartan in patients with type 2 diabetes and microalbuminuria study group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001;345:870–8.
19. **Lindholm LH, Ibsen H, Dahlof B, et al.** Cardiovascular morbidity and mortality in patients with diabetes in the Losartan intervention for endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet. 2002;359:1004–10.
20. **The EUCLID Study Group.** Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. Lancet. 1997;349:1787–92.
21. **Shlipak M.** Diabetic nephropathy. Clin Evid. 2005;13:149–54.
22. **Bennett PH, Haffner S, Kasiske BL, et al.** Screening and management of microalbuminuria in patients with diabetes mellitus: recommendations to the scientific advisory board of the national kidney foundation from an ad hoc committee of the council on diabetes mellitus of the national kidney foundation. Am J Kidney Dis. 1995;25:107–12.
23. **American Diabetes Association.** Standards of medical care for patients with diabetes mellitus. Diab Care. 1997;20(supp 1):S5–S13.
24. **Konstam M, Dracup K, Baker D, et al.** Heart failure: evaluation and care of patents with left-ventricular systolic dysfunction. In: MA Konstam, ed. Clinical Practice Guideline No. 11. Rockville, MD: Agency for Health Care Policy & Research; 1994.
25. **American Diabetes Association.** Standards of medical care in diabetes. Diab Care. 2005;28(suppl 1):S4–S36.
26. Sixth report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure. Arch Intern Med. 1997;157:2413–42.
27. **NHANES 1999–2000 Data Release.** Prescription medication subsection of dietary supplements and prescription medication section. Available at: http://www.cdc.gov/nchs/data/nhanes/frequency/rxq_rxdoc.pdf Accessed October 4, 2005.
28. **NHANES 2001–2002 Data Documentation: April 2005.** Prescription medication subsection of dietary supplements and prescription medication section. Available at: http://www.cdc.gov/nchs/data/nhanes/nhanes_01_02/rxq_rx_b_doc.pdf Accessed October 4, 2005.
29. **Paster RZ, Snavely DB, Sweet AR, et al.** Use of losartan in the treatment of hypertensive patients with a history of cough induced by angiotensin-converting enzyme inhibitors. Clin Therap. 1998; 20:978–89.
30. **Tanser PH, Campbell LM, Carranza JK, Toutouzas P, Watts Rfor the Multicentre Cough Study Group.** Candesartan cilexetil is not associated with cough in hypertensive patients with enalapril-induced cough. Am J Hypertens. 2000;13:214–8.
31. **NHANES.** NHANES analytic guidelines: June 2004 version. Available at: http://www.cdc.gov/nchs/data/nhanes/nhanes_general_june_04.pdf. Accessed March 3, 2005.
32. **Goldberg RB.** Cardiovascular disease in patients who have diabetes. Cardiol Clin. 2003;21:399–413.

33. **Kramer HJ, Nguyen QD, Curhan G, Hsu C.** Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA. 2003;289:3273–7.
34. **Dunn EJ, Burton CJ, Feest TG.** The care of patients with diabetic nephropathy: audit, feedback, and improvement. Q J Med. 1999;92: 443–9.
35. **Gold JA.** A word from WIPRO: improving use of ACE inhibitors in diabetic nephropathy. Wisc Med J 1996:588–9.
36. **Scarsi KK, Bjornson DC.** The use of ACE inhibitors as renoprotective agents in Medicaid patients with diabetes. Ann Pharmacother. 2000;34:1002–6.
37. **Gordian ME, Kelly J.** Why patients with diabetes, hypertension and/or proteinuria are NOT on angiotensin converting enzyme inhibitors. Alaska Med. 1998;40:51–4.
38. **Rosen AB, Karter AJ, Liu JY, Selby JV, Schneider EC.** Use of ACE-inhibitors and angiotensin receptor blockers in high-risk clinical and ethnic groups with diabetes. J Gen Intern Med. 2004;19:671–7.
39. **Gerstein HC, Mann JFE, Yi Q, et al.** Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001;286:421–6.
40. **Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M.** Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339:229–34.
41. **Hillen T, Coshall C, Tilling K, Rudd AG, McGovern R, Wolfe CDA.** Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London Stroke Register. Stroke. 2003;34:1457–63.
42. **Valmadrid CT, Klein R, Moss SE, Klein BEK.** The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. Arch Intern Med. 2000;160:1093–100.
43. **National Committee for Quality Assurance (NCQA).** The state of managed care quality, 2001. Available at: http://www.ncqa.org/somc2001/diabetes/cdc6_datx.html. Accessed September 12, 2002.
44. **Bicket DP.** Using ACE inhibitors appropriately. Am Fam Physician. 2002;66:461–8.
45. **Reardon LC, Macpherson DS.** Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. How much should we worry? Arch Intern Med. 1998;158:26–32.