What Evidence Supports Guidelines for Use of ACE Inhibitors and ARBs in Diabetes?

In this issue of JMCP, Cooke and Fatodu inform us that of 1,698 patients with diabetes, 13% (n= 215) had a medical claim indicating renal involvement. 1 In the subset of 215 diabetes patients with renal involvement, 177 had at least 1 medical claim with a diagnosis of hypertension, and the use of angiotensin-converting enzyme (ACEs) inhibitors or angiotensin receptor blockers (ARBs) was high (85.3%, n = 151). In the subgroup of 38 diabetes patients with renal involvement but without hypertension, the use of ACE inhibitors or ARBs was significantly lower (47%, n = 18, P <0.001). Overall, these administrative claims data for the dates of service from April 1, 2001, through March 31, 2002, revealed that 915 (33.9%) of the diabetes patients had at least 1 claim for either an ACE inhibitor or ARB. Relying on the 2002 and 2004 position statements of the American Diabetes Association on hypertension management in adults with diabetes, Cooke and Fatodu suggest that diabetes patients are undertreated with ACE inhibitors or ARBs. However, for their subgroup of patients with diabetes and hypertension (n = 1,072, 63.1%), more than 4 out of 5 (n = 951, 85.4%) were treated with an ACE inhibitor or ARB, and the authors acknowledge that only 20 diabetes patients (1.2% overall) who did not have hypertension but did have evidence of renal involvement did not receive either an ACE inhibitor or ARB.

While Cooke and Fatodu have support from clinical practice guidelines to claim undertreatment of diabetes patients with ACE inhibitors or ARBs, some scientists have recently questioned the evidence to support these guidelines. The results of a systematic review and meta-analysis performed last year for studies published through January 2005 refute the assumption that ACE inhibitors and ARBs, collectively renin-angiotensin system (RAS) inhibitors, have renoprotective effects that extend beyond reduction in blood pressure. 2 Casas et al. concluded that not only are the additional renoprotective actions of ACE inhibitors and ARBs beyond lowering blood pressure unproven in persons with diabetes, there is not sufficient evidence to conclude that there is renoprotection from these drugs in nondiabetic patients with renal disease.

Specifically, Casas et al. found a relative risk of 0.71 for doubling of serum creatinine for the RAS inhibitors, but the 95% confidence interval (CI, 0.49-1.04) crossed 1.0 (i.e., no risk reduction), and a small benefit on end-stage renal disease (ESRD, relative risk, 0.87; 95% CI, 0.75-0.99). When Casas et al. analyzed the results by study population size, there was a smaller benefit in large studies. For patients with diabetic nephropathy, there was no benefit for RAS inhibitors by the measure of a 2-fold increase in serum creatinine (relative risk, 1.09; 95% CI, 0.55-2.15) and no benefit in progression to ESRD (relative risk, 0.89; 95% CI, 0.74-1.07), glomerular filtration rate, or absolute creatinine amounts. This systematic review and meta-analysis of data from 13 studies generated a firestorm response, generally focused on the heavy reliance on the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). 3 Casas and coauthors pointed out in rebuttal to the letters that the ALLHAT results did contribute about half of the available evidence on renal outcomes, but ALLHAT included renal disease as a prespecified outcome, and ALLHAT is the only study with a population size near the size necessary (57,000) to demonstrate a 10% relative risk reduction in ESRD. 4

Aside from the specific question regarding the potential value of ACE inhibitors or ARBs in renoprotection beyond blood pressure reduction, the results of key clinical trials suggested that there might be some effect of ACE inhibitors on glucose metabolism and a potential role in diabetes prevention. Two studies in particular, neither of which was designed to assess specifically the outcome of a new diagnosis of diabetes, suggested that ACE inhibitors might be associated with a side effect in preventing diabetes. Ingellinger and Solomon in an editorial published earlier this month 5 inform us that the Captopril Prevention Project (CAPPP) found a 14% lower incidence of diabetes in the captopril group compared with diuretics or beta-blockers in hypertensive patients, and results of the Heart Outcomes Prevention Evaluation (HOPE) Study in patients at high risk for cardiovascular events found a 34% reduction in risk of newly diagnosed diabetes in patients who received ramipril 10 mg per day compared with placebo. 6 However, the absolute rates of a new diagnosis of diabetes were small. For the 5 years of follow-up in the HOPE Study, 102 (3.6%) patients in the ramipril arm developed a new diagnosis for diabetes versus 155 (5.4%) for placebo. In a study designed specifically to assess the development of a new diagnosis of diabetes in patients with either impaired glucose tolerance or impaired fasting glucose levels, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) results showed no difference in new diagnosis of diabetes for an average 3 years of therapy with ramipril (up to 15 mg per day), 17.1% versus 18.5% for placebo, (hazard ratio [HR], 0.91; 95% CI, 0.80-1.03). 7

The choice of a preferred antihypertensive agent in a particular patient involves consideration of multiple factors. 8 ALLHAT results showed that compared with the diuretic chlorthalidone, the ACE inhibitor lisinopril was associated with a higher risk of stroke (P = 0.02) and a higher risk of cardiovascular disease (P <0.001), including a higher risk of heart failure and higher risk of coronary revascularization. 9 TheValsartan Antihypertensive Long-term Use Evaluation (VALUE) trial involving 15,245 patients at high risk for cardiac events, including 31.7% with diabetes, found no difference in the primary composite outcome of sudden cardiac death, fatal myocardial infarction (MI), cardiovascular death, or cardiovascular morbidity (including heart failure) between the ARB valsartan and amloidipine. However, valsartan had a smaller effect compared with amloid-
While we await evidence of a renoprotective effect of RAS inhibition, the combination product of HCTZ and an ACE inhibitor appears to be a good investment to produce desired clinical outcomes in hypertensive patients with diabetes.

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REFERENCES


15. Data search performed October 6, 2006, of the data warehouse of a national pharmacy benefits manager representing approximately 500,000 beneficiaries of small employer drug benefit plans for pharmacy claims with dates of service from July 1, 2006, through September 30, 2006.