Optimizing ACE-Inhibitor and ARB Use in Diabetic Patients

By William H. Herman, MD, MPH

The HEDIS criteria for Comprehensive Diabetes Care measure medical attention for nephropathy in members 18 to 75 years of age with Type 1 and Type 2 diabetes. Each year, such members should have either a urine microalbumin test or evidence of treatment with an angiotensin converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB) medication.

The rationale for this measure is two-fold. First, diabetic nephropathy is the leading cause of chronic kidney disease requiring renal replacement therapy in the United States and is associated with increased cardiovascular mortality.

Second, identification of diabetic patients with microalbuminuria and intervention with ACE-inhibitors or ARBs prevents progression from microalbuminuria to macroalbuminuria, prevents decline of renal function, and reduces the occurrence of cardiovascular events.

Although numerous studies have demonstrated that treatment of hypertension in microalbuminuric diabetic patients reduces albuminuria irrespective of the class of antihypertensive agent used, renin-angiotensin system blockade with ACE-inhibitors or ARBs confers an additional benefit on renal function independent of blood pressure control.

Obviously, there are exceptions to every rule and this is true for the HEDIS measure of medical attention for nephropathy. ACE-inhibitors may cause a persistent dry cough in 5 to 20 percent of people who take them. Some people get used to the cough; others find it so disruptive that they discontinue ACE-inhibitors. For them, ARBs are a good alternative because ARBs are less likely to cause cough.

A few patients may develop hypotension with ACE-inhibitor or ARB treatment. This is relatively unusual because hypertension is common in diabetic patients, even when renal involvement is not present. Approximately 40 percent of Type 1 diabetic patients and 70 percent of Type 2 diabetic patients with normoalbuminuria have blood pressure levels greater than 140/90 mmHg. Blood pressure control in hypertensive diabetic patients often requires two, three or even four agents. Because of the known renoprotective effects of ACE-inhibitors and ARBs, treatment should start with one or the other of these agents. If a patient with treated hypertension experiences hypotension with the addition of an ACE-inhibitor or ARB, consideration should be given to reducing the dose or even discontinuing an alternative antihypertensive medication.

Some diabetic patients may experience an acute increase in serum creatinine when treated with ACE-inhibitors or ARBs. This is more likely to occur in proteinuric patients with serum creatinine levels >1.4 mg/dl. In general, if the serum creatinine increases by only 30 to 35 percent, the serum creatinine will stabilize after two months and treatment is associated with long-term preservation of renal function. For this reason, ACE-inhibitors or ARBs should not be stopped in patients who experience mild increases in serum creatinine.

Increases in serum creatinine greater than 50 percent should raise the suspicion of renal artery stenosis which may occur in up to 17 percent of hypertensive Type 2 diabetic patients. In these patients, the use of ACE-inhibitors or ARBs may lead to acute or chronic renal insufficiency if renal artery stenosis affects both kidneys or the sole functioning kidney. A rise in serum creatinine greater than 50 percent after use of these agents is a clue for the presence of renal artery stenosis and should prompt discontinuation of the ACE-inhibitor or ARB and additional evaluation.

Some diabetic patients may also develop hyperkalemia when ACE-inhibitors or ARBs are started. This is particularly likely in diabetic patients with baseline renal insufficiency and estimated glomerular filtration rate <30 ml/minute. In such patients, steps can be taken to minimize the risk of hyperkalemia. Patients should be instructed to
follow a low potassium diet and counseled against the use of salt substitutes that contain potassium. Foods rich in potassium including orange juice, melons, and bananas should be avoided.

Medications that interfere with renal potassium excretion including nonsteroidal anti-inflammatory drugs should be avoided, and if a potassium-sparing diuretic is added to an ACE-inhibitor or ARB, as in the treatment of congestive heart failure, close monitoring is required. Under such circumstances, the dose of spironolactone should probably not exceed 25 mg daily. Finally, diuretics which enhance the renal excretion of potassium are particularly effective in minimizing hyperkalemia. In patients with EGFR \( \geq 30 \) ml/minute, thiazide diuretics can be used.

In patients with more severe renal insufficiency, loop diuretics are often required. If potassium remains \( >5.5 \) mmol/l despite the steps described above, ACE-inhibitors or ARBs should be discontinued.

Finally, it is important to recognize that more is not always better. Although a number of studies have shown that dual therapy with both ACE-inhibitors and ARBs is better in reducing proteinuria than single drug therapy, recent studies that have evaluated the “hard outcomes” have demonstrated that combination therapy worsens major renal outcomes. Therefore, dual therapy with ACE-inhibitors and ARBs is not recommended.

In summary, medical attention for nephropathy is an important evidence-based quality measure for diabetic members 18 to 75 years of age. Screening for subclinical albuminuria will identify high-risk individuals in whom interventions with ACE-inhibitors or ARBs can prevent progressive kidney and adverse cardiovascular outcomes.

Clearly, there are exceptions to every rule and screening and treatment may not be indicated in patients with advanced comorbidities or terminal illnesses. Nevertheless, in light of the proven benefits of screening and treatment, these recommendations should apply to most diabetic patients. If a patient develops a cough with an ACE-Inhibitor, an angiotensin-receptor blocker should be employed. If a patient with treated hypertension develops hypotension when an ACE-inhibitor or ARB is added, other antihypertensive agents should be withdrawn or their dose should be reduced to minimize hypotension. Even if a patient develops a 30 to 35 percent increase in serum creatinine, ACE-inhibitor or ARB treatment should be continued as evidence suggests that in the long-run, treatment delays progression of CKD. Indeed, withholding ACE-inhibitors or ARBs solely on the basis of the level of renal function will unnecessarily deprive patients of the benefits that they would otherwise receive.

Finally, if hyperkalemia develops, measures should be taken to lower serum potassium while continuing treatment. For all of these reasons, blood pressure, serum creatinine, and potassium should be checked at least monthly during the first two or three months after starting treatment with ACE-inhibitors or ARBs.

References

William H. Herman, MD, MPH, is the Stefan S. Fajans/GlaxoSmithKline Professor of Diabetes and Professor of Internal Medicine and Epidemiology, University of Michigan, Ann Arbor, Michigan; Director, Michigan Center for Diabetes Translational Research; and Associate Medical Director, Blue Care Network.