Two Drugs Are Not Better Than One: Angiotensin Blockade to Control Proteinuria

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Story from the Frontlines:

A 61-year-old man with stage III chronic kidney disease (CKD) secondary to diabetic nephropathy, hypertension, lymphoproliferative B cell disorder, and type 2 diabetes mellitus (DM) complicated by neuropathy and retinopathy presented to renal clinic for follow-up of his diabetic nephropathy. He had been taking losartan 100 mg daily to control his proteinuria and blood pressure. However, his proteinuria remained elevated at 2.5 grams per day, and he was started on lisinopril 25 mg daily in addition to losartan 100 mg daily in order to get proteinuria under 1 gram per day. At another visit 2 months later, he was found to have proteinuria of 1.7 grams per day based on spot protein/creatinine ratio. His physician then increased his lisinopril to 40 mg daily while continuing losartan, which was decreased to 50 mg daily in the interim. At that appointment, they reinforced a goal of proteinuria less than 1 gram per day and planned on increasing the dose of lisinopril or losartan at the next visit if not at goal. He was maintained with lisinopril and losartan with a gradual decline in proteinuria and an increase in creatinine from 1.84 to 2.38 mg/dL. At his subsequent clinic visit, his proteinuria had dropped to 1.3 grams per day, but his home blood pressure recordings were as low as 90/56 mm Hg. The lisinopril was immediately stopped, and the patient’s blood pressure returned to normal at his next primary care visit.

Teachable Moment:

Proteinuria is a known complication of diabetic nephropathy with higher levels of proteinuria associated with increased mortality, cardiovascular events (myocardial infarction or stroke), and risk of progression to end-stage renal disease (ESRD)\(^1\)\(^2\)\(^3\). Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) are commonly used to reduce proteinuria and have been shown to retard progression to ESRD\(^4\). Combination ACE-I/ARB therapy also has been shown to decrease proteinuria more than either agent alone\(^4\). However, the safety of dual ACE-I/ARB therapy has come into question in recent years.

Several studies have shown that combined ACE-I/ARB therapy does not confer any additional benefits on mortality in spite of improvement in proteinuria and blood pressure. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) compared combination ACE-I/ARB therapy, ARB monotherapy, and ACE-I monotherapy in patients with vascular disease or diabetes with end-organ damage with respect to cardiovascular and renal endpoints\(^5\)\(^6\). Combination therapy was associated with decreased proteinuria but increased dialysis and doubling of creatinine compared to ACE-I monotherapy. In addition, patients treated with dual ACE-I/ARB therapy experienced a higher risk of hypotensive symptoms and syncope without any benefit in mortality compared to ACE-I patients.
The danger of dual ACE-I/ARB therapy is further supported by the Veteran Affairs Nephropathy in Diabetes (VA NEPHRON-D) trial\(^7\), which compared dual ACE-I/ARB therapy to ARB therapy plus placebo and found that there was no significant benefit in the combination therapy group with respect to mortality and cardiovascular events. However, the combination therapy group had higher rates of hyperkalemia and acute kidney injury than the ARB plus placebo group.

Mounting evidence from clinical trials, such as ONTARGET and VA-NEPHRON-D, have led to recommendations against combined ACE-I/ARB therapy. The 2012 update of the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Diabetes and CKD\(^8\) recommends against the combination of ACE-I and ARB due to increased risk for adverse events despite a decrease in proteinuria. The Eighth Joint National Committee (JNC-8) Hypertension Guidelines\(^9\) also recommend avoidance of combination ACE-I/ARB therapy.

The patient never achieved the 1 gram proteinuria target despite dual ACE-I/ARB therapy and suffered complications of low blood pressure and elevated creatinine. Treatment targets and their associated risks and benefits should be critically balanced in order to avoid potential harm.

References:


