Lisinopril Plus Telmisartan in Patients with Type 2 Diabetes, Microalbuminuria and Hypertension

A 62 year-old male with type II diabetes mellitus and hypertension presented to my clinic and was found to have microalbuminuria despite being on an angiotensin-converting enzyme inhibitor (ACEI). This led me to question if he would benefit from adding an angiotensin receptor blocker (ARB) to his regimen. I searched PubMed for “microalbuminuria AND ACE inhibitor AND ARB,” coming up with multiple studies. I selected the present paper as it addressed my specific question and had a much greater number of subjects than the others.

The study is a randomized, parallel-group, prospective, open-label evaluation of type II diabetics with hypertension and microalbuminuria. It was designed to evaluate the effects of combination therapy with an ARB and ACEI on microalbuminuria and blood pressure compared to monotherapy with either an ACEI or an ARB. Location was Sisli Etfal Education and Research Hospital in Instanbul, Turkey. The specific question addressed was: over 28 weeks does combination therapy with ACEI and ARB improve control of microalbuminuria and hypertension in type two diabetics with microalbuminuria and hypertension as compared to either medication alone?

Microalbuminuria has been shown to be an important predictor of mortality in patients with diabetes. Treatment with medications that block the renin-angiotensin system, including ACEIs and ARBs, have been shown to reduce the incidence of diabetic nephropathy in those with microalbuminuria. These medications alone, however, may insufficiently block the RAS system resulting in so-called breakthrough and persistent microalbuminuria as well as insufficient blood pressure control.

Subjects for the study were 40- to 65-year-old type 2 diabetics (WHO Criteria) with hypertension (SBP >140 or DBP > 90) and microalbuminuria (albumin excretion rate 30-300mg /24hr on at least 3 consecutive occasions). Exclusion criteria were type I diabetes mellitus (DM), BMI >40, secondary DM, alcoholism, thyroid disease, SBP >200, hypertension secondary to anything except DM, urinary tract infection, hematuria, chronic liver disease, carcinoma, cardiovascular event in the past 6 months, serum creatinine >150mmol/L, potassium >5.5, and pregnancy. After being off anti-hypertensives for 2 weeks, 219 patients were randomized to receive Lisinopril 20mg or Telmisartan 80mg daily for 24 weeks. Twenty-seven withdrew from the study during this stage due to intolerance of the medications, 15 in the Lisinopril group and 17 in Telmisartan group. Subsequently, these groups were further randomized to be treated with monotherapy for another 28 weeks or combination therapy with both medications for 28 weeks. Each of the four groups followed in the second half of the study had patients who required 12.5mg of hydrochlorothiazide daily to achieve “superior reductions in blood pressure,” though the number of patients getting this additional treatment was evenly distributed. All diabetic therapies were unchanged. Patients were instructed in diet, attempting to normalize across the subjects. Blood pressure, creatinine clearance, potassium, albumin excretion, glucose, hemoglobin A1c, and lipids were followed throughout the course and at the end of the 52 week course. The primary endpoints were blood pressure control and albumin excretion.

The experimental and control groups started out with similar prognoses and there were no differences in comorbidities between groups. Randomization was not concealed.
Patients were analyzed in the groups to which they were randomized. The study was open label, so the patients, physicians, and data analysts were aware of the treatment groups and what interventions were being performed. End points were assessed 28 weeks from the second randomization; all patients participated in this.

Evaluation of the primary endpoints in the study reveals a significant reduction of albumin excretion and blood pressure in all four groups as we would expect. Combination therapy appeared to be superior in both the attenuation of albumin excretion and control of the patient’s blood pressure. Reduction in excretion from baseline was as follows: 36% in the telmisartan group, 40.5% in the lisinopril group, 52.7% in the telmisartan + lisinopril group, and 53.6% in the lisinopril + telmisartan group. Adjusted mean blood pressure reductions were as follows (SBP/DBP): 15.1/10.2 in the telmisartan group, 16.4/10.4 in the lisinopril group, 25.5/15.4 in the telmisartan + lisinopril group, and 25.2/15.2 in the lisinopril + telmisartan group. In addition, 15 of the patients in the combination group had their microalbumin resolve compared with none in the monotherapy groups. Unfortunately, the 95% confidence intervals for the urinary albumin results were very large; the P-value between the groups was 0.04. Confidence intervals for the blood pressure changes were better and the P-value was 0.003.

The population in this study was consistent with my patient based on comorbid illnesses and age. Many of the other patients I see, however, are somewhat older and have comorbidities that were exclusion criteria in this study; this includes alcoholism, thyroid disease, and chronic liver disease. Individuals I would consider for dual blockade are within the limits for serum creatinine >150mmol/L (approximately 1.7mg/dl) and potassium >5.5 mmol/L (5.5 mg/dl). My clinic population is not ethnically consistent with the study subjects. It is not clear what effect, if any, these contradictory elements would have on the applicability of the results to my clinic population. Despite the fact that this study demonstrated a broad confidence interval in urine albumin levels, I would likely initiate combination therapy in patients who do not respond to maximum dose ACEI or ARB. I base this on the ability to follow a concrete outcome in their urinary albumin excretion and the known benefit of reducing this. Additionally, there were no adverse effects seen in the treatment groups and previous studies support the relatively benign nature if patients are selected carefully and followed closely. I have yet to be convinced that I should initiate combination therapy at the onset of microalbuminuria.

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