

Microalbuminuria in Type 2 Diabetes

Patients from the BENEDICT Trial were treated with trandolapril, verapamil or a combination to determine their effects on microalbuminuria.

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There is some evidence suggesting that the combination of angiotension-converting enzyme (ACE) inhibitors and nondihydropyridine calcium antagonists lower the level of urinary albumin and slow the progression of renal disease. However, their effectiveness in the prevention of microalbuminuria in type 2 diabetic patients remains unresolved.

My colleagues and I conducted the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT), at the Mario Negri Institute, Bergamo, Italy, to determine the effectiveness of the ACE inhibitor trandolapril (Mavik) and the calcium antagonist verapamil (Verelan) on the incidence of microalbuminuria in type 2 diabetic patients with hypertension and normal urinary albumin excretion (UAE).

ALONE OR IN COMBINATION

We enrolled 1,204 patients with type 2 diabetes for a duration of ≤ 25 years in the multicenter, double-blind, placebo-controlled study, and randomized them to receive trandolapril (2 mg/day) plus verapamil (180 mg/day in a sustained-release formula); trandolapril alone (2 mg/day); verapamil alone (240 mg/day in a sustained-release formula); or placebo. A total of 601 patients were treated with either an ACE inhibitor alone or in combination with verapamil; 603 patients were treated with either a calcium antagonist alone or in combination with trandolapril. Patients, aged ≥ 40 years, had an average UAE < 20 $\mu\text{g}/\text{minute}$ and a serum creatinine concentration ≤ 1.5 mg/dL at the beginning of the study.

As my colleagues and I recently reported in *The New England Journal of Medicine*, type 2 diabetic patients with normal UAE who were enrolled in the study and received the combination therapy of trandolapril plus verapamil had a significant reduction in the incidence of microalbuminuria. The incidence of microalbuminuria was also reduced in those who took trandolapril alone.

Because the goal of renoprotection, and perhaps now cardioprotection, is to prevent or delay the development of microalbuminuria, we concluded that this ACE inhibitor may be the best medication to control blood pressure and protect the kidney from developing the disease.

We determined the primary endpoint of BENEDICT to be the incidence of persistent microalbuminuria where at least two of three overnight urine collections were ≥ 20 $\mu\text{g}/\text{minute}$. This endpoint was confirmed approximately 2 months after collection. We used the interval-censoring method, which considers the true development of microalbuminuria to be the last time the patient had normoalbuminuria, and the first time that we validated the presence microalbuminuria.

Secondary endpoints included the cumulative incidence of major cardiovascular events, overall mortality rates and cardiovascular mortality rates. We included secondary endpoints in subgroups, and these were the decline of glomerular filtration rate and the progression of retinopathy.

EVALUATIONS THROUGHOUT THE STUDY

We conducted evaluations of blood pressure and morning urine samples at baseline, 1 week, 1 month and 3 months. Evaluations continued once every 3 months thereafter for the duration of the 3.6-year study. Measurements at baseline and once every 3 months were also taken for blood glucose, serum potassium, sodium, urea and creatinine levels, and we randomized evaluations of the levels of HbA1c, UAE and serum cholesterol at baseline and thereafter once every 6 months. These evaluations were also performed at all study endpoints or when there was a change to a patient's antihypertensive treatment.

The Beckman Array System, the Beckman Synchron Cx5 instrument and the Beckman Coulter Maxm were used to

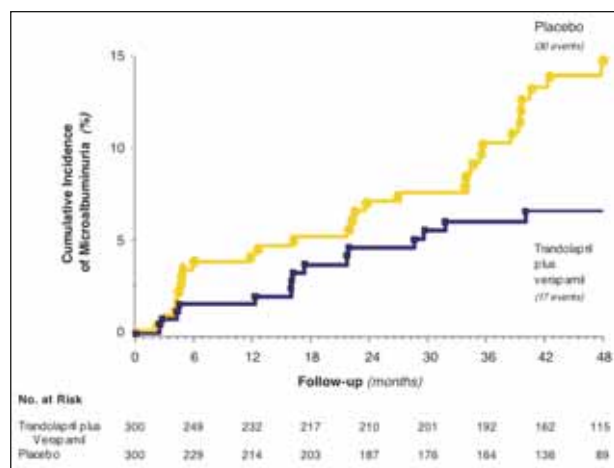


Figure 1. The cumulative incidence of microalbuminuria across patients in the combination and placebo groups.

measure UAE. Patients who had excretion levels <20 $\mu\text{g}/\text{minute}$ in two out of three collections were considered to have normal UAE. If patients had a urinary albumin concentration of <20 $\mu\text{g}/\text{mm}$, we considered them to have nondiabetic glomerular disease or infection.

A total of 30 of 300 patients in the placebo group developed microalbuminuria; 17 of 300 in the combination therapy group and 18 of 301 in the trandolapril only group developed the dysfunction (Figure 1). We found a decrease in the incidence of microalbuminuria among the patients who took trandolapril plus verapamil or trandolapril alone. Decreases were similar. The estimated acceleration factor between the groups was 0.39 (95% CI, 0.19-0.8; $P=.01$).

ONSET DELAYED

Microalbuminuria was delayed by a factor of 2.6 in patients who received the combination therapy, and we found that trandolapril delayed the onset of microalbuminuria by a factor of 2.1. Trandolapril caused an adjusted acceleration factor of 0.47 (95% CI, 0.26-0.83; $P=.01$) versus placebo. The factor was adjusted for predefined variables.

The onset of microalbuminuria was not delayed when patients used verapamil, as 36 of the 303 patients developed persistent microalbuminuria. When compared to the placebo group, there was an adjusted acceleration factor of 0.83 (95% CI, 0.45-1.51; $P=.54$).

The study showed that protection from microalbuminuria occurred when an ACE inhibitor was used alone. However, we did not see a protection against the development of microalbuminuria when study participants took the calcium antagonist alone.

Other study results showed that patients who took the combination therapy had an average trough systolic blood

pressure of 139 ± 10 mm/Hg and an average trough diastolic blood pressure of 80 ± 6 mm/Hg versus 139 ± 12 mm/Hg systolic and 81 ± 6 mm/Hg diastolic in patients who received trandolapril only; and 141 ± 10 mm/Hg and 82 ± 6 mm Hg in those who received verapamil only.

Patients in the placebo group had average trough systolic and diastolic blood pressure levels of 142 ± 12 mm/Hg and 83 ± 6 mm/Hg, respectively. There was a significant comparison ($P \leq .002$) between the placebo group, the combination-therapy group and the trandolapril-only groups, however, we did not find a significant comparison between the placebo and verapamil-only groups.

Twelve patients died during the study; one who received trandolapril, one who received verapamil and three who received placebo died from a cardiovascular event. However, there were no patients who received the combination therapy that had a fatal cardiovascular event.

Preventing microalbuminuria in diabetic patients impacts the longevity of their life, and avoiding renal disease lowers the number of complications including cardiovascular, retinal and peripheral artery diseases. Plenty of data exist showing that the mortality of diabetic patients increases over general population in relation to proteinuria and renal failure. Those diabetic patients that have normal urine do not show excess mortality.

ADVERSE EVENTS

We documented the presence of at least one serious adverse event, as classified by the Hoechst Adverse Reaction Terminology System, in 297 patients. Nonfatal serious adverse events occurred in 22.3% of patients in the combination group, 26.6% in the trandolapril-only group, 22.1% in the verapamil-only group and 23.3% in the placebo group. All groups also experienced similar rates of non-fatal cardiovascular events.

Results of the study indicated that there is a new agenda for nephrologists, diabetes specialists and general practitioners, where the final aim of preventing diabetic nephropathy is to limit cardiovascular events and death. The proposed treatment will prevent microalbuminuria, renal – and hopefully – cardiovascular diseases.

Further studies that list normotensives as inclusion criteria may expand the potential of ACE inhibitor therapy to include the prevention of hypertension and microalbuminuria in normotensive diabetic patients. ■

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Ruggenenti MD, Fassì A, Ilieva AP, et al. Preventing Microalbuminuria in Type 2 Diabetes. *N Engl J Med.* 2004;351:1941-1951.