

Trandolapril delayed persistent microalbuminuria in hypertension, type 2 diabetes, and normoalbuminuria

Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med.* 2004;351:1941-51.

QUESTION

In patients with hypertension, type 2 diabetes, and normoalbuminuria, do trandolapril and verapamil (used alone or in combination) prevent microalbuminuria?

METHODS

Design: Randomized placebo-controlled trial (Bergamo Nephrologic Diabetes Complications Trial [BENEDICT]).

Allocation: {Concealed}†.*

Blinding: Blinded {clinicians, patients, data collectors, outcome assessors, data analysts, and steering committee}†.*

Follow-up period: Median 3.6 years.

Setting: 9 centers in Italy.

Patients: 1209 patients ≥ 40 years of age (mean age 62 y, 53% men) who had hypertension, type 2 diabetes for < 25 years, a urinary albumin excretion rate < 20 µg/min, and serum creatinine level ≤ 1.5 mg/dL (133 µmol/L). Exclusion criteria were glycosylated hemoglobin level ≥ 11%, nondiabetic renal disease, or a specific indication for or contraindication to the study drugs.

Intervention: Trandolapril, 2 mg/d, plus verapamil, 180 mg/d (*n* = 302); trandolapril,

2 mg/d (*n* = 302); verapamil, 240 mg/d (*n* = 303); or placebo (*n* = 302). Additional antihypertensive drugs were allowed to help achieve the target of 120 mm Hg systolic and 80 mm Hg diastolic blood pressure.

Outcomes: Development of persistent microalbuminuria and adverse events.

Patient follow-up: 99.6% (intention-to-treat analysis).

MAIN RESULTS

Trandolapril, alone or with verapamil, but not verapamil alone, delayed the development of persistent microalbuminuria more than

did placebo (Table). The 4 groups did not differ for rates of serious adverse events.

CONCLUSION

In patients with hypertension, type 2 diabetes, and normoalbuminuria, trandolapril delayed development of persistent microalbuminuria.

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*See Glossary.

†Information provided by author.

Trandolapril and verapamil, in combination or alone, vs placebo for development of persistent microalbuminuria in hypertension, type 2 diabetes, and normoalbuminuria at median 3.6 years†

Comparisons	Event rates	Adjusted hazard ratio (95% CI)§	RRR (CI)	NNT (CI)
Trandolapril plus verapamil vs placebo	5.7% vs 10%	0.39 (0.21 to 0.73)	60% (26 to 78)	17 (13 to 39)
Trandolapril vs placebo	6% vs 10%	0.44 (0.24 to 0.81)	55% (18 to 75)	19 (14 to 55)
			RRI (CI)	NNH
Verapamil vs placebo	12% vs 10%	1.12 (0.68 to 1.85)	11% (-31 to 77)	Not significant

‡Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from hazard ratios provided by author.

§Hazard ratios adjusted for predefined baseline variables.

COMMENTARY

Blood pressure control is a key component of optimal diabetes care, with the United Kingdom Prospective Diabetes Study showing significant macrovascular and microvascular benefits (1). Diabetes care guidelines also emphasize the need for aggressive blood pressure control and recommend the use of angiotensin-converting enzyme (ACE) inhibitors for their renoprotective and cardioprotective effects (2).

The trial by Ruggenenti and colleagues contributes to our current evidence by showing that the antiproteinuric effects of ACE inhibitors begin even when albumin excretion rates are normal in patients with hypertension and type 2 diabetes. Trandolapril (but not verapamil) delayed the onset of persistent microalbuminuria. These results are consistent with those of the Heart Outcomes Prevention Evaluation study (3), which showed that patients with diabetes and ≥ 1 other cardiovascular risk factor benefited from ramipril.

Although it is tempting to believe that all patients with diabetes should be prescribed an ACE inhibitor regardless of cardiovascular risk factor status, the number needed to treat for patients without any other risk factors would be exceedingly high. Significant effort and cost would be required for minimal clinical benefit.

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References

1. **UK Prospective Diabetes Study Group.** Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ.* 1998;317:703-13.
2. **Canadian Diabetes Association Clinical Practice Guidelines Expert Committee.** Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes.* 2003;27(suppl 2).
3. **The Heart Outcomes Prevention Evaluation Study Investigators.** Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med.* 2000;342:145-53.