Preventing Microalbuminuria in Type 2 Diabetes

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ABSTRACT

BACKGROUND

The multicenter double-blind, randomized Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) was designed to assess whether angiotensin-converting–enzyme inhibitors and non-dihydropyridine calcium-channel blockers, alone or in combination, prevent microalbuminuria in subjects with hypertension, type 2 diabetes mellitus, and normal urinary albumin excretion.

METHODS

We studied 1204 subjects, who were randomly assigned to receive at least three years of treatment with trandolapril (at a dose of 2 mg per day) plus verapamil (sustained-release formulation, 180 mg per day), trandolapril alone (2 mg per day), verapamil alone (sustained-release formulation, 240 mg per day), or placebo. The target blood pressure was 120/80 mm Hg. The primary end point was the development of persistent microalbuminuria (overnight albumin excretion, ≥20 μg per minute at two consecutive visits).

RESULTS

The primary outcome was reached in 5.7 percent of the subjects receiving trandolapril plus verapamil, 6.0 percent of the subjects receiving trandolapril, 11.9 percent of the subjects receiving verapamil, and 10.0 percent of control subjects receiving placebo. The estimated acceleration factor (which quantifies the effect of one treatment relative to another in accelerating or slowing disease progression) adjusted for predefined baseline characteristics was 0.39 for the comparison between verapamil plus trandolapril and placebo (P=0.01), 0.47 for the comparison between trandolapril and placebo (P=0.01), and 0.83 for the comparison between verapamil and placebo (P=0.54). Trandolapril plus verapamil and trandolapril alone delayed the onset of microalbuminuria by factors of 2.6 and 2.1, respectively. Serious adverse events were similar in all treatment groups.

CONCLUSIONS

In subjects with type 2 diabetes and hypertension but with normoalbuminuria, the use of trandolapril plus verapamil and trandolapril alone decreased the incidence of microalbuminuria to a similar extent. The effect of verapamil alone was similar to that of placebo.

TYPE 2 DIABETES MELLITUS IS A PUBLIC health concern, and projections of its future effect are alarming. According to the World Health Organization, diabetes affects more than 170 million people worldwide, and this number will rise to 370 million by 2030.[1] About one third of those affected will eventually have progressive deterioration of renal function.[2] The first clinical sign of renal dysfunction in patients with diabetes is generally microalbuminuria (a sign of endothelial dysfunction that is not necessarily confined to the kidney),[4] which develops in 2 to 5 percent of patients per year.[5,6] In type 2 diabetes, unlike type 1 diabetes,[7] microalbuminuria is seldom reversible[8] but, instead, progresses to overt proteinuria in 20 to 40 percent of patients.[9,10] In 10 to 50 percent of patients with proteinuria, chronic kidney disease develops that ultimately requires dialysis or transplantation.[11-13] Forty to 50 percent of patients with type 2 diabetes who have microalbuminuria eventually die of cardiovascular disease[14,15]; this is three times as high a rate of death from cardiac causes as among patients who have diabetes but have no evidence of renal disease.[6]

In patients with diabetes and renal disease, lowering blood pressure and the levels of urinary albumin is effective in reducing the risk of end-stage renal disease as well as that of myocardial infarction, heart failure, and stroke.[16] Angiotensin-converting–enzyme (ACE) inhibitors or angiotensin II antagonists appear to be the most effective antihypertensive agents.[11,12,17-21] Data are available, although less consistent, that suggest that non-dihydropyridine calcium-channel blockers also may lower levels of urinary albumin[22] and the progression of renal disease[23] and that the combination of non-dihydropyridine calcium-channel blockers and ACE-inhibitor therapy is even more effective.[22-24] Treatment with the ACE inhibitor enalapril over a period of six years decreased the incidence of microalbuminuria in patients with type 2 diabetes who were normotensive and not obese.[25]

An unresolved issue is whether any of these medications can prevent microalbuminuria when given to patients with hypertension, type 2 diabetes, and normal urinary albumin excretion. The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT),[26] a multicenter, double-blind, placebo-controlled, randomized study, approached this issue by examining the effects of the ACE inhibitor trandolapril in combination with the non-dihydro-pyridine calcium-channel blocker verapamil, trandolapril alone, verapamil alone, and placebo on the incidence of microalbuminuria.

METHODS

We enrolled subjects who were 40 years of age or older and had hypertension and a known history of type 2 diabetes mellitus not exceeding 25 years, a urinary albumin excretion rate of less than 20 μg per minute in at least two of three consecutive, sterile, overnight samples, and a serum creatinine concentration of no more than 1.5 mg per deciliter (133 μmol per liter). Arterial hypertension was defined as an untreated systolic blood pressure of 130 mm Hg or more or a diastolic blood pressure of 85 mm Hg or more or as the need for antihypertensive therapy to attain a systolic or diastolic blood pressure under these levels.[27,28] Type 2 diabetes was diagnosed according to the criteria of the World Health Organization. Subjects with a glycosylated hemoglobin level of 11 percent or greater, nondiabetic renal disease, and a specific indication for or contraindication to ACE-inhibitor therapy or non-dihydropyridine calcium-channel blocker therapy were not included.[26]

All subjects provided written informed consent. The protocol was in accordance with the Declaration of Helsinki and was approved by the institutional review board at each center and the BENEDICT safety committee. This was an independent, academic study that was designed, conducted, and monitored by the Mario Negri Institute for Pharmacological Research. The principal investigator and the study coordinator wrote the protocol for the study and wrote the article. Dr. Richard Kay (Parexel International) designed the statistical analysis plan and provided suggestions for the statistical analysis, and Dr. Stuart Kupfer (Abbott) and Dr. Ruth Campbell (Division of Nephrology, University of Alabama, Birmingham) revised the paper.

After a six-week washout period during which any previous therapy with agents that inhibit the renin–angiotensin system was discontinued, and a three-week washout period during which any previous therapy with non-dihydropyridine calcium-channel blockers was discontinued, eligible subjects were randomly assigned to receive one of the study treatments: the non-dihydropyridine calcium-channel blocker verapamil (in a sustained-release formulation, at a dose of 240 mg per day), the ACE

inhibitor trandolapril (2 mg per day), the combination of verapamil (in a sustained-release formulation, 180 mg per day) plus trandolapril (2 mg per day), or placebo.

The target blood pressure was 120/80 mm Hg.[26] Additional antihypertensive drugs were allowed, to achieve the target blood pressure, in the following steps: step 1, hydrochlorothiazide or furosemide; step 2, doxazosin, prazosin, clonidine, methyldopa, or beta-blockers (allowed on the basis of specific indications, such as cardiac ischemic disease, but only if not contraindicated on the basis of electrocardiographic findings, such as bradyarrhythmias and delayed atrioventricular conduction); and step 3, minoxidil or long-acting dihydropyridine calcium-channel blockers. The use of potassium-sparing diuretics, inhibitors of the renin–angiotensin system, and non-dihydropyridine calcium-channel blockers different from the study drugs was not allowed. The subjects continued to receive their usual care for diabetes. A target glycosylated hemoglobin level of less than 7 percent was recommended for all subjects. No restriction of dietary salt or protein was implemented.

Blood pressure and randomly collected morning urine samples were evaluated at the time of randomization, at one week, one month, and three months after randomization, and every three months thereafter. Blood glucose, serum potassium, sodium, urea, and creatinine levels were measured at baseline and every three months thereafter. Glycosylated hemoglobin levels, urinary albumin excretion, and other laboratory values, including levels of serum cholesterol (total lipoprotein, high-density lipoprotein, and low-density lipoprotein) and triglycerides, were also measured at randomization and every six months thereafter. Additional evaluations were performed within one week after any change in antihypertensive therapy and whenever deemed clinically appropriate. All evaluations were also performed at the end of the study (after the last subject to have undergone randomization completed three years of treatment) and whenever subjects reached an end point.[26]

MEASUREMENTS

Trough systolic and diastolic (Korotkoff phases I and V, respectively) blood pressures were recorded as the mean of three morning measurements (to the nearest 2 mm Hg) taken before the administration of a study drug. The trough mean blood pressure was calculated as the diastolic blood pressure plus one third of the pulse pressure. Subjects with a urinary albumin concentration of less than 20 μg per milliliter (Micral test II, Boehringer Mannheim) in randomly collected urine samples without findings in the sediment suggestive of infection or nondiabetic glomerular disease submitted three timed overnight urine samples collected in bottles with a preservative (thimerosal, Sigma Chemical; 0.5 ml of a solution of 1 g per liter per bottle; and sodium hydroxide, 0.5 ml of a solution of 4 mol per liter per bottle). Subjects with urinary albumin excretion under 20 μg per minute in at least two of three collections were categorized as having normal urinary albumin excretion. Urinary albumin excretion was measured at the coordinating center with the use of nephelometry (Beckman Array System). Laboratory measurements were also evaluated centrally by means of a Beckman Syncron Cx5 instrument and a Coulter Maxm (Beckman Coulter). Glycosylated hemoglobin was measured with the use of ion-exchange high-performance liquid chromatography (normal range, 3.53 to 5.21 percent).[29]

SAMPLE SIZE

The primary measure of efficacy was the time to the onset of persistent microalbuminuria (urinary albumin excretion, 20 μg per minute or greater in at least two of three consecutive overnight urine collections and confirmed after approximately two months in at least two of three consecutive overnight urine collections[3,30]). Assuming a three-year incidence of microalbuminuria of 9.5 percent in the placebo group[22] and of 3.1 percent in the combination-therapy group, a total of 225 subjects in each of the four groups was calculated as necessary to provide the study with 80 percent power to detect a difference of this magnitude over a three-year follow-up period, with the use of a two-sided test with a type I error of 5 percent.[20] In order to account for possible dropouts, an enrollment of 300 subjects in each of the four groups was planned.

STATISTICAL ANALYSIS

For the analyses of the primary and secondary efficacy end points, the full set of data was used, including data on all subjects who underwent randomization — with the exception of four who never took study medication and one additional subject who was found at randomization to have microalbuminuria. For the safety analyses, the safety analyses set of data was used, excluding only the four subjects who never took the study medication. The

Table 1. Baseline Characteristics of Patients Randomly Assigned to Study Drugs.*

Characteristic	Trandolapril (N=301)	Verapamil (N=303)	Verapamil plus Trandolapril (N=300)	Placebo (N=300)
Age — yr	61.6±8.1	62.5±8.2	62.7±7.7	62.6±8.2
Male sex — no. (%)	157 (52.2)	164 (54.1)	165 (55.0)	149 (49.7)
Body-mass index†	29.1±4.7	29.5±4.6	29.2±5.3	28.6±4.2
Known duration of diabetes — yr	7.7±6.7	8.2±6.4	7.7±6.7	7.8±6.8
Smoking status — no. (%)				
Never smoked	169 (56.1)	185 (61.1)	157 (52.3)	187 (62.3)
Former smoker	91 (30.2)	88 (29.0)	107 (35.7)	76 (25.3)
Current smoker	41 (13.6)	30 (9.9)	36 (12.0)	37 (12.3)
Glycosylated hemoglobin — %‡	5.8±1.4	5.9±1.3	5.8±1.4	5.8±1.4
Glucose — mg/dl	160.9±46.8	162.6±47.7	160.8±47.0	161.4±47.2
Trough blood pressure — mm Hg				
Systolic	150.8±14.8	150.1±13.1	150.5±13.3	151.9±15.4
Diastolic	87.4±7.7	87.5±7.2	87.3±8.1	87.7±7.6
Mean arterial pressure	108.6±8.6	108.4±7.7	108.3±8.4	109.1±8.7
Urinary albumin excretion — μg/min§	5.02 (3.47–8.89)	5.91 (3.76–10.55)	5.31 (3.54–9.24)	5.07 (3.55–8.78)
Serum creatinine — mg/dl¶	0.9±0.2	0.9±0.2	0.9±0.2	0.9±0.2
Triglycerides — mg/dl‖	147.0±82.3	143.2±87.7	147.5±79.5	147.0±79.8
Cholesterol — mg/dl**				
Total	207.2±37.4	210.1±36.9	206.9±34.3	215.1±38.0
Low-density lipoprotein	160.0±36.4	163.4±36.0	159.7±34.0	168.0±37.5
High-density lipoprotein	46.9±12.2	46.9±12.1	47.0±12.2	46.9±11.9

* Plus–minus values are means ±SD.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Glycosylated hemoglobin was measured by ion-exchange high-performance liquid chromatography (normal range, 3.5 to 5.2 percent).[21]
§ Values shown are medians (interquartile ranges).
¶ To convert values for serum creatinine to micromoles per liter, multiply by 88.4.
‖ To convert values for triglycerides to millimoles per liter, multiply by 0.01129.
** To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

analyses were performed according to the randomly assigned treatment. Completeness of the follow-up was the same in the four treatment groups.

The primary end point of the time to the onset of microalbuminuria was measured from the date of administration of the first study drug and gave rise to interval-censored data.[31,32] The interval-censoring method takes into account the fact that the true date of the development of microalbuminuria lies within the last time the subject had normoalbuminuria and the first time the subject had microalbuminuria validated. This operational definition of microalbuminuria and its confirmation were applied by staff blinded to the randomized treatment assignments.

The primary analysis (i.e., the comparison be-

tween trandolapril plus verapamil and placebo) used the accelerated failure-time model with log normal error structure, implemented with the PROC LIFEREG procedure (SAS), which allowed the direct incorporation of interval-censored data[31,32] and took into consideration site, age, sex, smoking status (patients who had never smoked as compared with former smokers and current smokers), diastolic blood pressure, and log-transformed urinary albumin excretion (median of three readings) at baseline.

Secondary, exploratory analysis included follow-up systolic and diastolic blood pressure. The magnitude of the treatment effect was assessed by calculating the acceleration factor. This factor quantifies the effect of one treatment relative to another treat-

Table 2. Treatments in Patients with Type 2 Diabetes and Normal Urinary Albumin Excretion at Baseline and during Follow-up.*

Treatment	Baseline				Follow-up			
	Trandolapril (N=301)	Verapamil (N=303)	Verapamil plus Trandolapril (N=300)	Placebo (N=300)	Trandolapril (N=301)	Verapamil (N=303)	Verapamil plus Trandolapril (N=300)	Placebo (N=300)
			number (percent)					
Glucose-lowering regimen								
Diet alone	79 (26.2)	92 (30.4)	96 (32.0)	88 (29.3)	51 (16.9)	62 (20.5)	72 (24.0)	61 (20.3)
Oral hypoglycemic agent	195 (64.8)	169 (55.8)	165 (55.0)	175 (58.3)	199 (66.1)	183 (60.4)	175 (58.3)	186 (62.0)
Insulin and oral hypoglycemic agent	15 (5.0)	25 (8.3)	19 (6.3)	19 (6.3)	36 (12.0)	45 (14.9)	34 (11.3)	36 (12.0)
Insulin alone	12 (4.0)	17 (5.6)	20 (6.7)	18 (6.0)	15 (5.0)	13 (4.3)	19 (6.3)	17 (5.7)
Antihypertensive agents								
Any	172 (57.1)	162 (53.5)	161 (53.7)	169 (56.3)	193 (64.1)	188 (62.0)	165 (55.0)†	201 (67.0)
Diuretic	66 (21.9)	70 (23.1)	58 (19.3)	65 (21.7)	51 (16.9)	65 (21.5)	51 (17.0)	65 (21.7)
Beta-blocker	31 (10.3)	24 (7.9)	23 (7.7)	25 (8.3)	29 (9.6)	21 (6.9)	26 (8.7)	29 (9.7)
Calcium-channel blocker (dihydropyridine)	73 (24.3)	88 (29.0)	87 (29.0)	90 (30.0)	79 (26.2)	77 (25.4)‡	74 (24.7)‡	98 (32.7)
Sympatholytic agent	68 (22.6)	63 (20.8)	59 (19.7)	56 (18.7)	137 (45.5)‡	149 (49.2)	109 (36.3)§	163 (54.3)
Lipid-lowering agents								
Any	38 (12.6)	29 (9.6)	35 (11.7)	36 (12.0)	57 (18.9)	62 (20.5)	66 (22.0)	72 (24.0)
Statin alone	25 (8.3)	10 (3.3)	27 (9.0)	25 (8.3)	39 (13.0)	35 (11.6)‡	48 (16.0)	54 (18.0)
Fibrate alone	11 (3.7)	18 (5.9)	5 (1.7)	8 (2.7)	9 (3.0)	16 (5.3)	11 (3.7)	10 (3.3)
Statin and fibrate	1 (0.3)	0	1 (0.3)	2 (0.7)	7 (2.3)	8 (2.6)	4 (1.3)	5 (1.7)
Antiplatelet agent	7 (2.3)	7 (2.3)	7 (2.3)	7 (2.3)	26 (8.6)	25 (8.3)	25 (8.3)	19 (6.3)

* All differences between the treatment groups and the placebo group, other than those shown, were not significant.
† P<0.01 for the comparison with placebo.
‡ P<0.05 for the comparison with placebo.
§ P<0.001 for the comparison with placebo.

ment in accelerating or slowing the progression of the disease.[32] The 95 percent confidence interval for the acceleration factor was found by determining the confidence limits around the logarithm of the acceleration factor and then calculating the exponentials of these confidence limits. The primary comparison was made at a significance level of 0.05.

Secondary objectives involved comparisons of trandolapril or the sustained-release formulation of verapamil with placebo. This comparison was carried out in the same way as that for the combination of trandolapril plus verapamil with placebo, but the significance level was set at 0.025 to account for the use of Bonferroni's correction.[26] In addition, for exploratory purposes, the results of randomly assigned treatment with an ACE inhibitor (trandolapril plus verapamil or trandolapril alone) or without an ACE inhibitor (verapamil or placebo) and of randomly assigned treatment with non-dihydropyridine calcium-channel blockers (trandolapril plus verapamil or verapamil alone) or without non-dihydropyridine calcium-channel blockers (trandolapril alone or placebo) were compared.

A Cox regression model[32] was also applied, to ensure the robustness of the results. For graphical representation, Kaplan–Meier curves were plotted for each treatment group, with the use of the midpoint of the intervals as event times. Adverse events were coded with the use of the Hoechst Adverse Reaction Terminology System classification. Multiple reports of the same event were counted only once, and the least favorable report was used. Fatal and nonfatal adverse events were separately reported according to treatment group and overall.

The data were entered with the use of a Microsoft Access software user interface and were exported and analyzed with the use of SAS software (ver-

sion 8). Dichotomous and polychotomous baseline characteristics of the patients were compared with the use of the chi-square test or Fisher's exact test, and continuous characteristics were compared with the use of the Wilcoxon rank-sum test. The data were presented as numbers and percentages, means ±SD, or medians and interquartile ranges, as appropriate. All P values are two-sided.

RESULTS

A total of 1209 subjects were randomly assigned to one of four treatments, and of those, 1204 were followed for a median of 3.6 years (interquartile range, 1.3 to 4.3) (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). The follow-up period was similar for all four groups. The baseline demographic, clinical, and biochemical characteristics of the patients were balanced among the treatment groups (Table 1). The medications taken by the subjects at baseline and during follow-up are shown in Table 2.

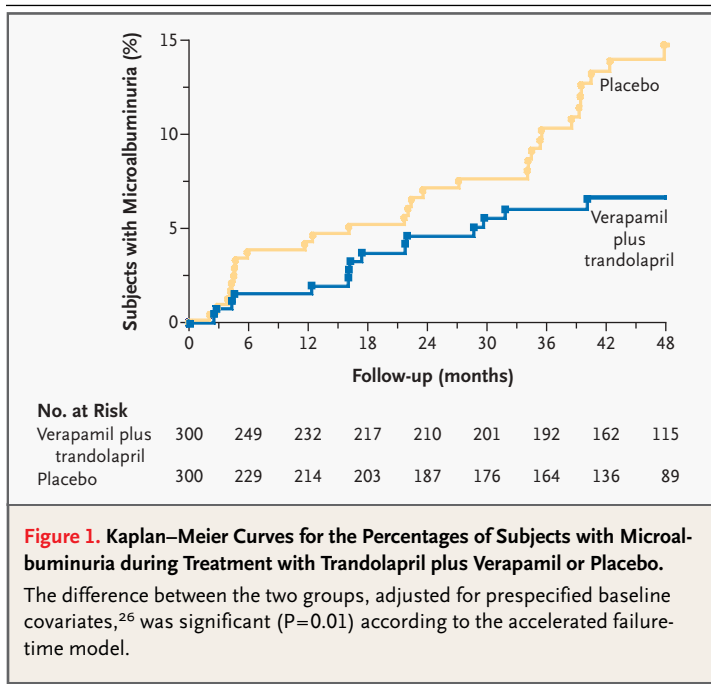### TRANDOLAPRIL PLUS VERAPAMIL AS COMPARED WITH PLACEBO

Persistent microalbuminuria developed in 17 of the 300 subjects receiving trandolapril plus verapamil (5.7 percent), as compared with 30 of the 300 subjects receiving placebo (10.0 percent). Kap-

Figure 1. Kaplan–Meier Curves for the Percentages of Subjects with Microalbuminuria during Treatment with Trandolapril plus Verapamil or Placebo.

The difference between the two groups, adjusted for prespecified baseline covariates,[26] was significant (P=0.01) according to the accelerated failure-time model.

lan–Meier curves for these two treatment groups clearly separated at three months (Fig. 1). The estimated acceleration factor when we controlled for predefined baseline variables was 0.39 (95 percent confidence interval, 0.19 to 0.80; P=0.01) in the trandolapril-plus-verapamil group as compared with the placebo group. Thus, the combination of trandolapril and verapamil significantly delayed the onset of microalbuminuria, by a factor of 2.6. The unadjusted comparison provided similar results. After separate adjustment for systolic and diastolic blood pressure at follow-up visits, the acceleration factor accounting for systolic blood pressure was 0.46 (95 percent confidence interval, 0.22 to 0.93; P=0.03) and that accounting for diastolic blood pressure was 0.46 (95 percent confidence interval, 0.22 to 0.95; P=0.04).

TRANDOLAPRIL ALONE OR VERAPAMIL ALONE AS COMPARED WITH PLACEBO

Persistent microalbuminuria developed in 18 of the 301 subjects in the trandolapril group (6.0 percent) and in 36 of the 303 subjects in the verapamil group (11.9 percent). Kaplan–Meier curves for the two groups clearly separated at three months and continued to diverge (Fig. 2A). The acceleration factor after control for predefined baseline variables was 0.47 (95 percent confidence interval, 0.26 to 0.83; P=0.01) in the trandolapril group as compared with the placebo group. Thus, the use of trandolapril significantly delayed the onset of microalbuminuria, by a factor of 2.1. The unadjusted comparison confirmed this result. After separate adjustment for systolic and diastolic blood pressure at follow-up visits, the acceleration factor was 0.50 (95 percent confidence interval, 0.28 to 0.90; P=0.02) and 0.52 (95 percent confidence interval, 0.30 to 0.92; P=0.03), respectively. The acceleration factor after control for predefined baseline variables was 0.83 (95 percent confidence interval, 0.45 to 1.51; P=0.54) in the verapamil group as compared with the placebo group (Fig. 2B). Without adjustment for baseline covariates, the acceleration factor was 1.34 (95 percent confidence interval, 0.67 to 2.68; P=0.41). Verapamil did not significantly delay the onset of microalbuminuria, even after we controlled for systolic and diastolic blood pressure at follow-up visits.

Trandolapril plus verapamil or trandolapril alone was associated with a delayed onset of microalbuminuria as compared with verapamil. The acceleration factor controlling for predefined baseline var-

iables was 0.40 (95 percent confidence interval, 0.19 to 0.85; P=0.02) and 0.53 (95 percent confidence interval, 0.29 to 0.96; P=0.04), respectively.

ACE INHIBITORS OR NON-DIHYDROPYRIDINE CALCIUM-CHANNEL BLOCKERS

A total of 601 subjects received an ACE inhibitor (trandolapril alone or with verapamil) and 603 subjects did not; 603 subjects received a non-dihydropyridine calcium-channel blocker (verapamil alone or with trandolapril) and 601 subjects did not. The baseline characteristics were balanced between those who did and did not receive an ACE inhibitor and between those who did and did not receive a non-dihydropyridine calcium-channel blocker (data not shown).
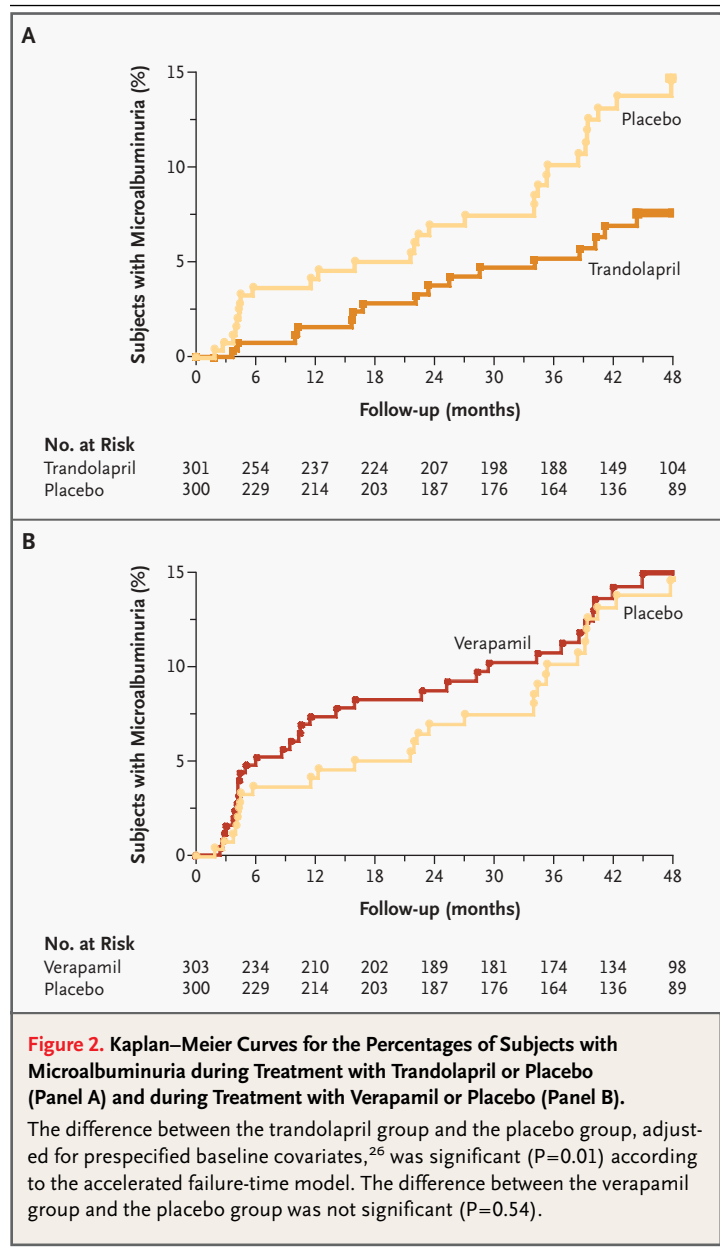
Persistent microalbuminuria developed in 35 of the 601 subjects who received ACE-inhibitor therapy (5.8 percent) and in 66 of the 603 subjects who did not (10.9 percent). Kaplan–Meier curves for the two groups clearly separated at three months and remained apart (Fig. 3A). The acceleration factor controlling for predefined baseline variables was 0.44 (95 percent confidence interval, 0.27 to 0.70; P<0.001) in the group receiving ACE inhibitors as compared with the group that did not receive them. Thus, the use of ACE inhibitors appeared to slow the progression to microalbuminuria by a factor of 2.3. After separate adjustment for systolic and diastolic blood pressure at follow-up visits, the acceleration factor was 0.51 (95 percent confidence interval, 0.32 to 0.81; P=0.005) and 0.50 (95 percent confidence interval, 0.32 to 0.79; P=0.003), respectively.
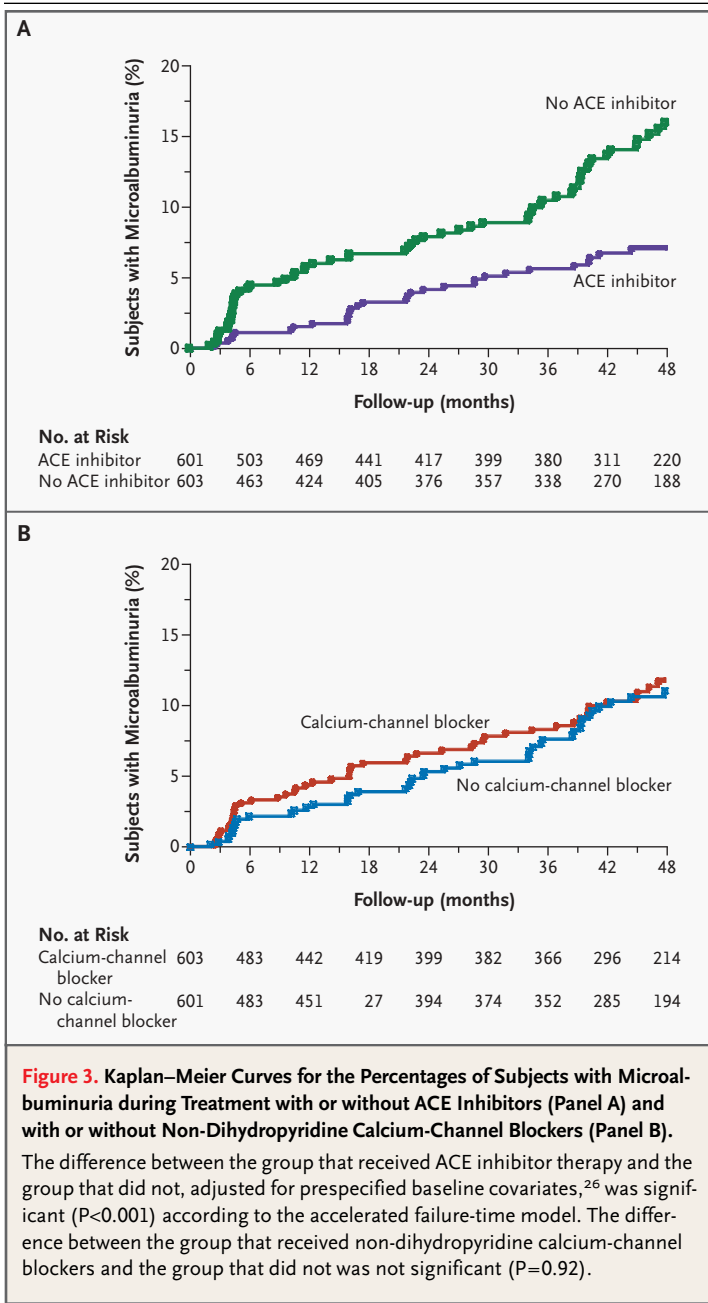
Persistent microalbuminuria developed in 53 of the 603 subjects (8.8 percent) who received non-dihydropyridine calcium-channel blockers and 48 of the 601 subjects (8.0 percent) who did not. Therapy with non-dihydropyridine calcium-channel blockers did not significantly delay the onset of microalbuminuria (Fig. 3B) even after we controlled for baseline covariates and systolic or diastolic blood pressure at follow-up visits.

OTHER OUTCOMES

Trough blood-pressure levels at baseline and at follow-up visits are shown in Table 1 and Figure 4. Throughout the study the average trough systolic blood pressure was 139±10 mm Hg and the average trough diastolic blood pressure was 80±6 mm Hg in the group receiving trandolapril plus verapamil; the corresponding values were 139±12 mm Hg

and 81±6 mm Hg, respectively, in the trandolapril group; 141±10 mm Hg and 82±6 mm Hg, respectively, in the verapamil group; and 142±12 mm Hg and 83±6 mm Hg, respectively, in the placebo group. The comparison was significant (P≤0.002) for systolic and diastolic blood pressure between either the trandolapril-plus-verapamil group or the trandolapril-alone group and the placebo group, but the results were not significant for the verapamil group as compared with the placebo group. The average trough mean arterial pressure through-

No. at Risk

Trandolapril	301	254	237	224	207	198	188	149	104
Placebo	300	229	214	203	187	176	164	136	89

No. at Risk

Verapamil	303	234	210	202	189	181	174	134	98
Placebo	300	229	214	203	187	176	164	136	89

Figure 2. Kaplan–Meier Curves for the Percentages of Subjects with Microalbuminuria during Treatment with Trandolapril or Placebo (Panel A) and during Treatment with Verapamil or Placebo (Panel B).

The difference between the trandolapril group and the placebo group, adjusted for prespecified baseline covariates,[26] was significant (P=0.01) according to the accelerated failure-time model. The difference between the verapamil group and the placebo group was not significant (P=0.54).

A

No. at Risk

ACE inhibitor	601	503	469	441	417	399	380	311	220
No ACE inhibitor	603	463	424	405	376	357	338	270	188

B

No. at Risk

Calcium-channel blocker	603	483	442	419	399	382	366	296	214
No calcium-channel blocker	601	483	451	27	394	374	352	285	194

Figure 3. Kaplan–Meier Curves for the Percentages of Subjects with Microalbuminuria during Treatment with or without ACE Inhibitors (Panel A) and with or without Non-Dihydropyridine Calcium-Channel Blockers (Panel B).

The difference between the group that received ACE inhibitor therapy and the group that did not, adjusted for prespecified baseline covariates,[26] was significant (P<0.001) according to the accelerated failure-time model. The difference between the group that received non-dihydropyridine calcium-channel blockers and the group that did not was not significant (P=0.92).

major differences in the blood glucose levels and the lipid profiles among the different treatment groups (data not shown). In all the treatment groups, the glomerular filtration rate was similar and did not significantly change during follow-up (data not shown).

ADVERSE EVENTS

A total of 297 subjects had at least one serious adverse event between the first dose of a study drug and two weeks after the discontinuation of the study. Twelve subjects died during the course of the study, and one additional subject in the trandolapril group died from colorectal adenocarcinoma 14 days after completion of the follow-up period. One subject receiving trandolapril, one receiving verapamil, and three receiving placebo died from a cardiovascular event. No fatal cardiovascular events occurred in the group receiving trandolapril plus verapamil. The incidence of nonfatal serious adverse events (22.3 percent in the trandolapril-plus-verapamil group, 26.6 percent in the trandolapril group, 22.1 percent in the verapamil group, and 23.3 percent in the placebo group), including nonfatal cardiovascular events (3.7 percent in the trandolapril-plus-verapamil group, 4.0 percent in the trandolapril group, 4.3 percent in the verapamil group, and 4.0 percent in the placebo group), was similar in the four treatment groups. Sinoatrial block with junctional rhythm was reported in one subject receiving trandolapril plus verapamil, and a second-degree atrioventricular block was reported in one subject receiving verapamil. Cough developed in 11 subjects (5 in the trandolapril-plus-verapamil group, 4 in the trandolapril group, and 2 in the placebo group), all of whom discontinued the study treatment and withdrew from the study.

DISCUSSION

Our study indicates that treatment with trandolapril plus verapamil significantly reduces the incidence of microalbuminuria in patients with type 2 diabetes and normal urinary albumin excretion, as compared with placebo. Trandolapril alone also appeared to decrease the incidence of microalbuminuria, whereas verapamil had no effect. The effect of trandolapril plus verapamil and trandolapril alone in preventing microalbuminuria exceeded expectations based on changes in blood pressure alone.

Preventing (or delaying) the development of microalbuminuria is a key treatment goal for reno-

out the study was 100±6 mm Hg in the trandolapril-plus-verapamil group, 101±7 mm Hg in the trandolapril group, 102±6 mm Hg in the verapamil group, and 103±7 mm Hg in the placebo group (P<0.001 for the comparison between the groups receiving trandolapril alone or in combination and the placebo group; but the results were not significant for the verapamil group as compared with the placebo group). Throughout the study there were no
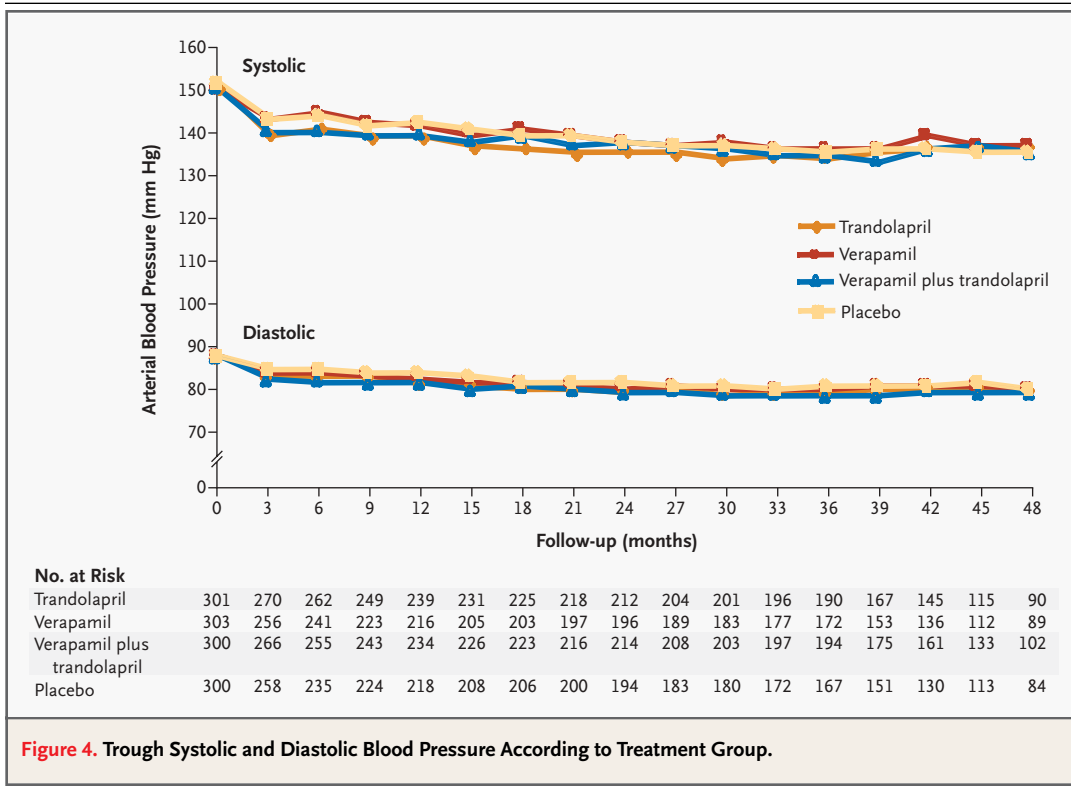
Figure 4. Trough Systolic and Diastolic Blood Pressure According to Treatment Group.

protection[33-35] and, possibly, for cardioprotection.[4] Recent clinical trials suggested that inhibition of the renin–angiotensin system may actually prevent nephropathy. The post hoc analyses of the reduction in hypertension in the Heart Outcomes Prevention Evaluation study[18] and in the Losartan Intervention for Endpoint study[36] found a lower incidence of overt nephropathy in subjects with type 2 diabetes who received therapy that inhibited the renin–angiotensin system than in controls. However, these studies were not designed to assess the incidence of microalbuminuria, because patients with microalbuminuria were included in them. Our results demonstrate that microalbuminuria can be prevented in type 2 diabetes.

No subject was prematurely withdrawn from the study because of acute deterioration of renal function or hyperkalemia. Nine subjects (five in the trandolapril-plus-verapamil group and four in the trandolapril group) discontinued treatment because of cough. It is of concern that two subjects, one in the trandolapril-plus-verapamil group and one in the verapamil group, discontinued treatment because of the development of delayed atrioventricular conduction, but both recovered after treatment was withdrawn. Five subjects died from cardiovascular disease: one in the trandolapril group, one in the verapamil group, and three in the placebo group.

In conclusion, in subjects with type 2 diabetes and arterial hypertension, normoalbuminuria, and normal renal function, ACE-inhibitor therapy with trandolapril plus verapamil or trandolapril alone prevented the onset of microalbuminuria. The renoprotective effect of ACE inhibition did not appear to be enhanced by the addition of a non-dihydropyridine calcium-channel blocker. These findings suggest that in hypertensive patients with type 2 diabetes and normal renal function, an ACE inhibitor may be the medication of choice for controlling blood pressure. The apparent advantage of ACE inhibitors over other agents includes a protective effect on the kidney against the development of microalbuminuria, which is a major risk factor for cardiovascular events and death in this population.[37]

APPENDIX

Members of the BENEDICT Study Organization were as follows (all in Italy unless otherwise noted): Principal investigator — G. Remuzzi (Bergamo); Study coordinator — P. Ruggenenti (Bergamo); Coordinating center — Mario Negri Institute for Pharmacological Research, Clinical Research Center for Rare Diseases Aldo e Cele Daccò, Villa Camozzi, Ranica (Bergamo); Participating centers — G. Nastasi, A. Ongaro, F. Querci, A. Anabaya (Alzano Lombardo); R. Trevisan, A.R. Dodesini, G. Lepore, I. Nosari, C. A. Aros Espinoza, A. Fassi (Bergamo); M. Songini, G. Carta, G. Piras (Cagliari); B. Minetti, P. Fiorina, G. Ghilardi, V. Grassia, E. Pezzali, E. Seghezzi, I. Villanova (Clusone); A. Spalluzzi, I. Codreanu, C. Flores (Ponte San Pietro, Villa d'Almè); C. Chiurchiu, F. Arnoldi, L. Mosconi, M. Monducci (Ranica); A. Bossi, M. Facchetti, V. Brusegan (Romano di Lombardia); F. Inversi, V. Bertone, R. Mangili, S. Bruno (Seriate); A. Bossi, A. Parvanova, I.P. Iliev, E. Terzieva (Treviglio); Ophthalmologists — M. Filipponi, I.P. Iliev, S. Tadini (Bergamo); Monitoring and drug distribution (Mario Negri Institute) — G. Gherardi, N. Rubis, S. Birolini, L. Bruni, W. Calini, V.A. Carrasco Oyarzun, R. D'Adda, O. Diadei, M. Ferrari, L. Mangili, A. Milani, G. Noris, K. Pagani, S. Quadri, A. Rossi, S. Secomandi, G. Villa (Ranica); Carriers (Mario Negri Institute) — G. Gaspari, S. Gelmi, G. Gervasoni, L. Nembrini (Ranica); Database and data validation (Mario Negri Institute) — A. Remuzzi, B. Ene-Iordache, V. Gambara (Ranica); Data analysis (Mario Negri Institute) — A. Perna, B.D. Dimitrov, M. Ganeva, J. Zamora (Ranica); Laboratory measurements (Mario Negri Institute) — F. Gaspari, F. Carrara, E. Centemeri, S. Ferrari, M. Pellegrino, N. Stucchi (Ranica); Genomic evaluations (Mario Negri Institute) — M. Noris, P. Bettinaglio, S. Bucchioni, J. Caprioli, B. Giussani (Bergamo); Regulatory affairs (Mario Negri Institute) — P. Boccardo (Ranica); Steering committee — S. Kupfer (Abbott Park, Ill., United States), L. Minetti (Bergamo), G. Remuzzi (Bergamo), U.F. Legler (Ludwigshafen, Germany), B. Kalsch (Ludwigshafen, Germany), D. Nehrdich (Ludwigshafen, Germany), A. Nicolucci (S. Maria Imbaro), A. Perna (Bergamo), P. Ruggenenti (Bergamo); Safety committee — G.L. Bakris (Chicago, United States), R. Kay (Sheffield, United Kingdom), G.C. Viberti (London, United Kingdom).

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