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Effects of Fosinopril and Pravastatin on Cardiovascular Events in Subjects With Microalbuminuria

Folkert W. Asselbergs, MD; Gilles F.H. Diercks, MD, PhD; Hans L. Hillege, MD, PhD; Ad J. van Boven, MD, PhD; Wilbert M.T. Janssen, MD, PhD; Adriaan A. Voors, MD, PhD; Dick de Zeeuw, MD, PhD; Paul E. de Jong, MD, PhD; Dirk J. van Veldhuisen, MD, PhD; Wiek H. van Gilst, PhD; for the Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators*

Background—Microalbuminuria is associated with increased risk of cardiovascular events. We assessed whether therapeutic intervention aimed at lowering urinary albumin excretion would reduce cardiovascular events in microalbuminuric subjects (15 to 300 mg/24 hours).

Methods and Results—From the Prevention of Renal and Vascular Endstage Disease (PREVEND) cohort (n=8592), 1439 subjects fulfilled the inclusion criteria of the PREVEND Intervention Trial (PREVEND IT). Of these subjects, 864 were randomized to fosinopril 20 mg or matching placebo and to pravastatin 40 mg or matching placebo. The mean follow-up was 46 months, and the primary end point was cardiovascular mortality and hospitalization for cardiovascular morbidity. Mean age was 51±12 years; 65% of subjects were male, and 3.4% had a previous cardiovascular event. Mean cholesterol level was 5.8±1.0 mmol/L, mean systolic/diastolic blood pressure was 130±18/76±10 mm Hg, and median urinary albumin excretion was 22.8 (15.8 to 41.3) mg/24 hours. The primary end point occurred in 45 subjects (5.2%). Fosinopril reduced urinary albumin excretion by 26% ($P<0.001$). Subjects treated with fosinopril showed a 40% lower incidence of the primary end point (hazard ratio 0.60 [95% CI 0.33 to 1.10], $P=0.098$, log-rank). Pravastatin did not reduce urinary albumin excretion, and subjects treated with pravastatin showed a 13% lower incidence of the primary end point than subjects in the placebo group (0.87 [0.49 to 1.57], $P=0.649$, log-rank).

Conclusions—In microalbuminuric subjects, treatment with fosinopril had a significant effect on urinary albumin excretion. In addition, fosinopril treatment was associated with a trend in reducing cardiovascular events. Treatment with pravastatin did not result in a significant reduction in urinary albumin excretion or cardiovascular events. (*Circulation*. 2004;110:2809-2816.)

Key Words: prevention ■ endothelium ■ risk factors ■ trials

Microalbuminuria is a common indicator for cardiovascular risk factors and is associated with an increased risk of cardiovascular morbidity and mortality in patients with an increased risk profile and in the general population.^{1,2} It has been suggested that microalbuminuria may reflect the renal manifestation of a global abnormality of vascular function even in subjects without diabetes or hypertension. Thus, microalbuminuria might be an easily detectable marker of generalized vascular dysfunction and might therefore identify subjects at risk for cardiovascular and renal events.³ Several antihypertensive agents and statins have been shown to decrease the incidence of cardiovascular and renal

events.⁴⁻⁷ In particular, ACE inhibitors and angiotensin II receptor antagonists appear to be superior to more conventional antihypertensive therapies.^{6,8,9} ACE inhibitors and angiotensin II receptor antagonists are also known to be superior in reducing urinary albumin excretion in diabetic, nondiabetic, and essential hypertensive populations.^{6,9-11} Interestingly, statins also lower urinary albumin excretion, although this is less unequivocally documented.^{12,13}

Small clinical studies and post hoc analysis of large trials show that the degree of reduction of proteinuria or albuminuria during ACE inhibitor or angiotensin II receptor antagonist therapy is associated with the degree of cardiovascular

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From the Department of Clinical Pharmacology, University of Groningen (F.W.A., D.d.Z., W.H.v.G.), Department of Cardiology (G.F.H.D., A.J.v.B., A.A.V., D.J.v.V.), Trial Coordination Center (H.L.H.), and Department of Nephrology (W.M.T.J., P.E.d.J.), University Hospital Groningen, Groningen, the Netherlands.

*Investigators for the PREVEND IT are in the Appendix.

The results of the PREVEND IT were presented at the 76th Scientific Sessions of the American Heart Association, November 9 to 12, 2003, in Orlando, Fla, and published in abstract form (*Circulation*. 2003;108:2723).

Correspondence to Wiek H. van Gilst, Department of Clinical Pharmacology, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands. E-mail w.h.van.gilst@med.rug.nl

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2 x 2 Factorial design

	Pravastatin	Placebo	Total
Fosinopril	216	215	431
Placebo	217	216	433
Total	433	431	864

Figure 1. Trial design.

and renal protection.¹⁴ However, it is unknown whether intervention specifically aimed at reducing urinary albumin excretion will reduce cardiovascular events. Therefore, in the Prevention of RENal and Vascular ENdstage Disease Intervention Trial (PREVEND IT), we aimed to assess the ability of the ACE inhibitor fosinopril and the statin pravastatin to reduce the incidence of cardiovascular death and hospitalization for cardiovascular morbidity in a microalbuminuric population (15 to 300 mg/24 hours).

Methods

The PREVEND IT is an investigator-initiated, single-center, double-blind, randomized, placebo-controlled trial with a 2×2 factorial design. Subjects were randomized to fosinopril 20 mg or matching placebo and to pravastatin 40 mg or matching placebo. Details of the PREVEND IT objectives, design, and methods have been reported previously¹⁵ and are summarized below.

Subjects

PREVEND IT is a substudy of the PREVEND program. The objective of the PREVEND program is to assess the value of microalbuminuria as an indicator of increased cardiovascular and renal risk in the general population. In 1997 to 1998, all inhabitants of the city of Groningen, the Netherlands, aged 28 to 75 years (n=85 421) were asked to send in a morning urine sample and to fill out a short questionnaire on demographics and cardiovascular history. Response was received from 40 856 subjects (47.8%). All subjects with a urinary albumin excretion of >10 mg/L (n=7768) in their morning urine together with a randomly selected control group with a urinary albumin concentration of <10 mg/L (n=3395) were invited to the outpatient clinic. A total of 8592 subjects completed the screening program. The key entry criteria of the PREVEND IT were persistent microalbuminuria (a urinary albumin concentration >10 mg/L in 1 early morning spot urine sample and a concentration of 15 to 300 mg/24 hours in 2 24-hour urine samples at least once), a blood pressure <160/100 mm Hg and no use of antihypertensive medication, and a total cholesterol level <8.0 mmol/L, or <5.0 mmol/L in case of previous myocardial infarction, and no use of lipid-lowering medication. The cutoff values for blood pressure and cholesterol were based on guidelines of general practitioners from the Netherlands in 1998. Important exclusion criteria were any of the following: creatinine clearance <60% of the normal age-adjusted value and use of ACE inhibitors or angiotensin II receptor antagonists. A total of 1439 subjects fulfilled the inclusion criteria of PREVEND IT. Those subjects received a letter informing them about PREVEND IT and were invited to the outpatient clinic. During this visit, subjects were verbally informed about the study and were asked to read the informed consent form. At the next visit, subjects were asked to sign the informed consent form. Subjects meeting the randomization criteria were allocated to a treatment number in the order in which they entered the randomized study period. Randomization was performed in blocks of 20 based on a computer-generated randomization list by the pharmacy of Academic Hospital Groningen, Groningen, the Netherlands. From April 1998 to June 1999, 864 subjects were willing to participate in PREVEND IT and were randomized to study medication (Figure 1). Every 3 months after study medication was begun, subjects were seen at the outpa-

tient clinic for registration of adverse events, primary end points, pill counts, and assessment of concomitant medication use. A subject was considered compliant when >75% of the supplied study medication was taken by the subject. When subjects developed an indication for primary prevention owing to natural course or to the implementation of new guidelines, they were advised by PREVEND IT to visit the general practitioner who was responsible for the primary care of the subject.

Methods

Urinary albumin excretion was measured as the mean of two 24-hour urine collections. Urinary albumin concentrations were determined by nephelometry with a threshold of 2.3 mg/L and intra-assay and interassay coefficients of variation of less than 2.2% and 2.6%, respectively (Dade Behring Diagnostic). Systolic and diastolic blood pressure measurements were calculated as the mean of the last 2 of 10 consecutive measurements with an automatic Dinamap XL model 9300 series device (Johnson-Johnson Medical Inc). Plasma glucose, serum total and LDL cholesterol, and serum creatinine were determined by Kodak Ektachem dry chemistry (Eastman Kodak).

The primary end point was the combined incidence of cardiovascular mortality and hospitalization for cardiovascular morbidity. Cardiovascular hospitalization was defined as hospitalization for documented (1) nonfatal myocardial infarction or myocardial ischemia, (2) heart failure, (3) peripheral vascular disease, and/or (4) cerebrovascular accident. Nonfatal myocardial infarction was defined as all nonfatal events accompanied by at least 2 of 4 of the following, which should include either new Q waves or enzyme elevation: (1) presence or history of typical or atypical chest pain of at least 15 minutes' duration; (2) ECG detection of ST-segment changes of at least 0.1 mV and/or T-wave inversion in at least 2 of 12 leads; (3) ECG detection of new significant Q waves in at least 2 of 12 leads; and (4) elevation of measurements of total creatine kinase (CK) and/or its isoenzyme CK-MB in at least 2 samples drawn within 48 hours of development of chest pain. CK levels had to be >2 times the upper limit of the normal local laboratory range and/or the CK-MB/CK ratio had to be >10%. Myocardial ischemia was defined as all ischemic events accompanied by the appearance of an ST-segment change of >0.1 mV or T-wave inversion in at least 2 of 12 leads, objective evidence by means other than ECG, or a need for revascularization (PTCA/CABG) that was severe enough to justify immediate hospital admission. Heart failure was regarded as heart failure for which hospital admission (hospitalization or documented outpatient clinic visit) was necessary and for which there was objective evidence of left ventricular dysfunction or for which specific medication (diuretics and ACE inhibitors) was needed. Peripheral vascular disease was diagnosed when PTA or bypass operation was necessary. Cerebrovascular accident was diagnosed when 1 of the following symptoms was present: recent onset of severe headache, loss of consciousness, or unequivocal objective findings of a localizing neurological deficit, duration >24 hours, and absence of other disease process-causing neurological deficit, such as neoplasm, subdural hematoma, cerebral angiography, or metabolic disorder in combination with an abnormal CT scan or MRI scan.

An independent end-point committee reviewed all end points. The members of this end-point committee had no knowledge of the subject's treatment assignment.

An independent data and safety monitoring committee regularly monitored the progress of the study. The study was approved by the Institutional Review Board and was conducted in accordance with the guidelines of the declaration of Helsinki. Informed consent was obtained from all subjects before randomization.

Statistical Analysis

The rate of renal and cardiovascular events in the present study population is unknown. In elderly nondiabetics with microalbuminuria, the 5-year mortality rate was 30%, whereas it was only 8% in elderly subjects without microalbuminuria.¹⁶ All-cause mortality in microalbuminuric diabetic subjects was ≈18% in 5 years versus 8% in normoalbuminuric diabetic subjects.¹⁷ In treated hypertension, combined cardiovascular mortality and morbidity was 15% after 4

years in patients with initial microalbuminuria and $\approx 4\%$ in patients without microalbuminuria.¹⁸ On the basis of these numbers, we estimated the event rate in the present study population at $\approx 15\%$. The planned sample size of 450 subjects in each medication group (450 fosinopril versus 450 placebo or 450 pravastatin versus 450 placebo given the 2×2 factorial design) provides $\approx 80\%$ power to detect a difference between medication and placebo in the incidence of events stated as primary end points. Assumptions include a 5% level of significance and an event rate of 9.5% in the fosinopril or pravastatin group and 15% in the placebo group. Baseline characteristics are given as mean \pm SD. In case of a skewed distribution, the median (interquartile range) was used. Two-way ANOVA was used to test whether the dependent variable changed significantly with each of the 2 treatments (while taking into account the effects of the other treatment) and to test whether the effect of fosinopril, for example, did not depend on pravastatin. Because of the skewed distribution, albuminuria was transformed to natural logarithm. Times to first occurrence of outcomes are presented as Kaplan-Meier estimates, and statistical differences between placebo and active treatment were analyzed by log rank. Furthermore, results are summarized by hazard (risk) ratios or relative risks with 95% CIs based on robust standard error estimates. The impact of baseline urinary albumin excretion was evaluated by post hoc dichotomization of the parameter into the lowest 4 quintiles against the highest quintile. A χ^2 test for heterogeneity was used to determine the proportional effects observed in the specific subcategories of albuminuria. All analyses were performed on an intention-to-treat basis, and probability values were 2-sided and had to be <0.05 to be significant. All calculations were performed with SPSS version 10.1 software.

Results

Baseline characteristics of all randomized subjects are summarized in Table 1. These characteristics show a middle-aged population with a low prevalence of diabetes mellitus and relatively normal mean blood pressure and cholesterol level at baseline. Furthermore, there was a low prevalence of subjects who had a previous cardiovascular event or used cardiovascular drugs.

In the fosinopril versus placebo arm, 70.7% of subjects in the placebo group and 63.3% in the fosinopril group showed compliance above 75% after 4 years of follow-up. In the pravastatin versus placebo arm, 66.4% of subjects in the placebo group and 74.1% in the pravastatin group showed compliance above 75% after 4 years of follow-up. During follow-up, 5.2% of subjects received an open-label ACE inhibitor and 3.5% received open-label statin as prescribed by their general physicians. The fosinopril dose was reduced to 10 mg in 29 subjects (3.4%) because of side effects. Reasons for permanent treatment withdrawal are presented in Table 2.

As shown in Table 3, fosinopril treatment resulted in a slight but significant fall in systolic and diastolic blood pressure on both short-term and long-term follow-up. In addition, pravastatin lowered total cholesterol and LDL cholesterol significantly during follow-up. No significant effect was found on the level of HDL cholesterol and triglycerides. No significant differences were found in lipid levels between the fosinopril and placebo groups. In addition, pravastatin did not lower systolic and diastolic blood pressure compared with placebo.

The effect of treatment on urinary albumin excretion is presented in Table 4. Urinary albumin excretion was significantly reduced by fosinopril compared with placebo during

the entire study period. Pravastatin did not have any effect on albuminuria during the 4 years of follow-up.

During a mean follow-up of 46 ± 7 months, the primary end point occurred in 45 subjects (5.2%). Subjects treated with fosinopril had a 40% lower incidence of the primary end point than subjects in the placebo group (3.9% versus 6.5%, $P=0.098$; Figure 2). Subjects treated with pravastatin had a 13% lower incidence of the primary end point than subjects in the placebo group (4.8% versus 5.6%, $P=0.649$; Figure 2). The incidences of the individual end points in the different treatment groups are given in Table 5. Interestingly, a 90% reduction was observed in cerebrovascular events in the group treated with fosinopril (relative risk of event 0.10 [95% CI 0.01 to 0.78], $P=0.03$). The incidence of noncardiovascular mortality was 1.9% in the fosinopril group versus 2.1% in its placebo group and 2.1% in the pravastatin group versus 1.9% in its placebo group. When a post hoc Cox regression analysis was performed, the effect of fosinopril and the effect of pravastatin did not change substantially after respective adjustment for systolic and diastolic blood pressure and after adjustment for total cholesterol levels. Similar point estimates were demonstrated after stratification for pravastatin or its placebo in the fosinopril analyses and for fosinopril or its placebo in the pravastatin analyses. When the study population was divided into 4 groups to investigate an additive effect between fosinopril and pravastatin, the event rate was 6.9% in the placebo group, 4.2% in the fosinopril group, 6.0% in the pravastatin group, and 3.7% in the group with both treatments. Event rates between fosinopril or pravastatin alone and the combination therapy were not significantly different.

Furthermore, subjects with a urinary albumin excretion in the upper quintile who received placebo had an increased risk for developing a cardiovascular event (Figure 3; $P=0.008$). In subjects with an albuminuria level below 50 mg/24 hours, fosinopril reduced the incidence of events from 5.1% to 3.6%, which is a relative risk reduction of 29%, whereas in subjects with a high albumin excretion, fosinopril reduced the incidence of events from 13.0% to 5.2%, a relative risk reduction of 60% (heterogeneity $P=0.35$). Subjects with a urinary albumin excretion in the upper quintile who received fosinopril had an event-free survival comparable to that of subjects with a urinary albumin excretion in the lowest 4 quintiles (Figure 3).

Discussion

This study showed that treatment of microalbuminuric subjects with fosinopril over a 4-year period had a significant effect on urinary albumin excretion. In addition, fosinopril treatment was associated with a trend in reducing cardiovascular events. Four years of treatment with pravastatin did not result in a significant reduction in urinary albumin excretion or cardiovascular events. Subjects with urinary albumin excretion in the highest quintile had a significantly higher incidence of the primary end point, and fosinopril had a marked protective effect in this group, bringing them to a level of risk that was comparable to the group with urinary albumin excretion in the lowest 4 quintiles.

TABLE 1. Summary of Demographics and Baseline Characteristics of PREVEND IT (n=864)

Variables	Fosinopril		Pravastatin	
	Placebo (n=433)	Active (n=431)	Placebo (n=431)	Active (n=433)
Age, y	51.5±11.4	51.1±12.2	50.5±11.7	52.1±11.9
Male gender, %	63.7	66.1	62.2	67.7
White, %	97.0	95.1	96.8	95.4
Smoking, %				
Past	31.4	34.4	34.1	31.6
Current	43.6	36.2	37.6	42.3
Systolic blood pressure, mm Hg	131±18	129±17	130±17	131±18
Diastolic blood pressure, mm Hg	76±10	76±10	76±10	77±10
Cholesterol, mmol/L*				
Total	5.7±1.0	5.8±1.1	5.8±1.0	5.8±1.0
HDL	1.0±0.4	1.0±0.3	1.0±0.4	1.0±0.3
LDL	4.0±0.9	4.1±1.0	4.0±1.0	4.1±1.0
Triglycerides, mmol/L*	1.3 (0.9 to 1.9)	1.4 (0.9 to 2.0)	1.3 (0.9 to 1.9)	1.4 (0.9 to 2.0)
Glucose, mmol/L	5.0±1.2	4.9±1.0	4.9±0.9	5.0±1.2
Serum creatinine, μmol/L	89±14	92±14	90±14	91±14
Albuminuria, mg/24 h	22.1 (15.3–39.4)	23.5 (16.8–43.9)	23.5 (16.1–42.5)	22.2 (15.6–40.8)
Body mass index, kg/m ²	26±5	26±4	26±4	26±4
Diabetes mellitus, %	2.8	2.3	2.3	2.8
Prior event, %	2.5	4.2	4.4	2.3
Myocardial infarction, %	0.2	0.7	0.7	0.2
Angina pectoris, %	0.5	0.7	0.5	0.7
Coronary angioplasty or bypass, %	0.5	1.2	0.9	0.7
Heart failure, %	0	0	0	0
Cerebrovascular accident, %	0.2	1.4	1.2	0.5
Peripheral vascular disease, %	0.5	0.7	0.7	0.5
Aspirin and antiplatelet agents, %	2.8	2.1	3.5	1.4
β-Blockers, %	1.4	0.7	1.4	0.7
Nitrate, %	0.5	0.5	0.9	0
Diuretics, %	0.7	0.7	0.9	0.5
Calcium channel blockers, %	0.9	0.9	1.2	0.7
Digoxin, %	0.9	0.7	0.9	0.7

Plus-minus values are mean±SD. Median (25th to 75th percentile) was used for triglycerides and albuminuria, which had a skewed distribution.

*To convert values for cholesterol to mg/dL, divide by 0.02586. To convert values for triglycerides to mg/dL, divide by 0.01129.

Microalbuminuria

PREVEND IT included subjects who had marginally increased urinary albumin excretion from 15 mg/24 hours at baseline. By definition, the level of microalbuminuria is set at a urinary albumin excretion rate of 30 to 300 mg/24 hours. These cutoff values were derived from prospective studies in insulin-dependent diabetes mellitus patients and were based on various stages of diabetic nephropathy.¹ It has been speculated that urinary albumin excretion levels relevant for predicting cardiovascular disease might be lower in the nondiabetic population, and studies showed that microalbuminuria can be a marker of cardiovascular disease at a lower cutoff value.^{2,19,20} Because there were no data available from prospective studies at the time of the design of the PREVEND IT study for normotensive or nondiabetic subjects, we defined

the entry criterion for an increased urinary albumin excretion as 15 to 300 mg/24 hours. The results of the present study show that there is a direct relation between the level of urinary albumin excretion and long-term clinical outcome.

Effect of ACE Inhibitor Intervention

In the present study, treatment with fosinopril resulted in a rapid and long-lasting reduction in urinary albumin excretion. Previous studies had documented the beneficial effect of ACE inhibitors on urinary albumin excretion.^{8,21} Clinical beneficial effects of ACE inhibition in microalbuminuric subjects have been well documented^{10,11,22}; however, it is important to realize that these previous studies with diabetic subjects used higher cutoff values than PREVEND IT. The study described by Ravid et al¹⁰ included normotensive

TABLE 2. Reasons for Premature Discontinuation (n=864)

	Fosinopril		Pravastatin	
	Placebo (n=433)	Active (n=431)	Placebo (n=431)	Active (n=433)
Intolerability for pravastatin	2 (0.5)	0	22 (5.1)	13 (3.0)
Intolerability for fosinopril	18 (4.2)	58 (13.5)	2 (0.5)	5 (1.2)
Death	4 (0.9)	5 (1.2)	4 (0.9)	6 (1.4)
Geographic reasons	3 (0.7)	3 (0.7)	3 (0.7)	2 (0.5)
Other medical reasons*	32 (7.4)	17 (3.9)	33 (7.7)	23 (5.3)
Refusal to continue study medication	36 (8.3)	34 (7.9)	42 (9.7)	27 (6.2)
Withdrawal consent	5 (1.2)	5 (1.2)	5 (1.2)	5 (1.2)
Other reasons	10 (2.3)	8 (1.9)	6 (1.4)	11 (2.5)

Values are n (%).

*Including study end points.

subjects and patients with type II diabetes with microalbuminuria (30 to 300 mg/24 hours) and demonstrated a beneficial effect of enalapril on albuminuria. The Collaborative Study Group performed a trial in subjects with type I diabetes with proteinuria (>500 mg/24 hours) in which urinary protein excretion was lower in the captopril group after 4 years of treatment.²² In addition, ramipril also decreased urinary albumin excretion, measured as the albumin/creatinine ratio.¹¹ In contrast to these previous studies, PREVEND IT included a few diabetics and used a lower cutoff value to identify high-risk subjects. Furthermore, PREVEND IT is the first study to evaluate the effect of ACE inhibition that was specifically designed to target microalbuminuria. Other clinical end-point studies evaluating the use of ACE inhibition in patients at risk of cardiovascular events are the HOPE (Heart Outcomes Prevention Evaluation Study) and EUROPA (European Trial of Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease) trials.^{4,5} Patients in HOPE were 55 years of age or older, with documented cardiovascular disease or diabetes plus an additional risk factor. Patients in EUROPA were at least 18 years of age and had documented coronary heart disease. Major annual event rates

were higher in HOPE than in EUROPA. Patients in PREVEND IT were at a substantially lower risk level than those in either HOPE or EUROPA. Nevertheless, ACE inhibition appeared to be beneficial in all 3 studies. In HOPE, EUROPA, and PREVEND IT, treatment with an ACE inhibitor inevitably resulted in a decrease in blood pressure; therefore, we cannot exclude the possibility that our results can be explained in part by the reduction in blood pressure, although adjustment for systolic and diastolic blood pressure did not change the effect of fosinopril on outcome. On the other hand, cerebrovascular events in the study were significantly reduced, which makes it tempting to suggest that pressure responses indeed played a role in this population.

Effect of Statin Intervention

This trial is the first to assess the effects of an intervention with a statin in microalbuminuric subjects with relatively normal plasma cholesterol. Only a limited number of studies have evaluated the effect of a statin on urinary albumin excretion. These studies were performed in type 2 diabetic patients with hyperlipidemia or in patients with proteinuria. A study performed by Tonolo et al¹² showed that simvastatin

TABLE 3. Mean (\pm SD) Blood Pressure and Lipid Levels by Treatment and Visit (n=864)

	Systolic Blood Pressure, mm Hg		Diastolic Blood Pressure, mm Hg		Total Cholesterol, mmol/L*		LDL Cholesterol, mmol/L*	
	Placebo	Fosinopril	Placebo	Fosinopril	Placebo	Pravastatin	Placebo	Pravastatin
Baseline	131 \pm 18 (n=433)	129 \pm 17 (n=431)	76 \pm 10 (n=433)	76 \pm 10 (n=431)	5.8 \pm 1.0 (n=430)	5.8 \pm 1.0 (n=432)	4.0 \pm 1.0 (n=427)	4.1 \pm 1.0 (n=432)
3 Months	133 \pm 18 (n=409)	124 \pm 17† (n=411)	76 \pm 10 (n=409)	72 \pm 9† (n=411)	5.7 \pm 1.0 (n=405)	4.7 \pm 0.9† (n=412)	3.8 \pm 0.9 (n=403)	2.9 \pm 0.8† (n=412)
1 Year	131 \pm 18 (n=418)	125 \pm 18† (n=409)	77 \pm 10 (n=418)	74 \pm 10† (n=409)	5.6 \pm 1.0 (n=409)	4.7 \pm 1.0† (n=412)	4.1 \pm 1.6 (n=409)	3.1 \pm 0.8† (n=412)
2 Years	130 \pm 18 (n=402)	126 \pm 18† (n=398)	77 \pm 9 (n=402)	75 \pm 10† (n=398)	5.6 \pm 1.0 (n=395)	4.7 \pm 1.0† (n=394)	3.9 \pm 0.9 (n=392)	3.1 \pm 0.9† (n=394)
3 Years	131 \pm 18 (n=394)	125 \pm 17† (n=384)	77 \pm 9 (n=394)	74 \pm 9† (n=384)	5.7 \pm 1.1 (n=385)	4.8 \pm 1.0† (n=385)	4.0 \pm 1.0 (n=384)	3.1 \pm 0.9† (n=385)
4 Years	132 \pm 18 (n=392)	129 \pm 18† (n=388)	78 \pm 9 (n=392)	76 \pm 9† (n=388)	5.6 \pm 1.1 (n=382)	4.8 \pm 1.0† (n=376)	3.9 \pm 0.9 (n=379)	3.1 \pm 0.9† (n=375)

*To convert values for cholesterol to mg/dL, divide by 0.02586.

† $P<0.05$, active treatment vs its matching placebo.

TABLE 4. Median (Interquartile Range) Urinary Albumin Excretion (mg/24 h) by Treatment and Visit (n=864)

	Fosinopril		Pravastatin	
	Placebo	Active	Placebo	Active
Baseline	22.1 (15.3–39.4) (n=433)	23.5 (16.8–43.9) (n=431)	23.5 (16.1–42.5) (n=431)	22.2 (15.6–40.8) (n=433)
3 Months	22.2 (14.0–41.4) (n=399)	17.6 (12.8–31.2)* (n=404)	20.1 (13.4–38.2) (n=398)	19.8 (13.2–34.5) (n=405)
1 Year	23.7 (15.5–41.7) (n=377)	19.2 (12.8–33.7)* (n=383)	21.2 (13.9–39.9) (n=372)	20.7 (13.3–36.7) (n=388)
2 Years	23.4 (14.9–45.0) (n=354)	19.1 (12.2–38.9)* (n=356)	21.4 (13.5–42.0) (n=345)	21.6 (13.4–42.7) (n=365)
3 Years	22.1 (13.1–43.0) (n=342)	17.8 (11.2–38.1)* (n=345)	20.1 (12.2–43.1) (n=335)	20.8 (11.9–39.1) (n=352)
4 Years	23.2 (13.4–42.6) (n=323)	18.6 (11.0–39.9)* (n=324)	20.3 (12.5–40.5) (n=314)	21.8 (11.6–41.9) (n=333)

* $P < 0.05$, active treatment vs its matching placebo.

decreases urinary albumin excretion in normotensive type 2 diabetic patients. In PREVEND IT, no early or late effect was seen on urinary albumin excretion when treatment was compared with placebo.

Treatment with pravastatin had no effect on the primary end point in PREVEND IT despite a significant reduction in total cholesterol and LDL cholesterol concentrations. On the basis of cholesterol lowering, a reduction in clinical events on the order of 25% could have been expected.²³ However, the study was powered to detect a reduction of 35% in the primary end point at an incidence rate of 15% in the placebo group. A long-term benefit of cholesterol lowering in this patient population cannot be excluded.

Study Limitations

At the time the present study was designed, no data were available about the event rate in microalbuminuric subjects derived from the general population. The event rate was lower than expected beforehand, which is an important message for researchers designing primary prevention trials. Despite this low event rate, a substantial relative risk reduc-

tion was observed after 4 years of treatment with fosinopril. When we divided the present study population into those with high and low albuminuria, the expected event rate was observed in subjects with a high level of albuminuria. Still, a relative risk reduction of 29% was demonstrated in subjects with low albuminuria. Regardless of the lower-than-expected power of the trial, the findings are very consistent. Therefore, we feel that the conclusions are not based on a chance finding.

Another limitation is the lack of an active control arm with blood pressure-lowering drugs that did not target the renin-angiotensin system. Only then would it be possible to deduce an effect of ACE inhibitors beyond the lowering of blood pressure.

Conclusions

PREVEND IT did not generate a definite answer to the question of whether primary prevention is indicated in microalbuminuric subjects without any other indication for primary prevention; however, the results of the intervention with fosinopril, particularly in the high-albuminuria (higher-

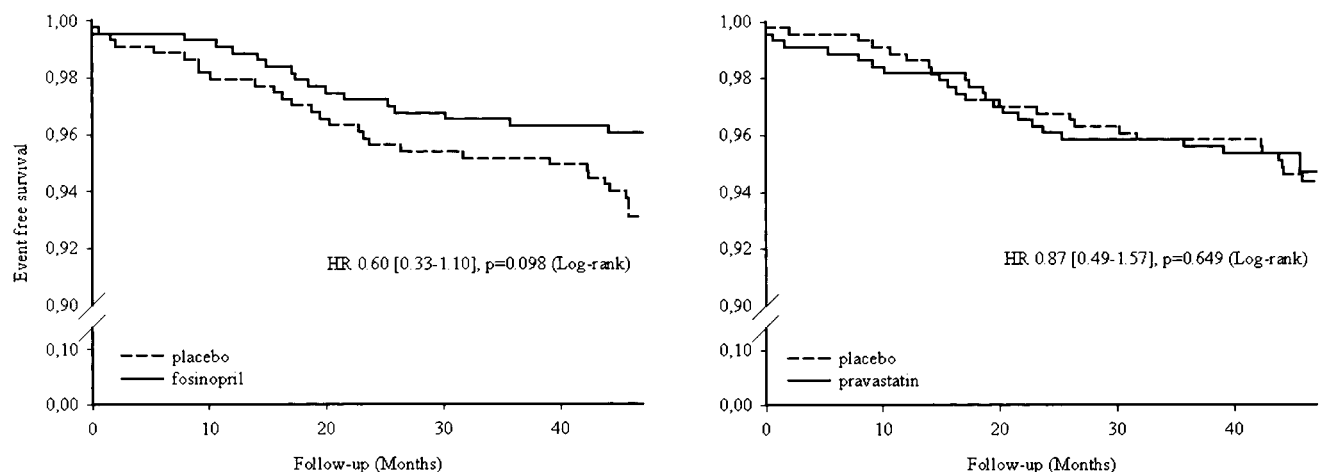


Figure 2. Kaplan-Meier estimates of incidence of cardiovascular events in fosinopril and matching placebo group and pravastatin and matching placebo group. Hazard ratios (HR) and 95% CIs are given.

TABLE 5. Primary End Points According to Study Group (n=864)

Events	Fosinopril		Pravastatin	
	Placebo	Active	Placebo	Active
Cardiovascular mortality	3 (0.7)	5 (1.2)	4 (0.9)	4 (0.9)
Hospitalization for:				
Nonfatal myocardial infarction and/or myocardial ischemia	11 (2.5)	12 (2.8)	15 (3.5)	8 (1.8)
Heart failure	2 (0.5)	0	1 (0.2)	1 (0.2)
Peripheral vascular disease	2 (0.5)	1 (0.2)	1 (0.2)	2 (0.5)
Cerebrovascular accident	10 (2.3)	1 (0.2)*	4 (0.9)	7 (1.6)

Values are n (%).

*P<0.05 active medication vs placebo.

risk) group, support the hypothesis that treatment that has a significantly favorable effect on urinary albumin excretion rate is associated with a beneficial clinical outcome. Therefore, the results of PREVEND IT favor further (larger) studies in subjects with microalbuminuria but with no other indication for primary prevention. Moreover, intervention directed at the renin-angiotensin system appears to be the therapy of first choice in such studies.

Appendix

PREVEND IT Steering Committee

From the University of Groningen and University Hospital Groningen, Groningen, the Netherlands: W.H. van Gilst (principal investigator), Department of Clinical Pharmacology and Department of Cardiology; D.J. van Veldhuisen, Department of Cardiology; P.E. de Jong, Department of Nephrology; D. de Zeeuw, Department of Clinical Pharmacology; A.J. van Boven, Department of Cardiology; H.L. Hillege, Trial Coordination Center; W.M.T. Janssen, Department of Nephrology; G.F.H. Diercks, Department of Cardiology; F.W. Asselbergs, Department of Clinical Pharmacology and Department of Cardiology.

PREVEND IT Investigators

From the University of Groningen and University Hospital Groningen, Groningen, the Netherlands: A.H. Boonstra, Department of Nephrology; S.J. Pinto-Sietsma, Department of Nephrology; E.M.

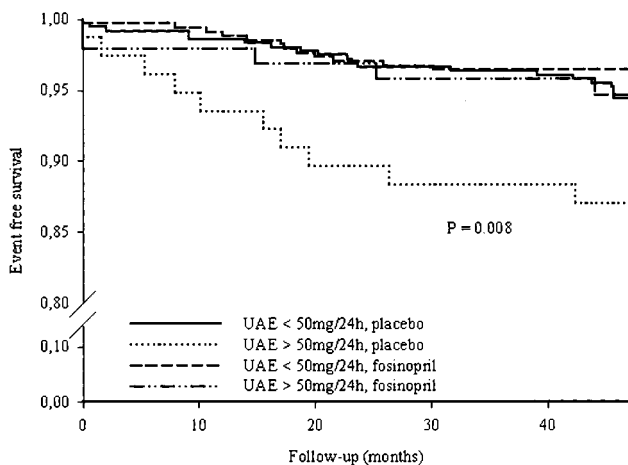


Figure 3. Kaplan-Meier estimates of incidence of cardiovascular events in fosinopril and placebo group divided by urinary albumin excretion (UAE) more than or less than 50 mg/24 hours.

Stuveling, Department of Internal Medicine; J.C. Verhave, Department of Nephrology; L.J. Wagenaar, Department of Cardiology.

End-Point Committee

F.W.A. Verheugt (chairman), Department of Cardiology, Academic Hospital, Nijmegen, the Netherlands; L. Schrijvers, Department of Cardiology, Martini Hospital, Groningen, the Netherlands; T. Kremer Hovinga, Department of Nephrology, Martini Hospital, Groningen, the Netherlands.

Safety and Data Monitoring Committee

B. Pitt (chairman), Division of Cardiology, University of Michigan, Ann Arbor, Mich; J. Shepherd, Department of Pathological Biochemistry, Royal Infirmary, Glasgow, Great Britain.

Data Management

R.J. Bieringa, Trial Coordination Center, Thoraxcenter, Academic Hospital, Groningen, the Netherlands.

Statistical Support

A.H. Zwinderman, Academic Medical Center, Amsterdam, the Netherlands.

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