Equivalence of indapamide SR and enalapril on microalbuminuria reduction in hypertensive patients with type 2 diabetes: The NESTOR* study

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Objectives To test whether microalbuminuria in patients with type 2 diabetes and hypertension is primarily dependent on the severity of hypertension, and to compare the effectiveness of two antihypertensive drugs with opposite effects on the renin–angiotensin system [the diuretic, indapamide sustained release (SR), and an angiotensin-converting enzyme inhibitor, enalapril] in reducing microalbuminuria.

Design A multinational, multicentre, controlled, double-blind, double-dummy, randomized, two-parallel-groups study over 1 year.

Methods After a 4-week placebo run-in period, 570 patients (ages 60.0 ± 9.9 years, 64% men) with type 2 diabetes, essential hypertension [systolic blood pressure (SBP) 140–180 mmHg, and diastolic blood pressure (DBP) < 110 mmHg], and persistent microalbuminuria (20–200 μg/min) were allocated randomly to groups to receive indapamide SR 1.5 mg ($n = 284$) or enalapril 10 mg ($n = 286$) once a day. Amlodipine, atenolol, or both were added, if necessary, to achieve the target blood pressure of 140/85 mmHg.

Results There was a significant reduction in the urinary albumin : creatinine ratio. Mean reductions were 35% [95% confidence interval (CI) 24 to 43] and 39% (95% CI 30 to 47%) in the indapamide SR and enalapril groups, respectively. Equivalence was demonstrated between the two groups [1.08 (95% CI 0.89 to 1.31%); $P = 0.01$]. The reductions in mean arterial pressure (MAP) were 16.6 ± 9.0 mmHg for the indapamide SR group and 15.0 ± 9.1 mmHg for the enalapril group (NS); the reduction in SBP was significantly greater ($P = 0.0245$) with indapamide SR. More than 50% of patients in each group required additional antihypertensive therapy, with no differences between groups. Both treatments were well tolerated.

Conclusions Indapamide-SR-based therapy is equivalent to enalapril-based therapy in reducing microalbuminuria with effective blood pressure reduction in patients with hypertension and type 2 diabetes. *J Hypertens* 22:1613–1622 © 2004 Lippincott Williams & Wilkins.

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Keywords: hypertension, type 2 diabetes, microalbuminuria, indapamide sustained release, enalapril, randomized trial, diuretics, angiotensin-converting enzyme inhibitors

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*Natrilix SR versus Enalapril Study in hypertensive Type 2 diabetics with MicrOalbuminuRia

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Introduction

Patients with type 2 diabetes display a serious cardiovascular risk profile [1] that is aggravated by hypertension [2]. Microalbuminuria [i.e. albumin excretion rate (AER) between normal values and those giving positive dipstick test results for proteinuria [3]] adds a two- to four-fold risk for cardiovascular and renal events [4–6] in these patients. Reduction in microalbuminuria may signal improvement in prognosis [7]. In this respect, drugs able to block the effectiveness of the renin–angiotensin system (RAS) are of special interest. The angiotensin-converting enzyme inhibitors (ACEI) reduce microalbuminuria and prevent or reduce the progression of diabetic nephropathy in patients with type 1 diabetes [8,9]. In patients with type 2 diabetes, ACEI, as compared with placebo, reduce the progression of microalbuminuria and prevent cardiovascular diseases [7], and angiotensin II type 1 (AT_1) receptor antagonists reduce microalbuminuria and prevent end-stage renal failure [10,11].

However, the respective contributions of ameliorations in systemic blood pressure and in renal haemodynamics to the benefits provided by the blockers of the RAS need to be examined in diabetic patients. The predominant role of the RAS in the genesis of microalbuminuria has been demonstrated in patients with type 1 diabetes, normotension and microalbuminuria, in studies in which the blood pressure was reduced to the same extent by two drugs having opposite effects on RAS effectiveness: hydrochlorothiazide, a diuretic, and enalapril, an ACEI. Microalbuminuria was reduced by enalapril, but not by hydrochlorothiazide over 1 year [12]. A large body of evidence supports the use of ACEI to treat nephropathy in type 1 diabetes [13]. Conversely, the special benefits of RAS blockade compared with those provided by blood pressure reduction by itself are less clear in patients with type 2 diabetes with microalbuminuria. For instance, the reductions in clinic blood pressure seen in the participants in the Heart Outcomes Prevention Evaluation (HOPE) study and the Microalbuminuria, Cardiovascular and Renal Outcomes substudy of the HOPE trial [7,14] were small in those given 10 mg ramipril in the evening compared with those on placebo, but the night-time blood pressure was clearly reduced by ramipril as compared with placebo in the subgroup of participants who underwent ambulatory blood pressure monitoring (ABPM) [15]. Also, it is well known that conventional antihypertensive drugs reduce a high AER in patients with essential hypertension without diabetes [16]. In this respect, a large proportion of patients with type 2 diabetes with microalbuminuria also display permanent hypertension [17]. Thus it remains debatable whether microalbuminuria is a consequence of the severity of essential hypertension or of abnormal renal haemodynamics as a result of diabetes in type 2 diabetic patients with essential hypertension.

To study this issue further, we compared the efficacy of two antihypertensive drugs with opposite effects on the RAS [indapamide sustained release (SR), a diuretic, and enalapril, an ACEI] in reducing microalbuminuria in type 2 diabetic patients with hypertension. In this 1-year, double-blind study, we hypothesized an equivalent effect of the two study drugs in reducing microalbuminuria.

Patients and methods

The design of this study has been published in detail previously [18]. Briefly, it was a multinational, double-blind, double-dummy, two-parallel-groups, randomized, 1-year study comparing indapamide SR (indapamide 1.5 mg in a sustained release formulation) with enalapril 10 mg per day. After a 4-week placebo run-in period, participants were allocated randomly to groups to receive orally, once-daily at breakfast, either indapamide SR or enalapril and their matched placebo, for a 52-week active treatment period. Visits were performed after 6, 12, 18, 24, 36 and 52 weeks. From the sixth week of treatment, additional, open-label antihypertensive treatment was prescribed if target blood pressure was not achieved [systolic blood pressure (SBP) $\leq$140 mmHg and diastolic blood pressure (DBP) $<$ 85 mmHg] in four steps separated by 6-week intervals: amlodipine 5 mg once daily, then amlodipine 10 mg once daily, then amlodipine 10 mg plus atenolol 50 mg once daily, and finally amlodipine 10 mg plus atenolol 100 mg once daily. Adaptation of the antidiabetic treatment, including insulin, and potassium supplements (if kalaemia was less than 3.5 mmol/l) were allowed from the sixth week of the study.

During the placebo period, eligibility determined by the presence of persistent microalbuminuria was assessed as an AER between 20 and 200 µg/min on at least two of three overnight urine collections. During the active treatment period, AER was assessed on overnight urine collected every 12 weeks until completion of the study. During each visit, the clinic blood pressure was measured by the investigators as described below. ABPM was performed in volunteer centres before random allocation to groups and at the end of the study.

Weight was measured at selection and at each visit from week 0 to week 52.

A standard 12-lead electrocardiogram (ECG) was recorded at week 0 and week 52 to screen for rhythm, conduction and repolarization disorders.

The following laboratory tests were performed before random allocation to groups and at the end of the study: fasting plasma sodium, potassium, creatinine, uric acid, glucose, glycated haemoglobin (HbA_{1c}), tri-

glycerides, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL). Urinary creatinine, sodium and potassium were measured on overnight urine collections.

Spontaneous reporting of adverse events was recorded at each visit.

Patients

Patients were recruited at 231 active centres (private or public hospitals, general practitioners or specialists), in 18 countries (see Appendix) between April 1997 and January 2000. Inclusion criteria were: men and women aged between 35 and 80 years, with type 2 diabetes [19], persistent microalbuminuria and essential hypertension. Diabetes was required to be controlled by diet with or without one or more oral antidiabetic treatment, unchanged for at least 3 months. At selection and at inclusion, in those receiving placebo, hypertension was defined as patients having SBP 140–180 mmHg and DBP < 110 mmHg. For selection, microalbuminuria had to be documented within the previous year. For inclusion, persistent microalbuminuria was defined as described above.

The main criteria for exclusion from the study were: severe hypertension, body mass index > 40 kg/m^2, ventricular rhythm disorders on ECG, urinary tract infection, haematuria or leucocyturia, plasma creatinine > 150 μmol/l, kalaemia < 3.5 mmol/l or > 5.5 mmol/l, uric acid > 536 μmol/l, treatment with potassium supplement or insulin and poor placebo compliance during the run-in period. Previously known intolerance to ACEI or diuretics was also a criterion for exclusion. The study was performed in accordance with Good Clinical Practice and approved by Ethics Committees of each country. Each patient gave his or her written informed consent before enrolment.

Investigations

Timed overnight urine samples were stored at 4–8°C, and sent by express carrier to a central laboratory (Biochemistry Department, University Hospital Angers, France). After urine screening for leucocyturia and haematuria using dedicated dipsticks (Multistix R; Bayer Diagnostics, Puteaux, France), urinary albumin was measured by nephelometry [20] (assay sensitivity 2 mg/l; inter- and intra-assay coefficients of variation 4 and 3%, respectively).

The central laboratory for all other biological analyses during the study was Institut Pasteur, Lille, France. Apart from haematology (Technicon H3; Bayer) and HbA_{1c} (Biorad kit manufacturer), all other parameters were measured using conventional methods on a Hitachi 917 analyser.

Creatinine was measured using the Jaffe method. Creatinine clearance was assessed with the Cockcroft formula [21]. LDL was calculated using the Friedwald formula.

Systolic and diastolic blood pressures were measured by the investigators using a mercury sphygmomanometer with a cuff sized to the patient's arm as recommended [22], in the morning before drug intake, after the patient had undergone a 10-min period of rest in the supine position (the mean of three measurements was calculated), then after they had been standing for 3 min.

For 24-h ABPM, only validated devices according to the British Hypertension Society or the American Association for the Advancement of Medical Instrumentation (grade B/B at least) [23–25] were accepted for use in this study, and the following devices were used: SpaceLabs 90202, 90207 and 90217 and Accutracker II. Examination was carried out on a normal working day, the last day of the placebo run-in period (week 0) and after 1 year of treatment (week 52), using the same recorder for the same patient, on the same arm. The drug was taken just after the recorder was fitted in the morning. Blood pressure was measured every 15 min during the 24-h period, or at least one measurement every 15 min in the daytime (0700 to 2200 h) and one measurement every 30 min at nighttime (2200 to 0700 h) [26,27].

All ABPM recordings were edited by the investigators and sent to the Central Committee for validation by an expert. Examination was validated if apparatus was fitted between 0800 and 1100 h, duration of the recording was 24 h including drug intake and at least 75% of valid measurements were present. Absence of two consecutive hourly averages, or missing data for the first and 24th hours were verified.

Assessment of safety was based mainly on analysis of adverse events, ECG parameters, body mass index and biochemical parameters.

Statistical analysis

Statistical efficacy analysis was performed on the intention-to-treat population, defined as all randomly assigned patients exposed to treatment. The primary objective of the analysis was to test the hypothesis of one-sided equivalence (non-inferiority) of indapamide SR in comparison with enalapril on microalbuminuria evaluated by urinary albumin : creatinine ratio (UACR), AER and fractional albumin clearance, calculated as: urinary albumin concentration × plasma creatinine concentration/urinary creatinine concentration × plasma albumin concentration. The secondary objectives were to evaluate the antihypertensive activity assessed by varia-

tions from baseline of supine SBP, DBP, MAP (calculated as one-third of SBP plus two-thirds of DBP), and safety.

The analysis of albuminuria after log transformation was determined using a limit of non-inferiority not greater than 35% of the value in the enalapril group at the final visit, this being the assumed clinically significant difference. It has been calculated that this study requires at least 253 patients per treatment group with a standard deviation of log(albuminuria) estimated to be 0.82 [28] with $\alpha = 2.5\%$ and a power of 80%. Taking into account expected withdrawals from the study, an additional 10% of patients were included. Microalbuminuria parameters were logarithmically transformed and are presented as the geometric means (Gmean) with their 95% confidence intervals (CI).

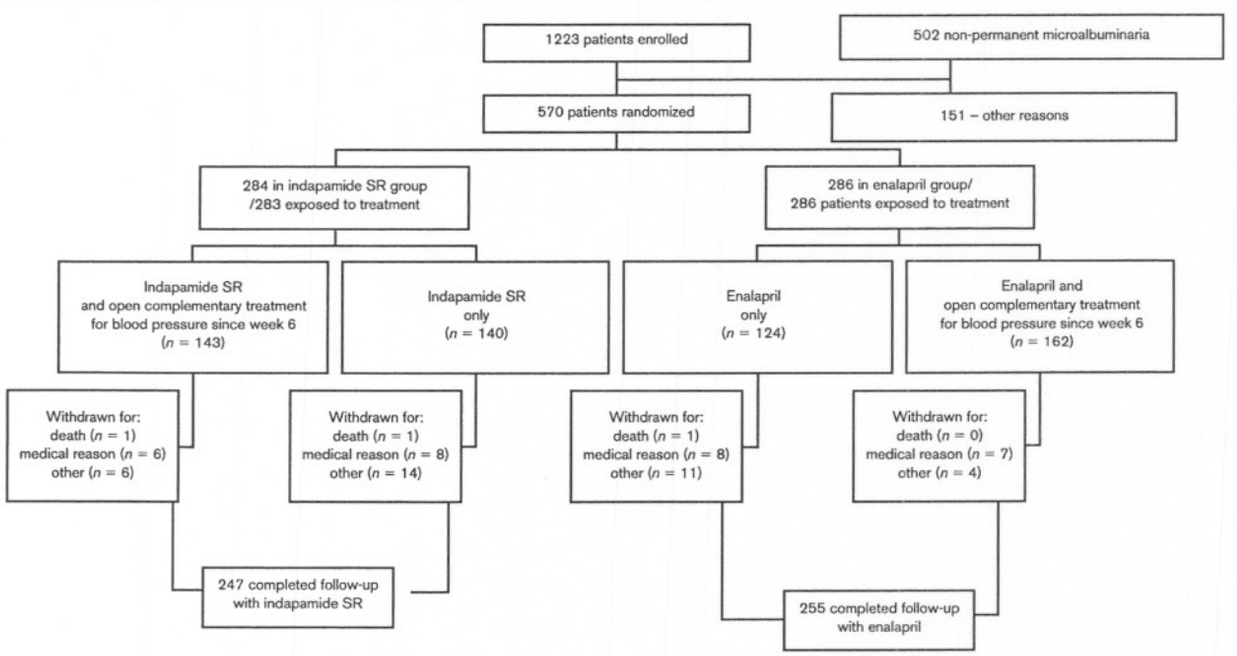
All analyses were adjusted on baseline value for each parameter. Changes from baseline in microalbuminuria and blood pressure were compared between groups with a linear model for analysis of covariance. SAS software 8.1 (SAS Institute, Cary, North Carolina, USA) was used.

Results

Of the 1223 patients enrolled, 570 patients were allocated randomly to groups (Fig. 1) and 653 were not eligible, 77% because urinary analyses performed in the central laboratory did not confirm microalbuminuria.

Two hundred and forty-seven (87%) and 255 (89%) patients completed the study at week 52 in the indapamide SR and in the enalapril groups, respectively. One patient allocated randomly to a study group was never exposed to the study drug, so there were a total of 569 patients assessable. None of the included patients was lost to follow-up during the study. Sixty-seven patients discontinued the treatment, including: three who died (one sudden death and one myocardial infarction in the indapamide SR group and one cardiac arrest in the enalapril group), 29 for medical reasons (one uncontrolled hypertension, one coughing, four cerebrovascular disorder, two angina pectoris, two myocardial infarction, one dizziness, one uterine carcinoma, one hepatic neoplasm and one kidney stone in the indapamide SR group; three uncontrolled hypertension, two coughing, two lymphocytic leukaemia, one fatigue, one headache, one thrombosis of retinal vein, one vertigo, one alcohol intolerance, one anorexia, one diabetes worsened and one appendicitis in the enalapril group); 20 for non-medical reasons, mainly the patient's decision (12 indapamide SR/8 enalapril); and 15 for major procedural deviations (eight indapamide SR/seven enalapril).

Fig. 1



Flow chart.

From the sixth week of study treatment, an adjunctive therapy for hypertension was taken by 305 patients (143 in the indapamide SR group and 162 in the enalapril group). The distribution of patients treated by monotherapy/+ amlodipine alone/+ atenolol alone/+ amlodipine + atenolol was similar in the two groups: 140/112/8/23 patients in the indapamide SR group and 124/121/7/34 patients in the enalapril group ($P = 0.322$). The mean global compliance with study treatments through the duration of the study was similar in the two groups: 98.1 and 98.5%, respectively. The baseline characteristics of the patients were similar in the two groups (Table 1).

The results of the analysis of efficacy criteria are shown in Figure 2 and Table 2.

At the follow-up visit, there was a significant decrease in UACR of 35 and 39% in the indapamide SR and the enalapril groups, respectively. The one-sided equivalence of treatment based on indapamide SR was demonstrated statistically ($P = 0.0121$), with a ratio of 1.08 (95% CI 0.89 to 1.31) when compared with treatment based on enalapril.

At the last observation, in the indapamide SR group, 112 patients (40%) had improved to normoalbuminuria (UACR < 2.5 mg/mmol in men and < 3.5 mg/mmol in women), 145 (51%) maintained microalbuminuria (UACR 2.5–25 mg/mmol in men and 3.5–25 mg/mmol in women), and 26 (9%) had deteriorated to macroalbuminuria (UACR > 25 mg/mmol in men and women). In the enalapril group, the values were 120 (42%), 148 (52%) and 18 patients (6%), respectively ($P = 0.418$; χ^2 test).

Both treatments showed antihypertensive efficacy (Table 2). There was a significant decrease ($P < 0.001$) in SBP, DBP and MAP in both treatments between baseline and endpoint. The change in MAP was not different between the two groups: −1.19 mmHg (95% CI −2.55 to 0.16), with a decrease of 16.6 ± 9.0 mmHg with indapamide SR and 15.0 ± 9.1 mmHg with enalapril. In addition, supine SBP was significantly more reduced ($P = 0.0245$) in the indapamide SR group (−23.8 ± 13.3 mmHg) than in the enalapril group (−21.0 ± 14.3 mmHg), but DBP was not ($P = 0.3395$): −13.0 ± 9.3 mmHg compared with −12.1 ± 8.6 mmHg, respectively.

This finding was confirmed in the subgroup of 99 patients who underwent a 24-h ABPM, with a non-significant mean difference of MAP over 24 h between the two treatment strategies of −0.63 mmHg (95% CI −3.57 to 2.31; Fig. 3).

Renal function did not change in either treatment group (Table 2).

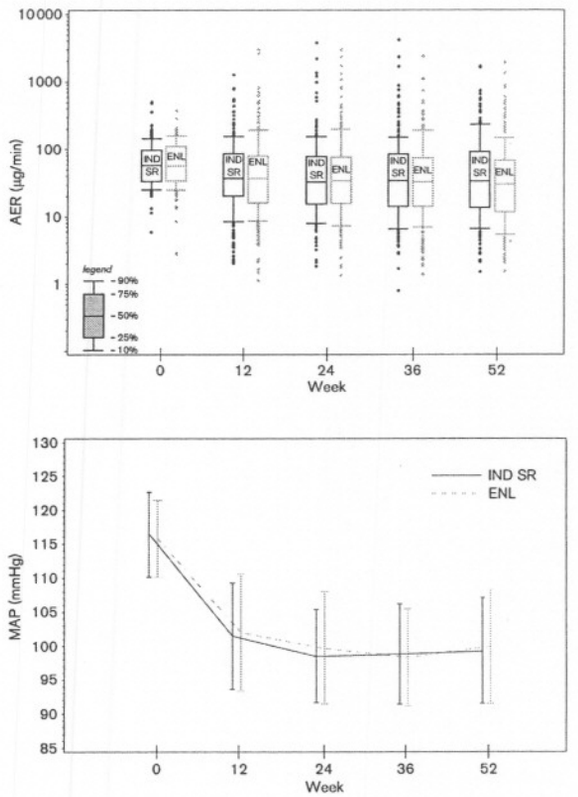
We calculated the relationship between change in the

Table 1 Baseline characteristics of patients

Demographics	IND SR ($n = 283$)	ENL ($n = 286$)
Age (years)	60.8 (9.9)	59.2 (9.9)
Men/women (%)	66/34	63/37
White/Black/Asian/other (%)	85/4/3/8	86/5/2/7
Body mass index (kg/m^2)	29.3 (4.0)	29.8 (4.2)
Smokers/ex-smoker/non-smoker (%)	13/24/63	15/22/63
Diabetes duration (months)	100.0 (81.5)	97.6 (81.5)
Family history of diabetes (%)	42	49
Oral hypoglycaemic agent[a]: 0/1/≥2 (%)	13/49/38	9/45/46
HbA_{1c} (%)	7.49 (2.00)	7.71 (1.90)
Hypertension duration (months)	107.4 (93.2)	92.7 (83.2)
Family history of hypertension (%)	38	41
Hypertension previously treated (%)	78	73

Values are mean ± SD or number. [a]Oral hypoglycaemic agent: 0 = diet alone; 1 = one agent; ≥2 = at least two at random allocation to groups. IND SR, indapamide sustained release; ENL: enalapril; HbA_{1c}, glycated haemoglobin.

Fig. 2



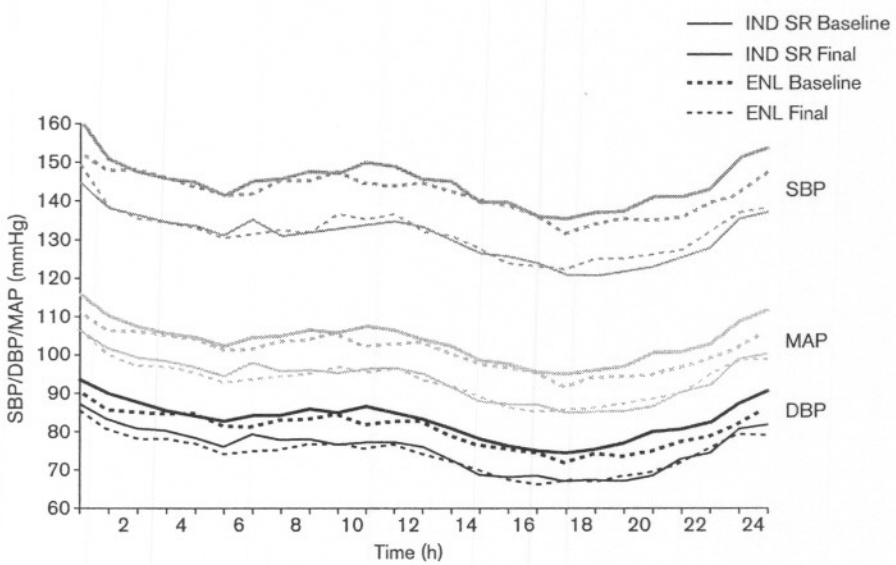
Albumin excretion rate (AER; semi-log scale) and mean arterial pressure (MAP; mean ± SD) in the two treatment groups (intention-to-treat populations) over the 52-week duration of the study. Bars in box plots correspond, from lower to upper, to 10%, 25%, 50% (median), 75% and 90% of the values and the extreme points. IND SR, indapamide sustained release; ENL, enalapril.

Table 2 Evolution of efficacy criteria

Criteria			IND SR ($n = 283$)	ENL ($n = 286$)	Inter-group comparison	P
UACR (mg/mmol)	Baseline	Gmean (Q1, Q3)	6.16 (3.50, 10.33)	6.17 (3.33, 10.97)		
	Final	Gmean (Q1, Q3)	4.03 (1.67, 9.00)	3.74 (1.40, 8.00)	1.08 (0.89 to 1.31)	0.0121§
	% Decline	Gmean (95% CI)	35 (24 to 43)	39 (30 to 47)		
AER (μg/min)	Baseline	Gmean (Q1, Q3)	58.42 (33.27, 96.77)	57.97 (34.07, 106.5)		
	Final	Gmean (Q1, Q3)	36.95 (13.90, 92.42)	32.10 (12.44, 72.22)	1.15 (0.93 to 1.41)	0.0616§
	% Decline	Gmean (95% CI)	37 (26 to 46)	45 (36 to 52)		
Creatinine clearance (ml/min)	Baseline	Mean (SD)	91.5 (29.5)	93.4 (29.2)		
	Final	Mean (SD)	87.9 (29.8)	89.4 (28.6)		
	Δ Decrease	Mean (95% CI)	−3.6 (−4.93 to −2.30)	−4.0 (−5.21 to −2.81)	0.26 (−1.48 to 2.00)	0.7701‡
Fractional albumin clearance (10^{-6})	Baseline	Gmean (Q1, Q3)	10.98 (6.21, 19.30)	11.06 (6.04, 20.06)		
	Final	Gmean (Q1, Q3)	7.57 (3.15, 17.78)	6.92 (2.70, 15.87)	1.09 (0.89 to 1.33)	0.0166§
	% Decline	Gmean (95% CI)	31 (21 to 41)	37 (28 to 45)		
Supine SBP (mmHg)	Baseline	Mean (SD)	161.1 (10.8)	160.2 (10.8)		
	Final	Mean (SD)	137.3 (12.0)	139.3 (14.3)		
	Δ Decrease	Mean (95% CI)	−23.8 (−25.4 to −22.2)	−21.0 (−22.6 to −19.3)	−2.34 (−4.38 to −0.30)	0.0245‡
Supine DBP (mmHg)	Baseline	Mean (SD)	94.0 (6.9)	93.5 (6.1)		
	Final	Mean (SD)	81.0 (8.1)	81.4 (7.9)		
	Δ Decrease	Mean (95% CI)	−13.0 (−14.1 to −11.9)	−12.1 (−13.1 to −11.1)	−0.62 (−1.90 to 0.65)	0.3395‡
Supine MAP (mmHg)	Baseline	Mean (SD)	116.3 (6.3)	115.7 (5.7)		
	Final	Mean (SD)	99.7 (8.1)	100.7 (8.9)		
	Δ Decrease	Mean (95% CI)	−16.6 (−17.7 to −15.5)	−15.0 (−16.1 to −14.0)	−1.19 (−2.55 to 0.16)	0.0847‡

Within-group variations in microalbuminuria are expressed as % Decline; within-group variations in blood pressure and creatinine clearance are expressed as Δ Decrease. IND SR, indapamide sustained release; ENL, enalapril; UACR, urinary albumin : creatinine ratio; Gmean, geometric mean; Q1, first quartile; Q3, third quartile; CI, confidence interval; AER, albumin excretion rate. §One-sided equivalence test: one-tailed Student's t-test for independent samples ($\alpha = 2.5\%$) after adjustment on baseline studied on the log-transformed values of albuminuria with a limit of non-inferiority of 30% – that is, 1.35 antilog limit; ‡difference test: two-tailed Student's t-test for independent samples ($\alpha = 5\%$) on adjusted mean difference.

Fig. 3



Mean changes over 24 h in systolic (SBP), diastolic (DBP) and mean arterial (MAP) blood pressures (ambulatory blood pressure monitoring). IND SR, indapamide sustained release; ENL, enalapril.

supine SBP, DBP and MAP and change in the UACR from the beginning to the end of the study for the two treatment groups. There was no difference between groups (data not shown).

The two treatment regimens were generally well tolerated and no unexpected adverse events occurred. Three instances of orthostatic hypotension were reported: one in the indapamide SR group and two in the enalapril group. Results concerning the urinary and plasma biochemistry are shown in Table 3. Among all biological parameters assessed during the study, a difference between groups was observed only for serum potassium, uric acid, total cholesterol and HbA_{1c} (Table

Table 3 Evolution of biochemistry parameters

Parameters	IND SR			ENL			Changes (IND SR – ENL)	P^a
	n	Baseline	Final	*n*	Baseline	Final		
Na (mmol/l)	273	139.8 ± 2.2	138.9 ± 2.4	280	139.8 ± 2.6	138.9 ± 2.7	−0.06	= 0.7348
K (mmol/l)	270	4.4 ± 0.4	4.2 ± 0.4	278	4.4 ± 0.4	4.5 ± 0.4	−0.32	< 0.001
Na_U (μmol/min)	261	169.6 ± 97.7	199.2 ± 115.0	269	173.2 ± 91.2	165.6 ± 90.8	34.87	< 0.001
K_U (μmol/min)	262	48.7 ± 26.0	55.5 ± 34.3	269	49.8 ± 29.2	51.5 ± 8.0	4.31	= 0.1622
Uric acid (μmol/l)	251	335.6 ± 76.8	365.2 ± 94.8	262	334.9 ± 88.5	340.8 ± 95.2	23.94	< 0.001
Total chol. (mmol/l)	236	5.2 ± 1.0	5.4 ± 1.1	251	5.4 ± 1.0	5.3 ± 1.1	0.16	= 0.0425
HDL chol. (mmol/l)	236	1.1 ± 0.3	1.1 ± 0.3	251	1.2 ± 0.3	1.2 ± 0.3	0.01	= 0.4750
LDL chol. (mmol/l)	210	3.3 ± 0.8	3. 3 ± 0.9	232	3.4 ± 0.9	3.3 ± 0.9	0.06	= 0.3031
Triglycerides (mmol/l)	235	2.1 ± 1.5	2.4 ± 2.1	251	1.9 ± 1.4	2.1 ± 1.9	0.21	= 0.1476
Glucose (mmol/l)[b]	249	8.9 ± .7	9.7 ± 3.9	261	9.3 ± 3.4	9.6 ± 3.5	0.30	= 0.2603
HbA_{1c} (%)	230	7.4 ± 2.0	8.1 ± 2.3	244	7.7 ± 1.9	7.9 ± 2.1	0.50	= 0.0006

IND SR, indapamide sustained release; ENL, enalapril; Na, plasma sodium; K, plasma potassium; Na_U, urinary sodium flow; K_U, urinary potassium flow; HDL, LDL, high- and low-density lipoproteins; chol., cholesterol. [a]Inter-group comparison; [b]fasting plasma glucose.

3). Twenty-nine patients (10.2%) in the indapamide SR group and three (1.0%) in the enalapril group had at least one emergent serum potassium concentration < 3.4 mmol/l. Only seven patients (2.5%) in the indapamide SR group and 10 patients (3.5%) in the enalapril group required insulin therapy during the year of treatment.

Discussion

In this study, we found that microalbuminuria in patients with type 2 diabetes with hypertension was reduced by an equivalent amount by two antihypertensive drugs that have opposite effects on the RAS: the diuretic, indapamide SR, and the ACEI, enalapril. These results support a predominant role of high systemic blood pressure in the development of microalbuminuria in this population of patients.

In a 1-year international study comparing it with enalapril, indapamide SR reduced SBP/DBP by 25.2/12.8 mmHg [29] and enalapril reduced them by 24.5/12.4 mmHg. In a comparative study of enalapril and bendrofluazide [30], enalapril reduced SBP/DBP by 25.0/16.0 mmHg. In the case of enalapril, an even smaller dose (5 mg/day) was able to reduce microalbuminuria in similar patients [31], and 10 mg/day of enalapril –the usual dose tested in the development of the drug [32] – was the dose used to prevent the doubling of serum creatinine in normotensive patients with type 2 diabetes with baseline microalbuminuria over 7 years [33].

The number of patients enrolled in this study was calculated to test one-sided equivalence between drugs on the primary outcome – that is, microalbuminuria. Patient compliance with treatment was excellent (98.3%). The proportion of patients requiring additional antihypertensive drugs (amlodipine, atenolol, or both) was more than 50%, and similar in both groups. The study can be considered to be a comparison between an antihypertensive strategy based on a diuretic and another based on an ACEI.

The reductions in MAP were equivalent between drugs, although SBP was reduced more with indapamide SR than with enalapril. Interestingly, analysis of ABPM in a subset of patients showed no inter-group difference for daytime/night-time or SBP/DBP/MAP. As MAP reflects the pressure transmitted to the patient's renal circulation, the equivalent effect of indapamide SR and of enalapril on microalbuminuria could not be explained by different antihypertensive effects of the two drugs. Urinary albumin excretion also depends on the amount of albumin filtered through the glomerular barrier. In the short term, ACEIs may reduce the glomerular filtration rate (GFR) more than other antihypertensive drugs [34], thereby accounting for a more pronounced anti-albuminuric effect. The reductions in UACR and in fractional albumin clearance, which both reflect the glomerular permeability to albumin by taking into account glomerular filtration rate, were equivalent with the two drugs. Thus we can assume that indapamide SR and enalapril strategies were equally effective with respect to microalbuminuria and glomerular permeability to albumin in these patients with type 2 diabetes with permanent hypertension.

The NESTOR study was a 1-year study – a duration sufficient for evaluation of the efficacy of an antihypertensive drug on microalbuminuria in diabetic patients. In a study of the same duration, in 21 normotensive patients with type 1 diabetes, the superiority of enalapril to hydrochlorothiazide with respect to microalbuminuria was demonstrated [12]. Nielsen *et al.* [35] showed that proteinuria in patients with type 2 diabetes with nephropathy was reduced more by lisinopril than by atenolol, although GFR was protected equally by both drugs after 4 years [36]. The findings of these studies are consistent with the hypothesis that ACEIs reduce

microalbuminuria better than conventional drugs for a given reduction in blood pressure and support the predominant role of the renal haemodynamics in the constitution of diabetic nephropathy. Here, we report that the reduction in microalbuminuria in patients with type 2 diabetes with permanent hypertension was primarily dependent on the reduction in systemic blood pressure. This interpretation is consistent with the findings of the hypertension study of the UK Prospective Diabetes Study Group [37]: the magnitude of the reduction in microalbuminuria or proteinuria onset was not different with captopril or with atenolol, compared with the conventional strategy. Also, our data fit with recent histological findings showing minimal glomerular lesions in patients with type 2 diabetes with microalbuminuria and hypertension [38], similar to those described in 'benign' hypertension many years ago [39].

Both treatments were well tolerated over the 1 year of follow-up. Some biological differences between groups reached a significant level. For plasma potassium concentration, the difference observed between the indapamide SR and enalapril groups is consistent with previous findings showing that ACEIs increase the potassium concentration, whereas diuretics decrease them. Concerning lipid profiles, only the total cholesterol concentration was significantly increased in the indapamide SR group; HDL, LDL and triglycerides concentrations were not. Whether such slight biological changes affect the cardiovascular prognosis in the long term is highly questionable in light of the recent data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study [40].

Despite the lack of change in fasting plasma glucose concentration, the absolute difference between groups for changes in HbA_{1c} was 0.5% in favour of enalapril. However, HbA_{1c} was not monitored throughout the study, but measured only at baseline and at 1 year of treatment. The modalities of diabetes control and antidiabetic strategy were decided freely by each investigator according to the local guidelines and national recommendations. In this respect, there were three fewer patients receiving indapamide SR than receiving enalapril among the 17 whose treatment was changed to insulin during the study. The 0.5% inter-group difference for HbA_{1c} in favour of enalapril against indapamide SR probably conferred no major excess cardiovascular risk to participants receiving indapamide SR. An inter-group difference of 0.9% HbA_{1c} led to a 25% (95% CI 7 to 40%) risk reduction for microvascular events over 10 years during the UKPDS glucose trial, but there was no inter-group difference for stroke, heart failure or diabetes-related mortality [41]; only the risk for myocardial infarction was slightly reduced over 10 years [41]. The current trial was not designed to test cardiovascular outcomes based on glycaemic strategies. It was a 1-year trial based on changes in AER, a surrogate endpoint that predicts high risk for cardiovascular and renal diseases in such patients [4–7].

Finally, this is the first randomized study over 1 year to test the effectiveness of a diuretic-based treatment on microalbuminuria in patients with type 2 diabetes with hypertension. Indapamide SR, a diuretic, was as effective as enalapril, a drug with a proven efficacy in this domain.The efficacy of indapamide SR may rely on a pathophysiological rationale, as diabetic patients are characterized by an increase in systemic sodium, which can favour hypertension. Diuretic drugs have proven their utility in essential hypertension, including in patients with diabetes [42]. ALLHAT [40] confirmed that, in the long term, diuretics are as effective as ACEIs for the primary prevention of cardiovascular disease in hypertensive individuals at high cardiovascular risk. In line with the Joint National Committee 7 Report [43] and European Society of Hypertension–European Society of Cardiology 2003 [44] recommendations, this finding is consistent with the use of indapamide SR as first-line treatment in hypertensive type 2 diabetic patients with microalbuminuria.

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