

## Efficacy of Indapamide SR Compared With Enalapril in Elderly Hypertensive Patients With Type 2 Diabetes

Juan Garcia Puig<sup>1</sup>, Michel Marre<sup>2</sup>, Franciszek Kokot<sup>3</sup>, Margarita Fernandez<sup>4</sup>, György Jermendy<sup>5</sup>, Lionel Opie<sup>6</sup>, Valentin Moiseev<sup>7</sup>, André Scheen<sup>8</sup>, Constantin Ionescu-Tirgoviste<sup>9</sup>, M. Helena Saldanha<sup>10</sup>, Aaron Halabe<sup>11</sup>, Bryan Williams<sup>12</sup>, Decio Mion Jr<sup>13</sup>, Maximino Ruiz<sup>14</sup>, Kjeld Hermansen<sup>15</sup>, Jaakko Tuomilehto<sup>16</sup>, Bartolomé Finizola<sup>17</sup>, Yves Gallois<sup>18</sup>, Philippe Amouyel<sup>19</sup>, Jean-Pierre Ollivier<sup>20</sup>, and Roland Asmar<sup>21</sup>

<sup>1</sup> Hospital La Paz, Servicio de Medicina Interna, Madrid, Spain

<sup>2</sup> Hôpital Bichat, Service de Diabétologie et d'Endocrinologie, Paris, France

<sup>3</sup> Śląska Akademia Medyczna, Klinika Nefrologii, Katowice, Poland

<sup>4</sup> Instituto Nacional de la Nutrición 'Salvador Zubrian' Mexico, Mexico City, Mexico

<sup>5</sup> Bajcsy Zsilinszky Korház III, Budapest, Hungary

<sup>6</sup> Groote Schuur Hospital, Cape Heart Centre, Department of Medicine, Medical School, Cape Town, South Africa

<sup>7</sup> Hospital no. 64, Therapevticheski korpus, Moscow, Russian Federation

<sup>8</sup> CHU du Sart Tilman, Service de Diabétologie, Liège, Belgium

<sup>9</sup> Institute of Nutrition and Metabolic Diseases 'N. Paulescu', Bucharest, Romania

<sup>10</sup> HUC, Serviço de Medicina I, Coimbra, Portugal

<sup>11</sup> Internal Medicine Ward E, Edith Wolfson Medical Centre, Holon, Israel

<sup>12</sup> Department of Medicine and Therapeutics, University of Leicester, School of Medicine, Leicester, United Kingdom

<sup>13</sup> Centro de Estudos de Nefrologia e Hipertensão Arterial, Hospital das Clínicas, Instituto Central Cerqueira Cesar, Sao Paulo, Brazil

<sup>14</sup> Hospital de Clínicas, Departamento de Medicina Interna, División Diabetología, Buenos Aires, Argentina

<sup>15</sup> Medicinsk afdeling C, Aarhus Amtssygehus Hospital, Aarhus, Denmark

<sup>16</sup> National Public Health Institute, Helsinki, Finland

<sup>17</sup> ASCARDIO, Barquisimeto, Estado Lara, Venezuela

<sup>18</sup> Centre Hospitalier Universitaire, Service de Médecine B, Angers, France

<sup>19</sup> U.508 INSERM, Département d'étude des lipides/lipoprotéines, Institut Pasteur de Lille, Lille, France

<sup>20</sup> Service de Cardiologie, Hôpital Militaire de Val-de-Grâce, Paris, France

<sup>21</sup> Institut Cardiovasculaire, Paris, France

### Abstract

**Background:** Blood pressure control is the main influential variable in reducing microalbuminuria in patients with type 2 diabetes. In this subanalysis of the NatriLix SR versus Enalapril Study in hypertensive Type 2 diabetics with microalbuminuria (NESTOR) study, we have compared the effectiveness of indapamide sustained release (SR) and enalapril in reducing blood pressure and microalbuminuria in patients  $\geq 65$  years of age.

**Methods:** Of the 570 hypertensive patients with type 2 diabetes and persistent microalbuminuria in the NESTOR study, 187 (33%) individuals  $\geq 65$  years of age were included in this analysis. Of these, 95 patients received indapamide SR 1.5 mg and 92 patients received enalapril 10 mg, taken once daily in both cases. Adjunctive amlodipine and/or atenolol was added if required.

**Results:** The urinary albumin-to-creatinine ratio decreased by 46% in the indapamide SR group and 47% in the enalapril group. Noninferiority of indapamide SR over enalapril was demonstrated ( $P = .0236$ ; 35% limit of noninferiority) with a ratio of 0.95 (95% CI: 0.68, 1.34). Mean arterial pressure decreased by 18 mm Hg and 15 mm Hg in the indapamide SR and the enalapril groups, respectively ( $P = .1136$ ). The effects of both treatments seen in these elderly patients were similar to those observed in the main population, although the extent of the reduction in microalbuminuria was slightly higher. Both treatments were well tolerated, and no difference between groups was observed regarding glucose or lipid profiles.

**Conclusion:** Indapamide SR is not less effective than enalapril in reducing microalbuminuria and blood pressure in patients aged  $>65$  years of age with type 2 diabetes and hypertension. *Am J Hypertens* 2007;20: 90-97

**Keywords:** hypertension ; type 2 diabetes ; microalbuminuria ; indapamide SR ; enalapril.

The prevalence of type 2 diabetes is increasing worldwide.<sup>1</sup> This is of particular concern, as the disease is associated with significant morbidity and mortality, particularly in terms of the increased risk of premature death from coronary heart disease, peripheral vascular disease or stroke.<sup>2</sup> Hypertension and diabetes are interlinked, as hypertension is observed in up to 75% of patients with type 2 diabetes,<sup>3</sup> and patients with elevated blood pressure (BP) being significantly more likely to develop type 2 diabetes.<sup>4</sup> Patients with hypertension and

diabetes also frequently present with microalbuminuria,<sup>5</sup> which increases cardiovascular risk still further.<sup>6</sup>

Microalbuminuria is recognized as a strong and early predictor for the development of diabetic renal diseases (including end-stage renal disease),<sup>7,8</sup> and is itself associated with an increased risk of morbidity and mortality from cardiovascular disease.<sup>9</sup>

The angiotensin-converting enzyme inhibitors (ACEI) are known to decrease proteinuria and to preserve glomerular filtration rate (GFR) in patients with diabetes,<sup>10,11</sup> but little is known about the effects of diuretic therapy on microalbuminuria in diabetic patients. The Natrilix SR versus enalapril study in hypertensive type 2 diabetics with microalbuminuria (NESTOR) set out to compare the effectiveness of two antihypertensive drugs: an ACEI, enalapril, and a diuretic, indapamide sustained release (SR)<sup>12</sup> with opposite effects on the renin-angiotensin system (RAS) in reducing microalbuminuria.<sup>13</sup> Results of the study suggested that indapamide SR and enalapril reduced microalbuminuria to a similar extent, with equivalent mean BP control.

The risks of developing type 2 diabetes and hypertension increase with advancing age,<sup>14</sup> and thus elderly patients presenting with both type 2 diabetes and hypertension are a growing population. It is well known, however, that elderly patients represent a difficult population to treat effectively with antihypertensive therapy, particularly those with isolated systolic hypertension (ISH).<sup>15</sup> In addition, renal function tends to decline with advancing age.<sup>16</sup>

The NESTOR study included patients up to the age of 80 years. This article therefore describes a subgroup analysis of the NESTOR study, evaluating the impact of indapamide SR or enalapril on microalbuminuria and BP in patients >65 years of age.

## **METHODS**

### **Study Design**

The design of this study has previously been published.<sup>13</sup> Briefly, NESTOR was a double-blind, double-dummy, two-parallel groups, randomized, multicenter, international, 1-year study. It compared indapamide SR with enalapril in patients with type 2 diabetes and hypertension. After an initial 4-week placebo run-in period, during which previous antihypertensive therapy was withdrawn, patients were randomized to receive either indapamide SR 1.5 mg or enalapril 10 mg once daily for 1 year. From week 6 of treatment, additional open-label antihypertensive treatment was administered in a stepwise manner to achieve target BP levels (systolic BP [SBP]  $\leq$ 140 mm Hg and diastolic BP [DBP]  $<$ 85 mm Hg). Additional antihypertensive treatment (if required) consisted of amlodipine 5 mg once daily, then amlodipine 10 mg once daily, then amlodipine 10 mg once daily plus atenolol 50 mg once daily, then amlodipine 10 mg plus atenolol 100 mg once daily, with each step separated by 6-week intervals. Modification of antidiabetic treatment was allowed as necessary, including the use of insulin. The use of potassium supplements was allowed if kalemia was  $<$ 3.5 mmol/L. The study was performed in accordance with Good Clinical Practice and approved by Ethics committees in each country. Each patient gave his or her written informed consent before enrollment.

### **Study Population**

As previously described,<sup>13</sup> patients were recruited at 231 centers in 18 countries. The main criteria for inclusion were men and women aged 35 to 80 years, with type 2 diabetes (controlled by diet with or without one or more oral antidiabetic medications unchanged for at least 3 months), persistent microalbuminuria (an albumin excretion rate [AER] of 20 to 200  $\mu$ g/min in at least two of three overnight urine samples collected during the run-in placebo period) and essential hypertension (SBP 140 to 180 mm Hg and DBP  $<$ 110 mm Hg). Main criteria for exclusion were severe hypertension, body mass index  $>$ 40 kg/m<sup>2</sup>, hematuria, or leucocyturia, and urinary tract infection. This subanalysis includes data only from patients who were eligible for the double-blind phase of the study and who were  $\geq$ 65 years of age.

### **Efficacy Evaluations**

The primary efficacy evaluation was comparison of albuminuria after treatment with indapamide SR or enalapril, as previously described.<sup>13</sup> During the run-in period and at weeks 12, 24, 36, and 52, urine samples were collected overnight for measurement of albumin using nephelometry (assay sensitivity 2 mg/L), and for measurement of creatinine using the Jaffe method. Creatinine clearance was estimated with the Cockcroft formula.<sup>17</sup> Results were expressed as urinary albumin-to-creatinine ratio (UACR), AER, and fractional albumin clearance, with baseline values being defined as the median of values determined from the three urine samples collected during the placebo run-in period. Secondary efficacy evaluations included changes in SBP and DBP, which were evaluated at weeks 6, 12, 18, 24, 36, and 52, as the mean of three measurements in the supine position using a mercury sphygmomanometer with a cuff sized to the patient's arm as recommended. Mean arterial pressure (MAP) was

therefore calculated as one third of SBP plus two thirds of DBP. In addition, alterations in biochemical parameters from baseline to the end of the study were evaluated.

### Acceptability Evaluations

Assessment of acceptability was based mainly on an analysis of adverse events reported during the study, ECG parameters, body mass index, and biochemical parameters.

### Statistical Analyses

Statistical analyses were conducted on the full analysis set population, defined as all randomized patients having received at least one therapeutic unit and having at least one evaluation of microalbuminuria available at baseline (placebo run-in) and after treatment. The main objective of the analysis was to test the hypothesis of one-sided equivalence (noninferiority) of indapamide SR compared with enalapril on microalbuminuria reduction, and similar BP level.<sup>18</sup> Safety was evaluated for all randomized patients who received at least one therapeutic unit.

Details of the statistical analyses are described in the main study publication.<sup>13</sup> Briefly, the analysis of microalbuminuria was performed on log-transformed values. The between-treatment difference (indapamide SR - enalapril) of adjusted means was analysed by a one-sided noncentral Student *t* test. A limit of noninferiority that was less than 35% of the value in the enalapril group at the final visit was used, this being the assumed clinically significant difference.<sup>13</sup> The results were expressed as a ratio of geometric means with an associated 95% confidence interval. All analyses were adjusted on baseline value for each parameter.

## RESULTS

### Demographic and Baseline Characteristics of Patients

Of the 570 patients enrolled in NESTOR, 187 (33%) were >65 years of age. Of these patients, 95 received indapamide SR and 92 received enalapril.

Patient demographics and baseline characteristics were similar between groups as shown in Table 1, although there were significantly more men in the indapamide SR group.

Of the 187 patients, 15 patients (10 in the indapamide SR group and five in the enalapril group) withdrew from the study. Ten of these withdrawals were for reason of adverse events; three for a major protocol deviation; one for lack of efficacy; and one for a nonmedical reason. The mean compliance with treatments throughout the duration of the study was similar in the two groups: 80% in the indapamide SR group and 84% in the enalapril group.

From week 6 of study treatment, one or more adjunctive therapies for hypertension (ie, amlodipine, atenolol, or both) were taken by 78 (42%) patients; 40 (42%) in the indapamide SR group and 38 (41%) in the enalapril group.

**Table 1.** Demographic and baseline characteristics of patients  $\geq 65$  years of age randomized in the NESTOR study

Demographics (full analysis set)	IND SR (n = 95)	ENL (n = 92)	P value
Age, years (SD)	71.1 (4.2)	70.0 (4.1)	.072
Men/women (%)	72/28	58/42	.046
White/African American/Asian/other (%)	92/3/1/4	92/2/1/4	.982
Body mass index; kg/m <sup>2</sup> (SD)	27.9 (3.7)	28.9 (4.1)	.081
Smoker/ex-smoker/non-smoker (%)	15/27/58	14/32/54	.823
Diabetes duration; months (SD)	129 (102)	135 (99)	.684
Family history of diabetes (%)	34	43	.169
$\geq$ One oral hypoglycaemic agent (%)			.779
Sulphonamides, urea derivatives	65	84	
Biguanides	43	46	
HbA <sub>1c</sub> ; mean % (SD)	7.5 (1.9)	7.6 (1.7)	.713
Hypertension duration, months (SD)	132 (102)	108 (93)	.095
Family history of hypertension (%)	25	36	.115
Hypertension previously treated (%)	80	72	.187

ENL = enalapril; HbA<sub>1c</sub> = glycosylated hemoglobin; IND SR = indapamide SR; NESTOR = NatriLix SR versus Enalapril Study in hypertensive Type 2 diabetics with micrOalbuminuria.

**Table 2.** Microalbuminuria and renal function evaluations at baseline and endpoint

Criteria		IND SR (n = 95)	ENL (n = 92)	Intergroup comparison mean (95% CI)	P value
UACR (mg/mmol)					
Baseline*	Gmean (Q1, Q3)	6.8 (3.7, 12.0)	8.5 (4.9, 12.9)		
Final	Gmean (Q1, Q3)	3.7 (1.8, 9.0)	4.5 (1.6, 10.4)	0.95 (0.68; 1.34)	.0236†
% Decline	Gmean (95% CI)	46 (31; 57)	47 (32; 59)		
AER ( $\mu\text{g}/\text{min}$ )					
Baseline*	Gmean (Q1, Q3)	55.9 (34.5, 94.9)	65.6 (39.4, 114.5)		
Final	Gmean (Q1, Q3)	31.6 (12.3, 89.7)	35.5 (14.0, 83.4)	1.00 (0.69; 1.45)	.0579†
% Decline	Gmean (95% CI)	43 (27; 56)	46 (28; 59)		
Creatinine clearance (mL/min)					
Baseline‡	Mean (SD)	70.5 (18.6)	70.2 (19.0)		
Final	Mean (SD)	66.4 (17.5)	67.3 (18.8)		
$\Delta$ Decrease	Mean (95% CI)	-4.1 (-5.5; -2.7)	-2.9 (-4.6; -1.3)	-1.09 (-3.12; 0.94)	.2904§
Fractional albumin clearance ( $10^{-6}$ )					
Baseline*	Gmean (Q1, Q3)	12.7 (7.6, 21.9)	16.3 (9.5, 26.1)		
Final	Gmean (Q1, Q3)	7.4 (3.5, 19.1)	9.2 (3.1, 23.0)	0.94 (0.67; 1.34)	.223†
% Decline	Gmean (95% CI)	43 (27; 55)	44 (27; 57)		

AER = albumin excretion rate; CI = confidence interval; ENL = enalapril; Gmean = geometric mean; IND SR = indapamide sustained release; Q1 = first quartile; Q3 = third quartile; UACR = urinary albumin : creatinine ratio.

Within-group variations in microalbuminuria are expressed as % decline; within-group variations in blood pressure and creatinine clearance are expressed as  $\Delta$  decrease.

\* Baseline: median of the three first clean and valid values of V1, V2, V3; † P value for noninferiority testing; ‡ Baseline value is calculated only for patients with final value; § P value for difference testing.

**Table 3.** Supine blood pressure (mm Hg) evaluations at baseline and endpoint

Variable		IND SR (n = 95)	ENL (n = 92)	Inter-group comparison (95% CI)	P value
SBP					
Baseline	Mean (SD)	165 (10)	165 (9)		
Final	Mean (SD)	138 (10)	141 (15)		
$\Delta$ Decrease	Mean (95% CI)	-27 (-29 to -24)	-23 (-26 to -20)	-3 (-7 to 0.5)	.0885
DBP					
Baseline	Mean (SD)	93 (8)	92 (7)		
Final	Mean (SD)	79 (8)	81 (8)		
$\Delta$ Decrease	Mean (95% CI)	-13 (-15 to -11)	-11 (-13 to -10)	-1 (-3 to 1)	.2527
MAP					
Baseline	Mean (SD)	117 (7)	116 (6)		
Final	Mean (SD)	99 (7)	101 (10)		
$\Delta$ Decrease	Mean (95% CI)	-18 (-20 to -16)	-15 (-17 to -13)	-2 (-4 to 0.5)	.1136

DBP = diastolic blood pressure; MAP = mean arterial pressure; SBP = systolic blood pressure.

Analyses are adjusted on baseline. Intergroup comparison = IND SR - ENL. P values are for difference testing.

### Microalbuminuria and Renal Function

Overall, there was a significant decrease in UACR of 46% (95% confidence interval [CI]: 31, 57) in the indapamide SR group and 47% (95% CI: 32, 59) in the enalapril group (Table 2). The noninferiority of indapamide SR to enalapril was statistically demonstrated ( $P = .0236$ ) in reducing UACR with a ratio of 0.95 (95% CI: 0.68, 1.34). At the end of the study, the UACR was normal ( $<2.5$  mg/mmol in men and  $<3.5$  mg/mmol in women) in 41/95 (43%) and 34/92 (37%) of patients in the indapamide SR and enalapril groups, respectively ( $P = .387$ ).

The results of the microalbuminuria evaluations are shown in Table 2. Renal function, as measured by creatinine clearance showed a statistically decrease from baseline to the end of the study in both treatment group but the difference in decrease between the two groups was not significant (Table 2). A sensitivity analysis including only those patients who completed the study without major protocol violations indicated that the results were of the same order (for UACR, AER, and FAC), but there were no statistically significant differences because of the lack of power associated with the lower patient numbers involved (77 receiving indapamide SR and 83

enalapril).

### Blood Pressure

Both treatments showed antihypertensive efficacy as illustrated in Table 3. A total of 87% of patients receiving indapamide SR and 77% of patients receiving enalapril reached target BP as defined by the protocol ( $P = .068$ ). There were no significant differences between groups in the magnitude of the reductions from baseline to endpoint in SBP, DBP or MAP with differences of 3 mm Hg, 1 mm Hg, and 2 mm Hg in favor of indapamide SR, respectively.

### Acceptability

The two treatment regimens were generally well tolerated over the 1-year follow up and the frequency of adverse events was similar in both groups. No orthostatic hypotension was reported. Adverse events were generally consistent with the known pharmacological properties of both products (kalemia changes for both indapamide SR [decrease] and enalapril [increase] and cough for the ACE inhibitor). Three patients (3.2%) in the indapamide SR group and two patients (2.2%) in the enalapril group reported at least one emergent adverse event considered to be related to treatment (dizziness, cough, and constipation in the indapamide SR group, and hyperuricemia and aggravated hypertension in the enalapril group).

Assessments of plasma biochemistry parameters at baseline and endpoint are presented in Table 4. Lipid profiles (total cholesterol, HDL, LDL, triglycerides), fasting plasma glucose, and HbA<sub>1c</sub> did not show any difference between the two groups. Among all biochemical parameters examined during the study, a difference between groups was only observed for serum potassium and uric acid (expected). Hepatic and renal functions appeared to be well preserved.

**Table 4.** Change in biochemistry parameters during the study

Parameter	IND SR (n = 95)		ENL (n = 92)		Change (IND-SR - ENL)	P value*
	Baseline	Final	Baseline	Final		
Na <sup>+</sup> , mmol/L (SD)	140.4 (2.0)	139.3 (2.4)	140.0 (2.3)	139.1 (2.1)	-0.01	.9816
K <sup>+</sup> , mmol/L (SD)	4.4 (0.4)	4.2 (0.5)	4.5 (0.4)	4.6 (0.4)	-0.34	.0000
Uric acid, μmol/L (SD)	338.6 (82.7)	374.9 (92.8)	334.7 (85.1)	348.1 (97.4)	23.82	.0227
Total chol., mmol/L (SD)	5.2 (0.9)	5.3 (1.0)	5.3 (1.1)	5.2 (1.2)	0.14	.2044
HDL chol., mmol/L (SD)	1.1 (0.3)	1.2 (0.3)	1.2 (0.4)	1.2 (0.3)	0.01	.7761
LDL chol., mmol/L (SD)	3.3 (0.7)	3.4 (0.9)	3.3 (0.9)	3.2 (1.0)	0.13	.1577
Triglycerides, mmol/L (SD)	1.6 (0.9)	1.7 (0.9)	1.7 (0.9)	1.8 (0.9)	-0.05	.6566
Glucose, mmol/L (SD)†	8.7 (3.2)	9.2 (3.7)	9.3 (3.4)	9.4 (3.0)	0.10	.8103
HbA <sub>1c</sub> , % (SD)	7.5 (1.9)	8.0 (1.9)	7.6 (1.7)	7.9 (1.8)	0.19	.3177

chol. = cholesterol; ENL = enalapril; HDL = high-density lipoproteins; IND SR = indapamide sustained release; K = plasma potassium; LDL = low-density lipoprotein; Na = plasma sodium. \* Intergroup comparison of changes adjusted on baseline; † Fasting plasma glucose (P values are for difference testing).

## DISCUSSION

In this analysis of the elderly (age 65 to 80 years) subset of hypertensive patients with type 2 diabetes from the NESTOR study, it was found that microalbuminuria was generally reduced by a similar extent in the indapamide SR and enalapril groups as evaluated by changes from baseline to endpoint in UACR, AER, and fractional albumin clearance. These are the first published data evaluating the long-term (1-year) impact of diuretic antihypertensive therapy on microalbuminuria in elderly hypertensive patients with type 2 diabetes. In hypertensive patients with type 2 diabetes who also have nephropathy, the Diabetics Exposed to Telmisartan and enalapril (DETAIL) study has most recently shown that long-term (5-year) treatment with enalapril or the angiotensin receptor blocker telmisartan results in small overall changes in urinary albumin excretion, suggestive of a renoprotective effect.<sup>19</sup>

Overall, the benefits of both treatments on microalbuminuria seen in this elderly subset of NESTOR patients are similar to those observed in the overall NESTOR population, although the extent of the reduction in microalbuminuria was generally slightly higher here than observed in the main study. This may be attributed to the fact that the baseline albumin levels in the elderly population were slightly higher, possibly indicative of a higher degree of renal damage in the elderly population, as would be anticipated based on the difference in age. Indeed, the baseline creatinine clearance observed in the elderly population was lower than in the overall population (in which values of 91.5 mL/min were seen in the indapamide SR group and 93.4 mL/min in the enalapril group at

baseline), supporting this suggestion.

Modulation of the RAS (using ACEI or angiotensin receptor blockers) has been shown to provide effective BP control in elderly hypertensive patients, as has diuretic therapy. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) recommends thiazide-type diuretics as the preferred initial antihypertensive agent, noting that they have been "virtually unsurpassed" in preventing the cardiovascular complications of hypertension and that low-dose diuretics are generally well tolerated.<sup>20</sup> However, the benefits of different antihypertensive treatments in elderly hypertensive patients who also have type 2 diabetes are less well characterized. In this sub-study, BP was decreased by both indapamide SR and enalapril. Reductions in MAP (which reflects the BP at the glomerular level of the kidney) were similar between groups, which may support the suggestion that the similar reductions in microalbuminuria seen were as a result of similar antihypertensive effects of the two agents. With regard to the mean supine SBP, this fell below target levels (<140 mm Hg) only in the indapamide SR group. This was not a statistically significant difference in the elderly subgroup, probably because of size effect, although the greater reductions in supine SBP seen with indapamide SR compared with enalapril in the overall NESTOR population were significant. Combination therapy is often required to achieve effective BP control in the elderly, but in this 1-year study, less than 45% of patients in either group required combination therapy.

Overall, these results indicate that the proposed predominant role of high systemic BP in the development of microalbuminuria in hypertensive patients with type 2 diabetes noted in the overall NESTOR population continues to apply when elderly patients are considered. The National Kidney Foundation note that increased excretion of albumin is a sensitive marker for chronic kidney disease because of diabetes, hypertension, or glomerular disease,<sup>21</sup> with microalbuminuria progressing to overt proteinuria in 20% to 40% of patients with type 2 diabetes.<sup>8,22</sup>

Although data in elderly hypertensive patients with type 2 diabetes are limited, the Systolic Hypertension in the Elderly Program (SHEP) and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) included large elderly diabetic populations. The SHEP study included only patients with isolated systolic hypertension (ISH); however, JNC 7 notes that by age 60 years, about two thirds of individuals with hypertension have ISH<sup>20</sup>; hence a large proportion of patients in the NESTOR elderly population are likely to have had this diagnosis. High BP was associated with reduced kidney function in SHEP, which involved 4736 hypertensive men and women >65 years of age. This study suggested that the incidence and relative risk of a decline in kidney function increased at higher levels of BP, mainly SBP, independent of age, sex, ethnicity, smoking, diabetes, and history of cardiovascular disease.<sup>23</sup> In SHEP, low-dose diuretic-based therapy was found to be effective compared with placebo in preventing cardiovascular complications in elderly patients with type 2 diabetes mellitus and isolated systolic hypertension.<sup>24</sup> In ALLHAT, which involved 33,357 participants aged  $\geq 55$  years with hypertension and at least one other coronary heart disease risk factor (diabetes in some patients), thiazide-type diuretics were found to be superior in preventing one or more major forms of cardiovascular disease compared with amlodipine or lisinopril.<sup>25</sup>

Microalbuminuria has been related to other "surrogate markers" of high cardiovascular risk such as left ventricular hypertrophy, independent of BP.<sup>26</sup> The reductions in microalbuminuria seen in this study are therefore consistent with the reductions in left ventricular mass index seen in various studies of indapamide SR and enalapril. However, in the 1-year left ventricular hypertrophy regression, indapamide versus enalapril (LIVE) study, indapamide SR was found to be significantly more effective than enalapril at reducing left ventricular mass index.<sup>27</sup>

Both indapamide SR and enalapril treatment were well tolerated in this study, and no new adverse events occurred. However, there were two unexpected adverse events, in that cough is not usually related to diuretic use, and hyperuricaemia is not typically associated with ACEI use. These results have been checked and confirmed as correct, and should be explained by the double-blind situation. The acceptability of treatment was similar to that observed in the main NESTOR study, which is noteworthy because concomitant diseases are more common in the elderly and polypharmacy is more frequently seen. For plasma potassium concentration, the difference observed between the indapamide SR and enalapril groups is consistent with previous findings showing that ACEI increase potassium concentrations and diuretics decrease them. In relation to cardiovascular risk, it is reassuring that neither treatment had a significant effect on other parameters associated with cardiovascular morbidity and mortality such as HDL cholesterol, LDL cholesterol and triglycerides. There were also no significant differences between the groups in terms of glucose or HbA<sub>1c</sub>, although it should be noted that choice of diabetic therapy was largely at the investigators discretion, and thus the impact of antihypertensive treatment on these two parameters cannot be clearly evaluated. Although these biochemical parameters were evaluated only at the beginning and end of the study, more intensive evaluation of such parameters supports the metabolic neutrality of indapamide SR therapy during long-term treatment in at-risk hypertensive patients at risk, including those with diabetes and those who are elderly.<sup>28,29</sup> The limited impact of enalapril on lipid parameters

has also been previously observed.<sup>30</sup>

In conclusion, indapamide SR was not less effective than enalapril in reducing microalbuminuria and BP in elderly hypertensive patients with type 2 diabetes, consistent with the use of indapamide SR as first-line antihypertensive treatment in this patient population.

## Acknowledgments

The authors thank Institut de Recherches Internationales Servier for their support, as well as all NESTOR committee members and study investigators. The list of all participating centers has been already published in the main study.

Supported by an unrestricted grant from Institut de Recherches Internationales Servier.

## References

1. World Health Organization: The Diabetes Programme 2004. ([www.who.int/diabetes/en/](http://www.who.int/diabetes/en/)). Accessed June 13, 2005.
2. Haffner AM: Coronary heart disease in patients with diabetes. *N Engl J Med* 2000;342:1040-1042.
3. American Diabetes Association: Treatment of hypertension in adults with diabetes. Position statement. *Diabetes Care* 2003;26: 80S-82S.
4. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL: Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med* 2000;342:905-912.
5. Pascual JM, Rodilla E, Gonzalez C, Perez-Hoyos S, Redon J: Long-term impact of systolic blood pressure and glycemia on the development of microalbuminuria in essential hypertension. *Hypertension* 2005;45:1125-1130.
6. Park HY, Schumock GT, Pickard AS, Akhras K: A Structured review of the relationship between microalbuminuria and cardiovascular events in patients with diabetes mellitus and hypertension. *Pharmacotherapy* 2003;23:1611-1616.
7. Adler AI, Stevens RJ, Manley SE: Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int* 2003;63:225-232.
8. Nelson RG, Knowler WC, Pettitt DJ, Saad MF, Charles MA, Bennett PH: Assessing risk of overt nephropathy in diabetic patients from albumin excretion in untimed urine samples. *Arch Intern Med* 1991; 151:1761-1765.
9. Hillege HL, Fidler V, Diercks GFH, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE; Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group: Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002; 106:1777-1782.
10. Heart Outcomes Prevention Evaluation Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253-259.
11. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomised trial. *Ann Intern Med* 2001;134:629-636.
12. Sassard J, Bataillard A, McIntyre H: An overview of the pharmacology and clinical efficacy of indapamide sustained release. *Fund Clin Pharmacol* 2005;19:637-645.
13. Marre M, Garcia-Puig J, Kokot F, Fernandez M, Jermendy G, Opie L, Moiseev V, Scheen A, Ionescu-Tirgoviste C, Saldanha MH, Halabe A, Williams B, Mon Junior D, Ruiz M, Hermansen K, Tuomilehto J, Finizola B, Gallois Y, Amouyel P, Ollivier JP, Asmar R: Equivalence of indapamide SR and enalapril on microalbuminuria reduction in hypertensive patients with type 2 diabetes: the NESTOR study. *J Hypertens* 2004;22:1613-1622.
14. Choi BC, Shi F: Risk factors for diabetes mellitus by age and sex: results of the National Population Health Survey. *Diabetologia* 2001;44:1221-1231.
15. Baruch L: Hypertension and the elderly: more than just blood pressure control. *J Clin Hypertens (Greenwich)* 2004;6:249-255.
16. Bauer JH: Age-related changes in the renin-aldosterone system. Physiological effects and clinical implications. *Drugs Aging* 1993; 3:238-245.
17. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
18. Dunnett CW, Gent M: An alternative to the use of two-sided tests in clinical trials. *Stat Med* 1996;15:1729-1738.
19. Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, Mustonen J; Diabetics Exposed to Telmisartan and Enalapril Study Group: Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004;351:1952-1961.
20. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: the JNC 7 report. *J Am Med Assoc* 2003;289:2560-2572.
21. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G; National Kidney Foundation: National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Ann Intern Med* 2003;139:137-147.

22. Mogensen CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 1984;310:356-360.
23. Young JH, Klag MJ, Muntner P, Whyte JL, Pahor M, Coresh J: Blood pressure and decline in kidney function: findings from the Systolic Hypertension in the Elderly Program (SHEP). *J Am Soc Nephrol* 2002;13:2276-2282.
24. Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G, Davis BR, Frost PH, Gonzalez N, Guthrie G, Oberman A, Rutan GH, Stamler J: Effect of diuretic-based antihypertensive treatment on cardiovascular disease in older diabetic patients with isolated systolic hypertension. *J Am Med Assoc* 1996;276:1886-1892.
25. ALLHAT officers and coordinators for the ALLHAT collaborative research group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *J Am Med Assoc* 2002;288:2981-2997.
26. Redon J, Baldo E, Lurbe E, Bertolin V, Lozano JV, Mralles A, Pascual JM: Microalbuminuria, left ventricular mass and ambulatory blood pressure in essential hypertension. *Kidney Int* 1996; 55(Suppl):S81-S84.
27. Gosse P, Sheridan D, Zannad F, Dubourg O, Gueret P, Karpov Y, de Leeuw PW, Palma-Gamiz JL, Pessina A, Motz W, Degaute JP, Chastang C: Regression of left ventricular hypertrophy in hypertensive patients treated with indapamide SR 1.5 mg versus enalapril 20 mg: the LIVE study. *J Hypertens* 2000;18:1465-1475.
28. Ambrosioni E, Safar M, Degaute JP, Malin PL, MacMahon M, Pujol DR, de Cordoue A, Guez D: Low-dose antihypertensive therapy with 1.5mg sustained-release indapamide: results of randomised double-blind controlled studies. *J Hypertens* 1998;16:1677-164.
29. Weidmann P: Metabolic profile of Indapamide sustained-release in patients with hypertension. Data from three randomised double-blind studies. *Drug Safety* 2001;24:1155-1165.
30. Mancia G, Omboni S, Agabiti-Rosei E, Casati R, Fogari R, Leonetti G, Montemurro G, Nami R, Pessina AC, Pirrelli A, Zanchetti A: Antihypertensive efficacy of manidipine and enalapril in hypertensive diabetic patients. *J Cardiovasc Pharmacol* 2000;35:926-931.