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HIGH-NORMAL ALBUMINURIA AND THE RISK OF CARDIOVASCULAR AND RENAL COMPLICATIONS IN HYPERTENSIVE MEN

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Background: Microalbuminuria (commonly defined as an overnight urinary albumin excretion >15mg/min) is associated with cardiovascular risk factors and predicts morbid events in hypertensive subjects. However, albuminuria is not a dichotomous variable and a relationship with cardiovascular risk factors may extend below that conventional threshold.

Methods: We studied 186 never treated, glucose tolerant normalbuminuric (overnight albuminuria>15mg/min) essential hypertensive men with normal renal function (serum creatinine<1.4 mg/dl). Study variables were 24-hr ambulatory blood pressure (ABP), relative wall thickness (RWT, IVST+PWT/EDD by echocardiography), body mass index (BMI), insulin sensitivity (the HOMA index) and creatinine clearance (CrCl) analyzed as a function of ascending urine albumin quartiles (cut-off points: 4.3, 6.3 and 9.4 mg/min, n=47, 45, 47 and 47 respectively).

Results (means±SD): As compared with the three bottom fourths, patients with high-normal albuminuria (9.4-15 mg/min) had greater 24-hr ABP (I:140±16/88±11, II:140±15/88±11, III:139±16/89±13 vs IV: 151±19/96±13 mmHg, p<0.01), RWT (I:0.44±0.04, II:0.44±0.04, III: 0.43±0.07 vs IV:0.47±0.07, p<0.02), BMI (I:25.9±2.1,II:26.2±2.2, III:25.7± 3.1 vs IV:27.2±2.9 Kg/m2, p<0.01), reduced insulin sensitivity (I:18.4±2.1, II:20.4±8.7, III:18.1±13.5 vs IV:27.4±19.8, p<0.02) and increased CRCl (I:107±30,II:126±38, III:139±44 vs IV: 144±44 ml/min x1.73m2, p<0.001).

Conclusions: High-normal albuminuria is associated with an adverse cardiovascular and metabolic risk profile in uncomplicated essential hypertensive men. Furthermore, hyperfiltration in presence of minimally increased albuminuria may underlie an augmented glomerular blood flow and hydraulic pressure, conducive to glomerular hypertension and eventually renal insufficiency. Overall, these data might suggest to shift downwards the limits for diagnosing microalbuminuria in essential hypertension.

Key Words: Albuminuria, Hyperfiltration, Insulin Resistance

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DOES LOSARTAN TREATED PATIENTS WITH ALBUMINURIA HAVE BETTER CARDIOVASCULAR OUTCOME THAN THOSE TREATED WITH ATENOLOL? THE LIFE STUDY

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Recently, we found that increased urine albumin creatinine ratio (UACR) as well as electrocardiographic (ECG) verified left ventricular hypertrophy (LVH) were independent predictors of all cause and cardiovascular mortality as well as a composite cardiovascular end-point consisting of CV death, myocardial infarction and stroke. However, it remains unclear whether treatment of albuminuric patients with a losartan-based protocol results in greater reduction in cardiovascular mortality and composite end-point compared to treatment with atenolol.

ECG and morning spot urine were obtained in 8,029 patients with stage II-III hypertension and LVH determined by ECG (Cornell voltage duration or Sokolow-Lyon voltage criteria) after 14 days placebo treatment. Renal glomerular permeability was evaluated by UACR and was defined as microalbuminuria if >3.5 and macroalbuminuria if >35.

1844 (20.1%) patients had microalbuminuria, 1844 (3.5%) had macroalbuminuria and 5865 (63.8%) patients were normoalbuminuric at baseline. During 61 [95% CI 54-71] months 816 (10%) deaths occurred. Of these 438 (5.5%) were cardiovascular deaths, which were added to myocardial infarction and stroke to compose the composite cardiovascular end-point (n=961, 12.0%).

As the LIFE study at the moment is blinded and will be so until the presentation of the main results in March of 2002, we will, in May 2002, be able to show whether treatment with a losartan as compared to an atenolol-based regimen significantly effects cardiovascular composite endpoint and mortality independent of the blood pressure reduction per se in albuminuric patients.

Key Words: Left Ventricular Hypetrophy, Microalbuminuria, Treatment

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TREATMENT BASED ON A LOW DOSE COMBINATION OF PERINDOPRIL AND INDAPAMIDE REDUCES ALBUMINURIA MORE EFFECTIVELY THAN ENALAPRIL IN HYPERTENSIVE TYPE 2 DIABETIC PATIENTS

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The objective was to compare on albuminuria excretion rate (AER) in hypertensive type 2 diabetic patients, the effects of two treatment strategies, one based on the very low dose combination Perindopril 2mg/ Indapamide 0.625mg (Per/Ind), and the other on a monotherapy (enalapril: ena).

The design was a 12-month international, randomised, double-blind, parallel group study. Albuminuria was centrally evaluated on overnight urinecollections.Patientswereenrolledwithhypertension(140mmHg≤SBP <180mmHg and DBP<110mmHg) and controlled NIDDM. After a 4 week placebo period, patients with albuminuria ≥20 and <500μg/min were randomised to Per/Ind or to ena od. A dose adaptation by doubling the dosage, from Per 2/Ind 0.625 mg to Per 8/Ind 2.5 mg or ena 10mg to 40mg was scheduled from W12 according to the blood pressure. Statistical analysis have been done on the log transformed values using a Student- t test with a 95% confidence interval and α=2.5%.

481 patients were randomised with age: 59.1±8.7 years, 61.1% male. Results from 457 patients (ITT) are shown:

AER (μg/min)	Per/Ind	Ena	E* (Per/Ind/Ena)
Gmean (Q1;Q3)	***N = 233***	***N = 224***	**[95% CI]**
Baseline (W0)	75.3 (36.4; 153.4)	89.1 (39.5; 192.5)	
Last observation (End)	43.7 (18.1; 92.8)	64.7 (27.2; 155.7)	0.76† [0.62; 0.92]
1-(End/W0) [95% CI]	−42% [−33%; −50%]	−27% [−16%; −37%]	

E : estimated treatment effect, adjusted on baseline value and country; † superiority test p = 0.002; Gmean: Geometric mean; [Q1; Q3]: 1st and 3rd quarter.*

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BP (mmHg) mean ± sd		Per/Ind *N = 233*	Ena *N = 224*	Difference [95% CI]
SBP	**W0**	158.0 ± 11.5	158.8 ± 12.1	
	ΔEnd-W0	−14.8 ± 15.8	−12.3 ± 15.5	−3.0 [−5.6; −0.4]§
DBP	**W0**	93.3 ± 8.7	93.3 ± 8.7	
	ΔEnd-W0	−8.8 ± 9.3	−7.3 ± 9.0	−1.5 [−3.0; −0.1]§

§ p = 0.012; §§ p = 0.019 after adjustment on baseline and country (Student-t test).

The albuminuria regression was 42% with Per/Ind and 27% with ena with a significant higher antihypertensive efficacy for Per/Ind. The rate of patients with adverse events was similar. There was no significant difference between groups for change in renal function.

A treatment strategy based on a low dose combination Perindopril 2mg and Indapamide 0.625mg reduces albuminuria, SBP and DBP more effectively than an equivalent dose of enalapril over a one-year period in type 2 diabetes.

Key Words: Low Dose Combination, Albuminuria, Clinical Trials

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EFFECT OF MANIDIPINE AND LISINOPRIL ON ALBUMINURIA AND VENTRICULAR MASS IN DIABETIC HYPERTENSIVE PATIENTS WITH MICROALBUMINURIA

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The purpose of this study was to evaluate the effect of long-term treatment with manidipine and lisinopril monotherapy on albumin excretion rate (AER) and left ventricular mass index (LVMI) in hypertensive patients with type 2 diabetes (NIDDM) and microalbuminuria.

We identified 116 mild to moderate hypertensive (DBP $>$ 90 $<$ 100 mmHg) patients with well controlled NIDDM and microalbuminuria, aged 45-69 years. After a 4 week placebo period they were randomized to manidipine 10 mg od or to lisinopril 10 mg od for 2 years; after 8 weeks the dose was doubled in the non responders (DBP $>$ 90 mmHg); after 16 weeks the non responders were excluded. The trial was completed by 73 patients. At the end of the placebo period and after 24, 48 and 96 weeks of treatment, BP, AER and LVMI were evaluated. The results are shown in the table.

The 2 drugs had the same antihypertensive efficacy; however AER showed an earlier and greater reduction in the lisinopril than in manidipine group. On the opposite LVMI was reduced more by manidipine than by lisinopril; this effect could be due to the impaired calcium homeostasis of diabetic cardiomyopathy. These two complementary effects outline the rational of a Ca antagonist-Ace inhibitor combination in the treatment of diabetic hypertensive patients.

		SBP (mmHg)	DBP (mmHg)	AER (mg/24h)	LVMI (g/m2)
Lisinopril (n = 36)	baseline	151 ± 10	95 ± 4	78 ± 26	106 ± 15
	24 weeks	137 ± 9**	85 ± 4**	44 ± 19**	103 ± 16
	48 weeks	134 ± 9**	82 ± 5**	32 ± 17**	100 ± 13
	96 weeks	133 ± 9**	81 ± 5**	35 ± 18**	96 ± 12*
Manidipine (n = 37)	baseline	150 ± 11	95 ± 4	82 ± 28	107 ± 17
	24 weeks	138 ± 10**	85 ± 4**	75 ± 27	101 ± 14
	48 weeks	132 ± 9**	81 ± 5**	69 ± 25	94 ± 12*
	96 weeks	131 ± 9**	80 ± 5**	51 ± 22*	89 ± 11**

** $p < 0.05$, ** $p < 0.01$ vs baseline.*

Key Words: Ventricular Mass, Albuminuria, Manidipine