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Prognostic Significance of Renal Function in Elderly Patients with Isolated Systolic Hypertension: Results from the Syst-Eur Trial

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Abstract. Several reports suggest that markers of renal function such as serum creatinine, serum uric acid, and urinary excretion of protein may be related to cardiovascular complications and mortality. This study analyzed the data from the Syst-Eur trial, which was a randomized, placebo-controlled, double-blind intervention trial in elderly patients with isolated systolic hypertension. The purpose was to evaluate whether serum levels of creatinine and uric acid and urinary protein excretion at entry are related to subsequent morbidity and mortality. Incidence rates of total mortality, cardiovascular mortality, stroke (fatal as well as nonfatal), coronary events, and all cardiovascular endpoints were calculated for each quintile of serum creatinine or serum uric acid or for each category of protein excretion (none, trace, and overt). Crude and adjusted relative hazard rates were also determined for each 20 μM increase in serum creatinine, each 50 μM increase in serum uric acid, and for each protein excretion category. Even when adjusted for age, gender, and various other covariates, serum creatinine was significantly associated with a worse prognosis. There was an U-shaped relationship between serum uric acid and total mortality, but otherwise no obvious relationships were detected between serum uric acid levels and complications when appropriate adjustments were made for confounding variables. Proteinuria at entry was a significant predictor of total mortality and all cardiovascular endpoints. It is concluded that higher levels of serum creatinine and trace or overt proteinuria are associated with an increased number of cardiovascular events and with a higher mortality in patients with isolated systolic hypertension.

Cardiovascular prognosis in patients with hypertension depends not only on the level of BP and associated risk factors but also on the presence of target organ damage. For instance, after left ventricular hypertrophy has developed as a result of long-standing hypertension, this complication becomes a risk factor in its own right and a predictor not only of further cardiac abnormalities (1) but also of other atherothrombotic events, such as ischemic stroke (2). Similarly, the presence of cerebrovascular abnormalities may raise cardiovascular risk over and above that conferred by hypertension itself. Although the brain and the heart are the prime targets of the hypertensive process, the kidney is also frequently affected. Evidence is accumulating that renal damage, once present, may also independently contribute to an increased cardiovascular risk (3). Many studies on this issue, however, were either retrospective or did not follow a rigid prospective protocol. Consequently, only limited information is available concerning the extent to which renal damage modifies the risk of future cardiovascular complications. This prompted us to address this question using the Syst-Eur database. The Syst-Eur trial was a large, prospective, double-blind, placebo-controlled trial that examined whether active antihypertensive treatment reduces cardiovascular risk in elderly patients with isolated systolic hypertension. The main results of this trial have already been described

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elsewhere (4,5). Here we report on the post-hoc analysis of the relationship between renal function at baseline and subsequent morbidity and mortality. Serum creatinine, serum uric acid, and degree of proteinuria were used as markers of renal function.

Materials and Methods

The protocol of the Syst-Eur trial was approved by the Ethics Committees of the University of Leuven and all participating centers. The study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki; informed consent was obtained from each participant. The inclusion and exclusion criteria, the definition of endpoints, and the procedures for recruitment and randomization have been published before (4). Eligible patients were aged 60 yr or older. On conventional measurement, they had a sitting systolic BP of 160 to 219 mmHg with a diastolic BP below 95 mmHg. The standing systolic BP was at least 140 mmHg. These entry criteria rested on the means of six BP readings obtained during the placebo run-in period (two readings in each position at three visits 1 mo apart). Patients with a serum creatinine concentration of $\geq$176.8 μmol/L (2.0 mg/dl) were excluded, but diabetic patients could be enrolled. Eligible patients were randomized to double-blind treatment with active medication or placebo. The study medications were stepwise titrated and combined to reduce the sitting systolic BP (mean of two readings at each follow-up visit) by $\geq$20 mmHg to $<$150 mmHg. Active treatment was initiated with nitrendipine (10 to 40 mg/d). If necessary, the dihydropyridine was combined with or replaced by enalapril (5 to 20 mg/d), hydrochlorothiazide (12.5 to 25 mg/d), or both drugs. Identical placebos were employed in the same way in the control group.

At randomization and at yearly intervals thereafter, serum creatinine and uric acid concentrations were measured by standard laboratory techniques, and fresh urine samples were examined for proteinuria ($>$300 mg/L) by using a semiquantitative dipstick method. Protein excretion was classified as *none* (negative dipstick reaction, *i.e.*, protein excretion less than 150 mg/L), *trace amounts* (150 to 300 mg/L), or *overt* ($>$300 mg/L). Serum creatinine levels were converted to GFR using Cockcroft-Gault formula (6).

We used SAS software, version 6.12 (SAS Institute Inc., Cary, NC) for database management and statistical analysis. The significance of mean unadjusted differences between groups was determined from the normal z distribution. To examine the relationship between initial renal function and subsequent morbidity and mortality, the total group of patients was divided into quintiles according to baseline levels of serum creatinine or serum uric acid. To analyze the association between protein excretion and cardiovascular complications, patients were divided according to the level of proteinuria, *i.e.*, none, trace, or overt. Incidence rates in quintiles of serum creatinine and uric acid or in categories of proteinuria were calculated with adjustments for age and gender. Relative hazard rates with 95% confidence intervals (CI) were estimated by single and multiple Cox regression, adjusted for treatment group and significant covariates (7). For each calculation, we first tested whether the proportional hazards assumption was satisfied (8). Results have been reported only when this was the case.

Results

Patient Characteristics at Randomization

At randomization, the patients in the placebo ($n = 2297$) and active-treatment ($n = 2398$) groups had similar clinical characteristics (4). Previous cardiovascular complications were present in 1402 patients (29.9%), of whom 614 had a Sokolow-Lyon voltage index (9) compatible with left ventricular hypertrophy. Of the 4695 patients, 2187 (46.6%) had been treated with antihypertensive drugs before enrollment, 343 (7.3%) were current smokers, and 525 (11.2%) consumed at least one glass of beer, wine, or liquor per day.

Baseline measurements of serum creatinine were available in 4688 patients, baseline uric acid levels in 4552 patients, and data on urinary protein excretion in 4658 patients. These patients form the basis of the present report.

Treatment and BP during Follow-Up

The median follow-up in the 4695 patients was 2.0 yr. Because the patients had been recruited over 8 yr and because the trial stopped early, follow-up of the individual patients ranged from 1 to 97 mo. The number of patient-years in the placebo and active-treatment groups amounted to 5844 and 6140, respectively.

At the time of the last BP measurement, 1896 patients of the active treatment group and 1601 patients of the placebo group were still on double-blind treatment. Of the actively treated patients, 1624 were taking nitrendipine (mean daily dose, 28.2 mg), 613 enalapril (13.8 mg), and 269 hydrochlorothiazide (21.6 mg); for the matching placebos in the control group, these numbers were 1445, 839, and 472, respectively.

In the intention-to-treat analysis with adjustment for baseline BP, the BP differences between the two treatment groups at the last evaluation averaged 11 mmHg systolic and 4 mmHg diastolic.

Serum Creatinine at Baseline and Incidence of Endpoints

Baseline data on serum creatinine were available for 4688 patients. Table 1 lists the clinical characteristics of those patients when stratified by quintiles of serum creatinine. These quintiles did not differ with respect to the percentage of patients on active treatment. Also, the proportion of diabetic patients was similar. Creatinine levels were positively correlated with age, male gender, the proportion of patients with previous cardiovascular complications, and systolic BP. In women, a higher creatinine was also associated with a lower diastolic BP. No differences between quintiles were observed, either in men or in women, with respect to body mass index, serum cholesterol levels, and percentage of patients who smoked or used alcohol. The same was true when GFR rather than measured creatinine concentration was taken as the dividing variable.

During follow-up, 280 patients in whom baseline serum creatinine was measured died; in 145 cases the cause of death was cardiovascular. As shown in Figure 1, the age- and gender-adjusted incidence rates of total, cardiovascular, and stroke mortality as well as fatal and non-fatal cardiovascular endpoints rose with higher baseline levels of serum creatinine. Table 2 illustrates that each 20 μM increase in serum creatinine was significantly associated with a worse prognosis, even when adjusted for age, gender, and other covariates (treatment, systolic BP, previous cardiovascular complications, smoking, and presence of diabetes mellitus). Even further adjustment for

Table 1. Characteristics of patients in quintiles of serum creatinine at baseline[a]

Characteristic	Range of Serum Creatinine, μmol/L				
	≤72	72.1 to 82.9	83 to 90	90.1 to 101.1	≥101.2
Number of patients	937	919	959	936	937
Serum creatinine, μmol/L	63.9 ± 7.7	77.6 ± 2.6	86.4 ± 2.5	96.1 ± 3.1	115.4 ± 13.3[e]
Age, yr	70.1 ± 6.5	69.9 ± 6.4	70.0 ± 6.5	69.8 ± 6.7	71.4 ± 7.2[e]
Active treatment, *n* (%)	490 (52.3)	447 (48.6)	500 (52.1)	480 (51.3)	475 (50.7)
CV complications, *n* (%)	265 (28.3)	242 (26.3)	262 (27.3)	287 (30.7)	344 (36.7)[e]
Diabetic patients, *n* (%)	108 (11.5)	94 (10.2)	80 (8.3)	99 (10.6)	109 (11.6)
Men, *n* (%)	109 (11.6)	222 (24.2)	293 (30.6)	413 (44.1)	518 (55.3)[e]
SBP, mmHg	172.4 ± 8.7	172.6 ± 8.9	172.8 ± 8.9	173.3 ± 10.2	174.8 ± 10.3[c]
DBP, mmHg	85.1 ± 5.7	85.7 ± 6.6	85.9 ± 5.9	86.0 ± 6.1	85.5 ± 5.9
BMI, kg/m^2	26.7 ± 3.6	26.3 ± 3.1	26.5 ± 3.2	26.2 ± 3.2	26.5 ± 3.2
total cholesterol, mmol/L	5.5 ± 1.1	5.6 ± 1.2	5.7 ± 1.2	5.8 ± 1.1	5.7 ± 1.1
current smokers, *n* (%)	21 (19.3)	32 (14.4)	42 (14.3)	63 (15.3)	72 (13.9)
current alcohol use,[b] *n* (%)	30 (27.5)	63 (28.4)	74 (25.3)	96 (23.2)	129 (24.9)
Women, *n* (%)	828 (88.4)	697 (75.8)	666 (69.4)	523 (55.9)	419 (44.7)[e]
SBP, mmHg	173.2 ± 10.2	173.6 ± 10.2	173.5 ± 9.8	174.6 ± 9.8	176.0 ± 9.9[e]
DBP, mmHg	85.8 ± 5.7	85.9 ± 5.8	85.3 ± 5.6	85.0 ± 6.0	84.1 ± 5.8[e]
BMI, kg/m^2	27.6 ± 4.8	27.3 ± 4.4	27.1 ± 4.1	27.3 ± 4.5	27.3 ± 4.1
total cholesterol, mmol/L	6.2 ± 1.2	6.1 ± 1.1	6.2 ± 1.2	6.2 ± 1.4	6.2 ± 1.3
current smokers, *n* (%)	26 (3.1)	20 (2.9)	27 (4.1)	21 (4.0)	18 (4.3)
current alcohol use,[b] *n* (%)	52 (6.3)	24 (3.4)	24 (3.6)	15 (2.9)	17 (4.1)

[a] Values are mean ± SD, unless otherwise indicated. CV, cardiovascular; SBP, systolic BP; DBP, diastolic BP; BMI, body mass index.
[b] Patients drinking at least 1 unit of alcohol per day. The significance of difference between quintiles 1 and 5 are given: [c] $P \leq 0.05$; [d] $P < 0.01$; [e] $P < 0.001$.

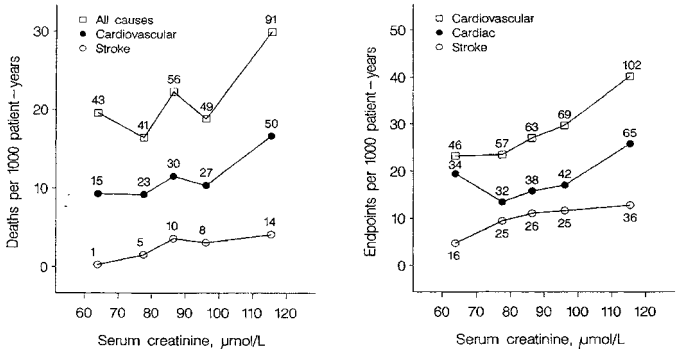

Figure 1. Relationship between serum creatinine at baseline and outcome. Left panel: Age- and gender-adjusted death rates in quintiles of serum creatinine. The number of deaths is given for each quintile. Right panel: Age- and gender-adjusted fatal and nonfatal event rates in quintiles of serum creatinine. The number of endpoints is given for each quintile.

serum cholesterol levels did not change any of the significant relationships. In other words, serum creatinine at baseline appeared to be a significant independent indicator of future total and cardiovascular mortality. When the data were analyzed according to GFR rather than serum creatinine, GFR appeared to be a powerful predictor for all endpoints. For instance, for each 20 ml/min decline in GFR, cardiovascular mortality rose by 60% (95% CI, 49 to 69%; $P < 0.001$) and the risk for any cardiovascular complication by 48% (95% CI, 39 to 55%; $P < 0.001$).

Taking all fatal and nonfatal endpoints together, there were 337 cardiovascular endpoints, 211 cardiac endpoints, and 128 strokes during follow-up. Serum creatinine appeared to be a significant risk indicator for these endpoints as well (Table 2).

When data were analyzed separately for the placebo and the active treatment group, relative hazard rates appeared to be greater in the former but the interaction between serum creatinine and treatment group was NS. Similarly, hazard rates tended to be higher in nondiabetic patients compared with diabetic patients, but again the interaction term between creatinine and diabetes was NS. Relative hazard rates for total mortality ($P = 0.03$), cardiovascular mortality ($P = 0.04$), and all cardiac endpoints ($P = 0.02$) were higher in women than in men.

Serum Uric Acid at Baseline and Incidence of Endpoints

Serum uric acid was measured at entry in 4552 patients. When broken down by quintiles of serum uric acid (Table 3), patients in the quintiles were comparable with respect to age, treatment status, and the proportion of patients with diabetes. In the highest quintile, there were more men and more patients with previous cardiovascular complications. Serum uric acid was positively associated with body mass index in both genders, with diastolic pressure in men, and with serum cholesterol

Table 2. Association between serum creatinine at baseline and outcome[a]

Events	Endpoints *n*	Crude RHR	Adjusted[d] RHR
Mortality			
total	280	1.44 (1.29 to 1.62)[c]	1.13 (1.00 to 1.28)[b]
cardiovascular	145	1.54 (1.32 to 1.79)[c]	1.23 (1.04 to 1.45)[b]
stroke	38	1.73 (1.31 to 2.28)[c]	1.46 (1.09 to 1.98)[b]
Fatal and nonfatal cardiovascular endpoints			
all	337	1.45 (1.31 to 1.61)[c]	1.23 (1.10 to 1.37)[c]
cardiac	211	1.43 (1.25 to 1.62)[c]	1.19 (1.03 to 1.37)[b]
stroke	128	1.40 (1.18 to 1.65)[c]	1.25 (1.05 to 1.50)[b]

[a] RHR indicates relative hazard rate. Values are relative hazard rate with 95% CI calculated for a 20 μmol/L increase in serum creatinine. The significance of the relative hazard rates is given: [b] $P \leq 0.05$; [c] $P < 0.001$.
[d] Adjusted for age, gender, active treatment, systolic BP, smoking status, previous cardiovascular complications, and diabetes mellitus.

Table 3. Characteristics of patients in quintiles of serum uric acid at baseline[a]

Characteristic	Range of Serum Uric Acid, μmol/L				
	≤220	221 to 271	272 to 319	320 to 369	≥370
Number of patients	902	903	906	902	939
Serum uric acid, μmol/L	183.6 ± 31.7	249.7 ± 14.2	294 ± 12.0	338.3 ± 14.1	427.5 ± 62.9[e]
Age, yr	70.1 ± 6.7	70.2 ± 6.5	70.3 ± 6.8	70.1 ± 6.6	70.2 ± 6.7
Active treatment, *n* (%)	459 (50.9)	468 (51.8)	459 (50.7)	453 (50.2)	487 (51.9)
CV complications, *n* (%)	247 (27.4)	241 (26.7)	267 (29.5)	272 (30.2)	308 (32.8)[c]
Diabetic patients, *n* (%)	97 (10.8)	101 (11.2)	88 (9.7)	89 (9.9)	97 (10.3)
Men, *n* (%)	172 (19.1)	224 (24.8)	270 (29.8)	358 (39.7)	476 (50.7)[e]
SBP, mmHg	174.1 ± 8.9	173.4 ± 9.5	173.8 ± 10.0	172.5 ± 9.5	173.9 ± 10.1
DBP, mmHg	84.7 ± 6.0	85.6 ± 5.6	85.9 ± 5.6	85.7 ± 6.5	86.1 ± 6.1[c]
BMI, kg/m^2	26.0 ± 3.0	26.2 ± 3.2	26.2 ± 3.1	26.4 ± 3.1	26.9 ± 3.3[d]
total cholesterol, mmol/L	5.5 ± 1.1	5.7 ± 1.1	5.8 ± 1.1	5.7 ± 1.1	5.7 ± 1.1
current smokers, *n* (%)	28 (16.3)	34 (15.2)	40 (14.8)	53 (14.8)	70 (14.7)
current alcohol use,[b] *n* (%)	51 (29.7)	64 (28.6)	60 (22.2)	91 (25.4)	119 (25.0)
Women, *n* (%)	730 (80.9)	679 (75.2)	636 (70.2)	544 (60.3)	463 (49.3)[e]
SBP, mmHg	173.6 ± 9.9	173.3 ± 9.6	173.8 ± 10.0	174.7 ± 10.0	174.7 ± 10.7
DBP, mmHg	85.5 ± 5.5	85.5 ± 5.9	85.1 ± 5.7	85.6 ± 6.0	85.0 ± 5.8
BMI, kg/m^2	26.5 ± 4.2	26.9 ± 4.2	27.6 ± 4.6	28.0 ± 4.5	28.3 ± 4.5[e]
total cholesterol, mmol/L	6.1 ± 1.1	6.1 ± 1.1	6.2 ± 1.2	6.3 ± 1.2	6.3 ± 1.5[c]
current smokers, *n* (%)	21 (2.9)	24 (3.5)	22 (3.5)	21 (3.9)	19 (4.1)
current alcohol use,[b] *n* (%)	27 (3.7)	27 (4.0)	36 (5.7)	14 (2.6)	27 (5.8)

[a] Values are mean ± SD, unless otherwise indicated. CV, cardiovascular; SBP, systolic BP; DBP, diastolic BP; BMI, body mass index.
[b] Patients drinking at least 1 unit of alcohol per day. The significance of difference between quintiles 1 and 5 are given: [c] $P \leq 0.05$; [d] $P < 0.01$; [e] $P < 0.001$.

in women. No differences between quintiles were observed, either in men or in women, with respect to systolic BP and percentage of patients who smoked or used alcohol.

During follow-up, 261 patients in whom baseline serum uric acid was measured died with a cardiovascular cause of death in 136. When all fatal and nonfatal endpoints were combined, there were 324 cardiovascular endpoints during follow-up, 125 strokes, and 202 cardiac endpoints. Figure 2 shows the relationship between serum uric acid at entry and total, cardiovascular, and stroke mortality as well as fatal and nonfatal cardiovascular endpoints. Relative hazard rates for mortality and morbidity were first calculated for each 50 μM increment in baseline serum uric acid (Table 4). No statistically significant effects were found for either total, cardiovascular, or stroke mortality. Although crude hazard rates were marginally significant when all endpoints or all cardiac endpoints (*i.e.*, fatal plus nonfatal) were considered, adjusted hazard ratios were not. Also, no significant relationship could be detected with fatal plus nonfatal strokes. Because the data in Figure 2 suggest the existence of an U-shaped relationship between serum uric acid and risk, we tested this possibility by introducing a quadratic term in the Cox-model. After adjustment for possible con-

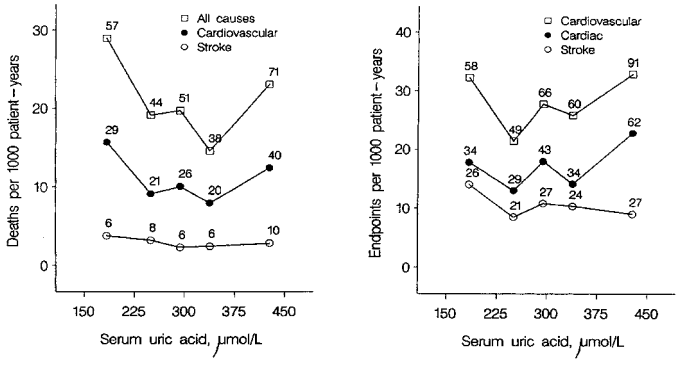

Figure 2. Relationship between serum uric acid at baseline and outcome. Left panel: Age- and gender-adjusted death rates in quintiles of serum uric acid. The number of deaths is given for each quintile. Right panel: Age- and gender-adjusted fatal and nonfatal event rates in quintiles of serum uric acid. The number of endpoints is given for each quintile.

founders, a significant U-shaped relationship was found only for total mortality, with a nadir of serum uric acid at 308 μmol/L. Although an increase in uric acid from 150 to 200 μmol/L was associated with a nonsignificant fall in total mortality (−12%; 95% CI, −1 to +23%), a rise in uric acid from 400 to 450 μmol/L led to a significant rise in total mortality by 11% (95% CI, 3 to 21%; $P < 0.01$).

When analyzed separately for the two treatment groups, hazard rates (crude and adjusted) in relation to serum uric acid concentration at baseline were slightly greater in the active treatment group, but the interaction between uric acid and treatment group was NS. Similar hazard rates were found in nondiabetic patients compared with diabetic patients (interaction term NS). Also, no differences in relative hazard rates were found between men and women.

Urinary Protein Excretion at Baseline and Incidence of Endpoints

Data on protein excretion at the time of randomization were available for 4658 patients. These patients were divided into three groups depending on whether there was no proteinuria ($n = 4225$), trace proteinuria ($n = 324$), or overt proteinuria ($n = 109$) at entry. Groups were comparable with respect to age, gender, and treatment status. The proportion of patients with previous cardiovascular complications, however, was significantly higher in those with overt proteinuria compared with the group without proteinuria. The same was true for the percentage of patients with diabetes (Table 5). Both in men and in women, systolic BP was significantly higher in patients with overt proteinuria than in those without.

During follow-up, 278 of the 4658 patients died; the cause of death was cardiovascular in 145 cases. As shown in Figure 3, the age- and gender-adjusted incidence rates of total, cardiovascular, and stroke mortality as well as fatal and nonfatal cardiovascular endpoints rose with the degree of proteinuria. Table 6 lists the crude and adjusted hazard ratios for various endpoints in relation to the degree of proteinuria, whereas Figure 4 shows the survival curves for patients with no, trace, or overt proteinuria. When trace and overt proteinuria groups were lumped together, adjusted hazard ratios for total mortality, all cardiovascular endpoints, and all strokes were statistically significant. Further adjustment for serum cholesterol levels did not change any of the significant relationships.

When data were analyzed separately for the placebo and the active treatment group, relative hazard rates appeared to be greater in the former, but the interaction between proteinuria and treatment group was NS. Higher hazard rates for all cardiovascular endpoints ($P = 0.03$) as well as for all strokes ($P = 0.03$) were found in nondiabetic patients compared with diabetic patients. Relative hazard rates were higher in women than in men for total ($P = 0.02$) and cardiovascular ($P = 0.03$) mortality and for all fatal plus nonfatal endpoints ($P = 0.04$), all strokes ($P = 0.01$), and all cardiac complications ($P = 0.005$).

Because serum creatinine and proteinuria both predicted outcome, we have also tested whether these two markers have an independent effect on prognosis. Forcing both variables in the Cox model showed, indeed, that serum creatinine and proteinuria were independent determinants for all cardiovascular endpoints, *i.e.*, cardiovascular mortality, stroke mortality, and all types of fatal and nonfatal endpoints. With respect to

Table 4. Association between serum uric acid at baseline and outcome[a]

Events	Endpoints *n*	Crude RHR	Adjusted[d] RHR
Mortality			
total	261	1.04 (0.97 to 1.11)	1.03 (0.96 to 1.11)
cardiovascular	136	1.05 (0.96 to 1.16)	1.03 (0.93 to 1.14)
stroke	36	1.08 (0.90 to 1.29)	1.06 (0.88 to 1.29)
Fatal and nonfatal cardiovascular endpoints			
all	324	1.08 (1.02 to 1.15)[b]	1.06 (0.99 to 1.13)
cardiac	202	1.09 (1.01 to 1.18)[b]	1.07 (0.99 to 1.16)
stroke	125	1.02 (0.92 to 1.13)	1.00 (0.90 to 1.12)

[a] RHR indicates relative hazard rate. Values are relative hazard rate with 95% CI calculated for a 50 μmol/L increase in serum uric acid. The significance of the relative hazard rates is given: [b] $P \leq 0.05$.

[c] Adjusted for age, gender, active treatment, systolic BP, smoking status, previous cardiovascular complications, and diabetes mellitus.

Table 5. Characteristics of patients according to the level of proteinuria[a]

Characteristic	Proteinuria		
	None	Traces	Overt
Number of patients	4225	324	109
Age, yr	70.1 ± 6.6	71.6 ± 7.4	72.0 ± 7.1
Active treatment, *n* (%)	2158 (51.1)	169 (52.2)	53 (48.6)
CV complications, *n* (%)	1236 (29.3)	108 (33.3)	45 (41.3)[d]
Diabetic patients, *n* (%)	413 (9.8)	55 (17.0)	21 (19.3)[d]
Men, *n* (%)	1382 (32.7)	122 (37.7)	42 (38.5)
SBP, mmHg	173.3 ± 9.6	175.0 ± 11.0	177.7 ± 11.5[d]
DBP, mmHg	85.7 ± 6.1	85.9 ± 6.1	85.5 ± 5.5
BMI, kg/m^2	26.4 ± 3.2	26.2 ± 2.9	26.3 ± 3.1
total cholesterol, mmol/L	5.7 ± 1.1	5.9 ± 1.3	5.4 ± 1.1
current smokers, *n* (%)	199 (14.4)	23 (18.9)	8 (19.0)
current alcohol use,[b] *n* (%)	346 (25.0)	33 (27.0)	11 (26.2)
Women, *n* (%)	2843 (67.3)	202 (62.3)	67 (61.5)
SBP, mmHg	173.7 ± 9.9	176.3 ± 11.0	177.5 ± 12.4[c]
DBP, mmHg	85.4 ± 5.7	84.8 ± 6.2	84.5 ± 7.2
BMI, kg/m^2	27.4 ± 4.4	26.9 ± 4.5	27.9 ± 4.5
total cholesterol, mmol/L	6.2 ± 1.2	6.1 ± 1.2	5.9 ± 1.1[c]
current smokers, *n* (%)	89 (3.1)	16 (7.9)	5 (7.5)[c]
current alcohol use,[b] *n* (%)	119 (4.2)	7 (3.5)	4 (6.0)

[a] Values are mean ± SD, unless otherwise indicated. CV, cardiovascular; SBP, systolic BP; DBP, diastolic BP; BMI, body mass index.
[b] Patients drinking at least 1 unit of alcohol per day. The significance of difference between no and overt proteinuria is given: [c] $P \leq 0.05$; [d] $P < 0.01$; [e] $P < 0.001$.

total mortality a similar trend was found, although that was not statistically significant.

Discussion

This study shows that renal function in elderly patients with isolated systolic hypertension is a significant predictor of future morbidity and mortality. In this respect, serum creatinine and urinary protein excretion may be taken as markers of renal function. Although this confirms and extents the data from other trials in isolated systolic hypertension (10,11), our study differs from the others in several respects. For instance, the Syst-China trial included patients with a relatively low risk of cardiovascular complications, and, as the investigators from that study indicate, their results cannot a priori be extrapolated to Western populations (10). Moreover, proteinuria was not measured in the Chinese study. The latter also applies to the SHEP trial, which focused only on serum creatinine (11) and uric acid (12). An important new finding emerging from Syst-Eur is that serum creatinine and proteinuria predict risk independently from each other. Moreover, the risk that goes along with these markers of kidney function is greater in women than in men and greater in patients without than in those with diabetes.

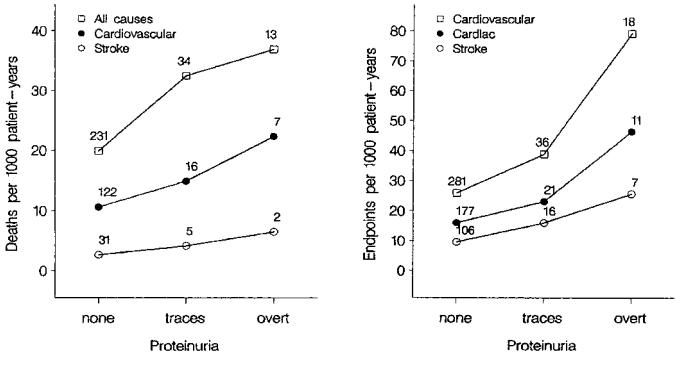

Figure 3. Relationship between proteinuria at baseline and outcome. Left panel: Age- and gender-adjusted death rates according to the level of proteinuria. The number of deaths is given for each category. Right panel: Age- and gender-adjusted fatal and nonfatal event rates according to the level of proteinuria. The number of endpoints is given for each category.

The observation that serum creatinine predicted cardiovascular morbidity and mortality in our population fits well with data from other studies, which have shown an independent association between serum creatinine and cardiovascular or overall prognosis. Probably, this association is least obvious in unselected populations. For instance, during a 15-yr follow-up in the community-based Framingham Heart Study, mild renal insufficiency (defined as a serum creatinine of 136 to 265 μmol/L in men and 120 to 265 μmol/L in women) was not associated with cardiovascular disease (fatal and nonfatal) in women when adjustments were made for coexisting risk factors (13). In men, however, the relationship between renal impairment and all-cause mortality remained significant, even after such adjustments (the reason that we found the opposite

Table 6. Association between proteinuria at baseline and outcome[a]

Events	Endpoints *n*	Crude RHR			Adjusted[e] RHR		
		Traces	Overt	Traces or Overt	Traces	Overt	Traces or Overt
Mortality							
total	278	1.80 (1.25 to 2.58)[c]	2.34 (1.34 to 4.09)[c]	1.92 (1.40 to 2.63)[d]	1.37 (0.95 to 1.97)	1.32 (0.78 to 2.45)	1.37 (1.00 to 1.89)[b]
cardiovascular	145	1.64 (0.97 to 2.76)	2.34 (1.09 to 5.00)[b]	1.80 (1.15 to 2.81)[c]	1.23 (0.72 to 2.08)	1.36 (0.63 to 2.97)	1.27 (0.80 to 2.00)
stroke	38	2.03 (0.79 to 5.22)	2.56 (0.61 to 10.7)	2.16 (0.95 to 4.90)	1.38 (0.53 to 3.58)	1.39 (0.32 to 5.94)	1.38 (0.60 to 3.18)
Fatal and nonfatal CV endpoints							
all	335	1.64 (1.16 to 2.32)[c]	2.91 (1.81 to 4.70)[d]	1.92 (1.44 to 2.57)[d]	1.34 (0.94 to 1.90)	1.92 (1.18 to 3.12)[c]	1.48 (1.10 to 2.00)[c]
cardiac	209	1.48 (0.94 to 2.34)	2.75 (1.50 to 5.06)[c]	1.76 (1.21 to 2.57)[c]	1.20 (0.76 to 1.90)	1.79 (0.96 to 3.34)	1.35 (0.92 to 1.99)
stroke	129	1.92 (1.13 to 3.24)[b]	2.75 (1.28 to 5.91)[c]	2.11 (1.34 to 3.31)[c]	1.62 (0.95 to 2.75)	1.87 (0.85 to 4.08)	1.68 (1.06 to 2.67)[b]

[a] RHR indicates relative hazard rate (as compared to no proteinuria). Values are relative hazard rate with 95% CI. The significance of the relative hazard rates is given: [b] $P \leq 0.05$; [c] $P < 0.01$; [d] $P < 0.001$.

[e] Adjusted for active treatment, gender, age, systolic BP, smoking status, previous cardiovascular complications, and diabetes mellitus.

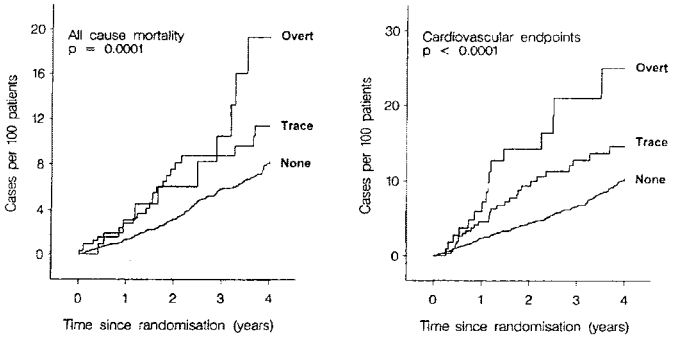

Figure 4. Kaplan-Meier survival curves for all-cause mortality (left panel) and all fatal and nonfatal cardiovascular endpoints (right panel) according to the level of proteinuria at baseline. The *P* value of the log rank statistic is given.

may be that most patients in our study still had serum creatinine concentrations within the normal range). In more selected populations, stronger relationships have been described between serum creatinine and cardiovascular outcome. This may be illustrated by the data from the Hypertension Detection and Follow-up Program (HDFP), which was a community-based randomized trial of stepped-care *versus* referred-care in hypertensive patients (14) and which showed that the 8-yr mortality risk rose progressively with increasing baseline serum creatinine concentrations. A serum creatinine concentration above 150 μmol/L appeared to be independently associated with a twofold higher mortality rate, mostly due to cardiac or cerebrovascular causes. Likewise, the investigators from the HOT trial recently reported that an elevation in serum creatinine and a reduction in estimated creatinine clearance in treated hypertensive patients are powerful predictors of cardiovascular events and death (3). Several other observations support such relationships. For instance, in the British Regional Heart Study, which is a prospective study on middle-aged men, a serum creatinine level $\geq$116 μmol/L significantly increased the risk of stroke, even after adjustment for a wide range of cardiovascular risk factors (15). At a serum creatinine level of $\geq$130 μmol/L, the risk for ischemic heart disease was significantly increased as well, but this did not hold after adjustment for potential confounders. Other studies found serum creatinine to be an independent predictor of mortality in healthy elderly subjects (16), in elderly patients with a recent stroke (17), in normotensive survivors of myocardial infarction (18), and in older Chinese patients with isolated systolic hypertension (10). Finally, in patients with asymptomatic or symptomatic heart failure, renal impairment is associated with an increased risk for all-cause mortality (19) and predicts mortality even better than left ventricular ejection fraction (20). Importantly, in hypertensive subjects, creatinine levels that are still in the normal range may already predict outcome (21).

As far as patients with isolated systolic hypertension are concerned, the SHEP trial has already shown that the proportion of any cardiovascular events, strokes, coronary events, and deaths increases with increasing serum creatinine levels in this population as well (11). In this regard, our data are consistent with those from SHEP and all the other studies that examined the relationship between serum creatinine and prognosis. It would seem, therefore, that this relationship is relatively independent of the type of treatment, suggesting that creatinine is a rather robust marker of the atherosclerotic process. Serum creatinine may not be an accurate indicator of renal function *per se* nor of the extent of nephrosclerosis (18); it is therefore possible that a rise in creatinine, or for that matter a reduction in GFR, reflects a critical fall in renal perfusion secondary to progression of left ventricular dysfunction (19).

Although we assessed the impact of serum uric acid on prognosis as well, our data indicate that this variable is a much weaker predictor of hypertension-related complications. At first sight, this may seem surprising because several studies in the past few years have shown an association between the level of uric acid and cardiovascular events. For instance, Fang and Alderman (22) evaluated the data of 5926 subjects from the community-based NHANES epidemiologic follow-up study and found that increased serum uric acid levels are independently and significantly associated with the risk of cardiovascular mortality. In fact, they showed that for each 60 μM

increase in serum uric acid the adjusted relative hazard ratio for the risk of cardiovascular death was 1.09 in men and 1.26 in women after adjustment for age, race, body mass index, smoking status, alcohol consumption, cholesterol level, history of hypertension and diabetes, and diuretic use. Except for the smaller number of patients and shorter duration of follow-up in the Syst-Eur trial, the obvious difference in study design may well account for the discrepancies. On the other hand, it is by no means certain that uric acid acts as an independent cardiovascular risk factor because the data from the Framingham study do not support such a role for uric acid when appropriate adjustments are made for several confounding variables (23). But even when one compares the Syst-Eur data to other clinic-based studies on (treated and untreated) hypertensive patients (24), our results cannot confirm the alleged role of uric acid as a predictor of cardiovascular prognosis.

Unlike the three studies mentioned above, Syst-Eur was a prospective intervention trial that allowed patients to be followed in a standardized way. In this respect, the Systolic Hypertension in the Elderly Program (SHEP) trial (12) and the Syst-China trial (10) are the only studies that qualify for a meaningful comparison with Syst-Eur. Both studies were placebo-controlled and included approximately the same number of patients with isolated systolic hypertension. Recently, the SHEP investigators have reported that after adjustment for age, gender, race, body mass index, history of heart attack, stroke and diabetes, serum creatinine, glucose, cholesterol, HDL-cholesterol, and triglycerides, uric acid remained an independent risk factor for cardiovascular events (12). Thus, also in the SHEP trial uric acid appears to be far more powerful as a predictor of cardiovascular complications than in Syst-Eur. One of the major differences between the two studies was the type of treatment (diuretic-based in SHEP and calcium channel blocker–based in Syst-Eur); it is therefore tempting to speculate that the prognostic influence of uric acid is either enhanced by diuretic treatment or attenuated by calcium channel blocker treatment. The discrepancy with the results from the Syst-China trial, which also found a relationship between uric acid and complications, may be explained by the fact that other risk factors, such as elevated cholesterol, were less prominent in the Chinese patients (10). The reason that we found uric acid to be a less conspicuous indicator of cardiovascular risk could also be due to the limited increase in serum creatinine that we encountered in this study (25). Perhaps, a greater loss of renal function or a more pronounced fall in extracellular fluid volume (such as may occur during diuretic treatment) is necessary to unmask the role of uric acid as an independent marker of risk. Finally, we should consider the possibility that part of the discrepancies may be due to the fact that an U-shaped rather than a linear relationship exists between serum uric acid and risk. Indeed, evidence for such a U-shaped association was provided by the PIUMA study (26). Although the Syst-Eur data suggest a similar phenomenon, we found this to be statistically significant only for total mortality. Interestingly, though, event rates started to rise from a nadir of 308 μmol/L, a figure comparable to that described by the PIUMA investigators (26).

Proteinuria is another well-known marker of future cardiovascular complications, notably in patients with diabetes mellitus. It is increasingly recognized that proteinuria is also an indicator of risk in patients with hypertension and even in normotensives. For instance, Miettinen *et al.* (27) found that clinical proteinuria (defined as proteinuria of $>$300 mg/L) in nondiabetic subjects aged 45 to 64 yr is an independent predictor of stroke and other atherosclerotic vascular lesions. Similarly, the Framingham study showed that all-cause mortality in men and all-cause as well as cardiovascular mortality in women are also related to baseline proteinuria when elderly subjects (mean age, 68 yr) are classified into those with no, trace, or greater-than-trace proteinuria (28). The present study now extends such data to the elderly with isolated systolic hypertension. Although nowadays most studies focus on (micro-)albuminuria, the data from the Syst-Eur trial pertain only to proteinuria which was recorded as none, trace, or overt. Indeed, at the time the study started, it was not feasible to implement in all participating centers a reliable method for detecting microalbuminuria. However, even though our results may have been more complete if we had analyzed microalbuminuria, we can still conclude that there is a relationship between urinary protein excretion and outcome in elderly patients with isolated systolic hypertension. Whether microalbuminuria has similar predictive power in this population remains a matter of further investigation.

The three measurements (creatinine, uric acid, protein excretion) that we have used in this study are neither very sensitive nor very specific markers of renal function. Indeed, serum concentrations of creatinine and uric acid are dependent also on extrarenal factors and urinary protein excretion may well reflect the hydraulic consequence of an elevated (intrarenal) pressure rather than true glomerular damage. Despite this caveat, both serum creatinine and proteinuria turned out to be renal markers of future (cardiovascular) complications, suggesting that glomerular damage is somehow associated with the progression of atherosclerotic lesions. Although several investigators favor the opinion that proteinuria or a higher serum creatinine reflects generalized endothelial dysfunction or a prothrombotic state, others on equally reasonable grounds argue against these possibilities (15,18). Clearly, more work has to be done before the pathophysiologic connection between renal function and atherosclerotic complications will be elucidated.

One of the limitations of this study is that there may be unmeasured confounders that could have influenced our results. Although the observed relationships between renal function and cardiovascular prognosis remained statistically significant after correction for classical risk factors (including cholesterol status), we did not account for the more recently reported risk factors such as hyperhomocysteinemia or certain infections. Second, one should bear in mind that our results apply to elderly people with systolic hypertension only. Therefore, the data cannot be extrapolated to other patient populations.

In conclusion, we have shown in elderly patients with isolated systolic hypertension that both serum creatinine and

proteinuria are (independent) indicators of future mortality and morbidity, whereas serum uric acid is not.

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A complete list of the Syst-Eur investigators appears in references 4 and 5.

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See related editorial, "Chronic Kidney Disease and Cardiovascular Risk: Time to Focus on Therapy," on pages 2415–2416.