Abstract—Whether changes over time of urinary albumin excretion have prognostic value is a matter of discussion. The objective was to assess the prognostic value of changes in urinary albumin excretion over time in cardiovascular risk during antihypertensive treatment. Follow-up study of 2835 hypertensives in the absence of previous cardiovascular disease (mean age 55 years, 47% men, BP 138/80 mm Hg, 19.1% diabetics, and calibrated systemic coronary risk estimation 5 or >10.6%). Usual-care of antihypertensive treatment was implemented to maintain blood pressure <140/90 mm Hg. Urinary albumin excretion was assessed yearly, and the values were expressed as the creatinine ratio. Incidence of cardiovascular events, fatal and nonfatal, was recorded during the follow-up. During a median follow-up of 4.7 years (17 028 patients-year), 294 fatal and first nonfatal cardiovascular events were recorded (1.73 CVD per 100 patients/year). Independently of blood pressure, estimated glomerular filtration rate, level of cardiovascular risk, and antihypertensive treatment, microalbuminuria at baseline and at any time during the follow-up resulted in higher risk for events, hazard ratio (HR) 1.35 (95% confidence interval [CI], 1.08–1.79) and HR 1.49 (95% CI, 1.14–1.94), respectively. Likewise, development of microalbuminuria (HR 1.60; 95% CI, 1.04–2.46) or persistence from the beginning (1.53; 95% CI, 1.13–2.06) had a significantly higher rate of events than if remained normoalbuminuric (HR 1) or regress to normoalbuminuria (HR 1.37; 95% CI, 0.92–2.06) with an 18%, 18%, 8%, and 11% events, respectively, P<0.001. The study supports the value of urinary albumin excretion assessment as a prognostic factor for cardiovascular risk, but also opens the way to consider it as an intermediate objective in hypertension. (Hypertension. 2014;64:1228-1234.)

Key Words: cardiovascular events ■ hypertension ■ renal function ■ SCORE

Recognition of the importance of urinary albumin excretion (UAE) as a prognostic marker in hypertension is based on cross-sectional studies, which demonstrate clustering of cardiovascular risk factors and organ damage associated with an increase in UAE, as well as on follow-up studies in which a given value of UAE measured at the beginning is associated with total and cardiovascular morbidity and mortality over time. Therefore, microalbuminuria assessment is now recommended in a risk stratification strategy not only in diabetic subjects but also for hypertension management. Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ONTARGET), and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRASCEND) have reported positive results in terms of a reduction in UAE being followed by risk reduction. However, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) does not confirm the potential prognostic value. Likewise, a prospective study Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes Mellitus (ROADMAP) also reported no association between changes in microalbuminuria and cardiovascular events during the double-blind period, although an observational follow-up concluded that development of microalbuminuria was a marker of cardiovascular events. These studies, which were heterogeneous in terms of patients and analysis of data, did not contribute to the clarification of the potential role of microalbuminuria during antihypertensive treatment. In fact, although the European Society of Hypertension and the European Society of Cardiology (ESH-ESC) guidelines in hypertension recommend the use of microalbuminuria to assess target organ damage, the recent US-released recommendations for cardiovascular risk assessment also qualify albuminuria as Grade N (no recommendation for or against) and recommendations for hypertension management do not mention the potential role of microalbuminuria.

To gain further insight in the issue, the prognostic value of changes in UAE over time was assessed in a 1-center prospective study in which hypertensive subjects were followed during...
usual care. The potential prognostic value was assessed considering also the changes in the major modifier factors of UAEm, such as blood pressure (BP) values, renal function, kind of antihypertensive treatment, and cardiovascular risk profile.

Subjects and Methods

Study Participants and Design

The study included subjects, all Caucasians, recruited from the Hypertension Outpatient Clinic of the General Hospital of Sagunto (Sagunto, Spain) from May 1988 to April 2012. The inclusion criteria were office systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg in each of 3 visits at 1 month intervals or current antihypertensive treatment. Patients with secondary hypertension, nephropathy, urinary tract infection, chronic kidney disease stage 4/5, or previous vascular, cardiac, or cerebral disease were excluded. The study was approved by the Ethical Committee of Sagunto Hospital, and all participants gave informed written consent.

After the initial evaluation, patients were followed in the outpatient clinic. From a total group of 3592 patients who were screened, 2835 patients were included. The remaining 757 patients were excluded, 204 for secondary hypertension or nephropathy, 24 for previous cardiovascular disease, 122 for concomitant general disease, and 407 for not having 6-month follow-up. Antihypertensive treatment was monitored by means of frequent office BP measurements, and when appropriate, changes in the number, class, and dose of antihypertensive drugs (diuretics, β-blockers, α-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors [ACEi], angiotensin-receptor blockers [ARB] and vasodilators) were made to maintain a BP goal of <140/90 mmHg. Incidence of new cardiovascular events, fatal and nonfatal, was recorded during the follow-up. In subjects experiencing multiple nonfatal events, only the first is considered. Events to be recorded included cardiovascular (myocardial infarction, angina, coronary revascularization), cerebrovascular (ischemic or hemorrhagic stroke, transitory ischemic attack), aortoiliac or other peripheral occlusive disease, and new occurrence of heart failure. Definitions of the events were the same as previously published.24 Cardiovascular events included myocardial infarction, angina pectoris, coronary revascularization, stroke, transient ischemic attack, sudden death, aortoiliac occlusive disease, progressive heart failure, and hypertensive emergency. Myocardial infarction was diagnosed on the basis of ≥2 of 3 standard criteria (typical chest pain, ECG QRS changes, and transient elevation of myocardial enzymes by >2-fold the upper normal laboratory limits). Angina pectoris was defined as chest pain accompanied by typical ischemic changes in the ECG. Stroke was diagnosed on the basis of rapid onset of localizing neurological deficit lasting ≥24 hours in the absence of any other process that could explain the symptoms. Transient ischemic attack was defined as any sudden focal neurological deficit that cleared completely in <24 hours, based on a diagnosis made by a physician. Progressive heart failure was defined as symptoms when appearing during the follow-up in patients without previous heart failure symptoms. All cause death included cardiovascular, noncardiovascular causes and unknown in whom the data were collected from the civil registry. The adjudication of events was done independently of information about UAE values. The follow-up of patients without events was censored at the last visit.

Procedures

BP was measured using a mercury sphygmomanometer following the recommendations of the British Hypertension Society. Systolic BP (SBP) and diastolic BP were the average of 3 readings measured at 5-minute intervals. Blood samples were obtained in the morning after a minimum of 8 hours of fasting. The glomerular filtration rate was estimated (eGFR) by the Modification of Diet in Renal Disease abbreviated formula.25 Cardiovascular risk was estimated with systemic coronary risk estimation (SCORE) calibrated for low risk populations (SCOREc) in nondiabetic subjects.26 UAE was measured in 2 separate morning urine collections using a nephelometric immunoassay (Behring Institute). Albuminuria was the average of the 2 values expressed as albumin (mg)/creatinine (g) ratio (UACR). Microalbuminuria was defined as ≥22 mg/g in men and ≥31 mg/g in women. The coefficient of reproducibility for the UACR measurement was intra-assay 2%; interassay 6%, and intraindividual 12% in our laboratory. Microalbuminuria regression or progression was defined when at each of the visits, the UACR changed class and additionally the change was equal or superior to 50% as compared with baseline.27

Statistical Analysis

Values were expressed as mean±SD or as a median and interquartile range. Differences between groups were sought by using independent samples t test for continuous and χ² for categorical variables. Event rates for new cardiovascular events, fatal plus nonfatal, during follow-up were presented as the number of events per 100 patient-year. Survival curves were estimated with the Kaplan–Meier product-limit method. The proportional Cox hazard model was used to assess the effect of the prognostic factor on event-free survival. We tested the independent significance of (a) variables at the beginning: microalbuminuria (yes or no), left ventricular hypertrophy (LVH; yes or no), antihypertensive treatment with ACEi or ARB (yes or no), SCOREc risk in nondiabetic (3 categories of risk, low 0–1, moderate 2–4, 25), and diabetes mellitus, eGFR (2 categories, ≥60 mL/min/1.73m² or <60 mL/min/1.73m²) and (b) variables with repeated measures during follow-up: microalbuminuria (yes or no), office BP (higher than or equal to versus lower than office systolic BP 140 and diastolic BP 90 mmHg), LDL (≥3.0 and >100 mg/dL). Likewise, changes during the follow-up (persistent normoalbuminuria or microalbuminuria, regression, or progression) were also analysed. Adjusted hazard ratios (HR) in the Cox model were calculated and expressed with 95% confidence intervals (CI). STATA/SE 8.0 (College Station, Texas, EEUU) was used for statistical analysis.

Results

General Characteristics of the Study Population

The general characteristics of the study population at baseline of the 2835 patients included 47% men, mean age 55 years, and are shown in Table 1. At the time to begin the study, 35% of subjects had only SBP ≥140 mmHg, 10% had only diastolic BP ≥90 mmHg, and 27% had both elevated SBP and diastolic BP. Microalbuminuria was present in 616 (21.7%) and antihypertensive treatment in 1711 (60.4%). Five hundred and forty-eight (19.3%) were diabetic patients. The 10-year risk of fatal cardiovascular diseases assessed by SCOREc in nondiabetic patients was low-risk 1440 (63.2%), moderate 609 (26.2%), and high risk 232 (10.1%).

Follow-Up and Occurrence of Events

Median follow-up was 4.7 years (range 0.6–25.7 years), and 17028 patient-years observations were obtained. Median number of follow-up visits was 4 (minimum 2 and maximum 25) with a median interval time within visits of 1 year (interquartile range 0.7–1.3 years). At the starting point, 1711 (60.4%) patients were receiving antihypertensive treatment with the number increasing during the follow-up, 2536 (89.5%) at the last monitoring, 75% of them with ≥2 antihypertensive drugs. Two thousand hundred and twenty-nine (83.9%) subjects received ACE or ARB.

Four hundred and two cardiovascular events were recorded, although only 294, the fatal and the first nonfatal cardiovascular events, were included in the analysis (1.73 events per 100 patients/year). Eighty-four developed an acute coronary heart disease event (39 myocardial infarction, 43 angina, 2 coronary revascularization), 82 stroke, 24 peripheral vascular disease,
74 first occurrence of congestive heart failure, and 30 patients died from cardiovascular cause. The baseline characteristics of the patients with and without events are shown in Table 1.

### Prognostic Value of Microalbuminuria at Baseline

The Kaplan–Maier plot of event-free survival of the study population grouped by normo- or microalbuminuria at baseline is shown in Figure 1. Subjects with microalbuminuria at baseline had a significantly higher risk to develop cardiovascular events, 2.33 per 100 patient-years as compared with the normoalbuminuric, 1.47 per 100 patient-years (Breslow 17.5, \( P \leq 0.001; \) HR 1.56; 95% CI, 1.22–2.00). Likewise, LVH, eGFR <60 mL/min/1.73 m², SCOREc, and diabetes mellitus were also related to risk for cardiovascular outcomes (Table 2). Using Cox proportional hazard models, baseline microalbuminuria was significantly associated with the occurrence of cardiovascular events, HR 1.35 (95% CI, 1.05–1.74), after controlling by CV risk, eGFR, LVH, and antihypertensive treatment with ACEi or ARBs at the beginning of follow-up. The prognostic value of microalbuminuria was independent of the eGFR, HR 1.39 (95% CI, 1.08–1.79) for eGFR <60 mL/min/1.73 m²; and of the CV risk, HR 3.16 (95% CI, 2.19–4.56) for moderate risk, 5.66 (95% CI, 3.79–8.44) for high risk, and 3.76 (95% CI, 2.35–5.32) for diabetic patients, compared with low risk.

### Prognostic Value of Microalbuminuria During the Follow-Up

The Kaplan–Maier plot of event-free survival of the study population grouped by normo- or microalbuminuria during the follow-up is shown in Figure 2. Univariate Cox proportional hazard model with repeated measurements in the follow-up demonstrated that the presence of microalbuminuria at any time was significantly associated with risk for cardiovascular events (HR 1.95; 95% CI, 1.51–2.52). In a multivariate model, in which LVH, cardiovascular risk, eGFR, and treatment antihypertensive with ACEi or ARBs at the beginning and SBP <140 mm Hg and LDL <100 mg/dL during the follow-up were included, microalbuminuria was still significantly associated

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### Table 1. Characteristics at Baseline of the Patients With and Without CVE During the Follow-Up

<table>
<thead>
<tr>
<th>Characteristics at Baseline</th>
<th>Total, N=2835</th>
<th>CVE, N=294</th>
<th>Non-CVE, N=2541</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (men), n (%)</td>
<td>1344 (47.4)</td>
<td>144 (49.0)</td>
<td>1200 (47.2)</td>
<td>0.57</td>
</tr>
<tr>
<td>Age, y</td>
<td>55 (14)</td>
<td>65.1 (0.8)</td>
<td>53.5 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>519 (18.3)</td>
<td>44 (15.0)</td>
<td>475 (18.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>LVH, n (%)</td>
<td>758 (26.7)</td>
<td>97 (33.0)</td>
<td>661 (26.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>97 (13)</td>
<td>99.1 (0.8)</td>
<td>96.9 (0.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79 (16)</td>
<td>78.1 (0.9)</td>
<td>79.5 (0.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.0 (5.3)</td>
<td>30.4 (0.3)</td>
<td>29.9 (0.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>138 (24)</td>
<td>143.8 (1.8)</td>
<td>137.8 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>80 (15)</td>
<td>76.5 (0.9)</td>
<td>80.1 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>75 (14)</td>
<td>72.2 (0.9)</td>
<td>75.4 (0.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Antihypertensive treatment</td>
<td>1711 (60.4)</td>
<td>235 (79.9)</td>
<td>1476 (58.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>111 (32)</td>
<td>123.1 (2.5)</td>
<td>109.2 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>548 (19.3)</td>
<td>100 (34.0)</td>
<td>448 (17.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.98 (0.27)</td>
<td>1.10 (0.02)</td>
<td>0.97 (0.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m²*</td>
<td>77 (65–90)</td>
<td>67 (52–78)</td>
<td>78 (66–91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>5.8 (1.6)</td>
<td>6.29 (0.09)</td>
<td>5.79 (0.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>206 (38)</td>
<td>205 (2)</td>
<td>206 (1)</td>
<td>0.77</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dL</td>
<td>52 (15)</td>
<td>49.7 (0.8)</td>
<td>52.8 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dL</td>
<td>126 (37)</td>
<td>126.6 (2.2)</td>
<td>126.3 (0.7)</td>
<td>0.88</td>
</tr>
<tr>
<td>Triglycerides, mg/dL*</td>
<td>115 (85–164)</td>
<td>121 (90–171)</td>
<td>114 (84–163)</td>
<td>0.03</td>
</tr>
<tr>
<td>UACR, g/g Cr*</td>
<td>10 (5–23)</td>
<td>13 (7–44)</td>
<td>9 (5–21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Microalbuminurics, n (%)</td>
<td>616 (21.7)</td>
<td>94 (32.0)</td>
<td>522 (20.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10-year risk of fatal CVD (SCOREc) in nondiabetics, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (0–1)</td>
<td>1446 (63.2)</td>
<td>64 (33.0)</td>
<td>1382 (66.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate risk (2–4)</td>
<td>609 (26.6)</td>
<td>77 (39.7)</td>
<td>532 (25.4)</td>
<td></td>
</tr>
<tr>
<td>High risk (≥5)</td>
<td>232 (10.1)</td>
<td>53 (27.3)</td>
<td>179 (8.4)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as average (standard error mean)

BMI indicates body mass index; CVD, cardiovascular disease; CVE, cardiovascular events; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; SBP, systolic blood pressure; SCOREc, calibrated systemic coronary risk estimation; and UACR urinary albumin/creatinine ratio.

\( P \) value between groups: t test, *U Mann–Whitney test, and \( \chi^2 \) test for categorical variables.

*Data are presented as median (interquartile interval).
with risk for events (HR 1.49; 95% CI, 1.14–1.94). When the analysis was performed in subjects who were or were not receiving antihypertensive treatment at baseline, microalbuminuria was still significantly associated with occurrence of events in the first case (HR 1.46; 95% CI, 1.08–1.99) and not in the second case (HR 1.49; 95% CI, 0.90–2.49; Table 3). Likewise, the prognostic value of microalbuminuria was significant in subjects receiving ACEi or ARBs during the follow-up (HR 1.56 95% CI, 1.20–2.04).

Prognostic Value of Changes in Microalbuminuria Status During the Follow-Up
From the total 2835 subjects, 2056 remained normoalbuminuric and 344 microalbuminuric. In contrast, 272 changed from microalbuminuria to normoalbuminuria and 163 became microalbuminuric during the study. A total of 170 events (1.35 per 100 patients/year) were recorded in normoalbuminuric status, 63 (2.57 per 100 patients/year) in microalbuminuric status, 31 (2.10 per 100 patients/year) in regression status, and 30 (4.13 per 100 patients/year) in progression status. As it is shown in the Kaplan–Meir plot of event-free survival (Figure 3), the risk for events is higher in either group that had microalbuminuria (persistent, regression, or progression) as compared with normoalbuminuria. In Cox proportional hazard model, adjusted by LVH, eGFR, cardiovascular risk, SBP <140 mm Hg, and LDL< 100 mg/dL, only persistent and progression to microalbuminuria have significant differences in risk with the persistent normoalbuminuria. The percent of events and the risk for the 4 situations was as follows: normoalbuminuria 8% and HR 1; persistent microalbuminuria 18% and HR 1.53 (95% CI, 1.13–2.06); regression 11% and HR 1.37 (95% CI, 0.92–2.06), and progression 18% and HR 1.60 (95% CI, 1.04–2.46).

Discussion
The present study reported for first time that in hypertension an increment of UAE at any time is a marker of cardiovascular risk. The study also confirms previous observations about the prognostic value of microalbuminuria in the risk to develop cardiovascular events and the worse prognosis of persistent microalbuminuria or progression during treatment.

The study was performed in a population of subjects representative of hypertensives who attend a Hypertension Clinic in a Community Hospital in the absence of previous cardiovascular or renal disease. The patients enrolled were a predominantly low-moderate risk population assessed by SCOREc risk; 87.6% and only 19% were diabetics. The fact that at baseline the prevalence of microalbuminuria was relatively large for a low-moderate risk population (21%) can be explained because a large proportion of subjects were untreated at baseline (40%). These characteristics differed largely from the patients enrolled in previous studies reporting the prognostic value of microalbuminuria in the risk to develop cardiovascular events and the worse prognosis of persistent microalbuminuria or progression during treatment.

Table 2. Baseline Characteristics Associated With Risk of Cardiovascular Events

<table>
<thead>
<tr>
<th>Variables Baseline</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
<th>HRm</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVH</td>
<td>1.45</td>
<td>1.13–1.84</td>
<td>0.003</td>
<td>1.23</td>
<td>0.96–1.58</td>
<td>0.11</td>
</tr>
<tr>
<td>EGFR &lt;60 mL/min/1.73m²</td>
<td>1.98</td>
<td>1.55–2.53</td>
<td>&lt;0.001</td>
<td>1.39</td>
<td>1.08–1.79</td>
<td>0.01</td>
</tr>
<tr>
<td>ACEi or ARB treatment</td>
<td>3.16</td>
<td>2.45–4.08</td>
<td>&lt;0.001</td>
<td>1.73</td>
<td>1.30–2.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (SCOREc 0–1)</td>
<td>4.28</td>
<td>3.05–6.02</td>
<td>&lt;0.001</td>
<td>3.16</td>
<td>2.19–4.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate risk (SCOREc 2–4)</td>
<td>7.75</td>
<td>5.33–11.27</td>
<td>&lt;0.001</td>
<td>5.66</td>
<td>3.79–8.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High risk (SCOREc &gt;=5)</td>
<td>11.44</td>
<td>7.95–16.87</td>
<td>&lt;0.001</td>
<td>7.95</td>
<td>5.33–11.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5.14</td>
<td>3.74–7.07</td>
<td>&lt;0.001</td>
<td>3.76</td>
<td>2.35–5.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>1.56</td>
<td>1.22–2.00</td>
<td>&lt;0.001</td>
<td>1.35</td>
<td>1.08–1.79</td>
<td>0.02</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blocker; CI, confidence interval; EGFR, estimated glomerular filtration rate; HR, univariate hazard ratio; HRm, multivariate hazard ratio; LVH, left ventricular hypertrophy; and SCOREc: calibrated systemic coronary risk estimation.
Microalbuminuria in hypertension is a marker of risk for cardiovascular morbidity and mortality but not for end-stage renal disease. The link between changes in UAE and risk of cardiovascular events is based on the effect of the cardiovascular risk factors on the endothelium, not only because of the changes induced and their consequences but also because it is a sensor of the interaction between the intensity of the risk factors and the individual capacity of response. After the seminal studies of the interaction between the intensity of the risk factors and their consequences but also because it is a sensor of the interaction between the intensity of the risk factors and the individual capacity of response. After the seminal studies demonstrating that an increment in UAE is dependent of vascular permeability to albumin, many studies have focused on the factors related to its development. Both cross-sectional and follow-up studies have demonstrated that UAE is associated with a clustering of factors in which insulin resistance and high BP values are the main factors, although some others, such as obesity, smoking, and genetics, can also play a role. Then, changes in UAE during the follow-up are a proxy of the effect of cardiovascular risk factors on the vascular tree.

In the present study, the changes in UACR and the effect on events occurred during antihypertensive treatment with ACEi or ARB in the majority of patients. These drugs produce a blockade of the renin–angiotensin system and reduce UACR beyond the BP lowering effect because of the changes in intraglomerular pressures and glomerular filtration rate. After given ACEi or ARB, glomerular filtration rate decreases because of a functional and reversible mechanism because withdrawal of the drugs increases glomerular filtration rate to the previous values even 2 years later. This initial rapid drop in glomerular filtration rate could contribute to the UACR reduction shortly observed after starting treatment, although it does not affect the long-term changes in UACR. A previous prospective study of our group, which analysed the factors related to long-term changes in UACR, demonstrated the absence of influence of the kind of drug.

Cardiovascular risk assessment in clinical practice is mostly based on risk charts, such as Framingham risk score and SCORE. Risk charts, however, do not take into account subclinical organ damage, which exert independent influence on risk. Available evidence suggests a tangible clinical advantage of adding the evaluation of simple organ damage markers to risk charts in cardiovascular risk prediction. Sehested et al found that subclinical organ damage, LVH, carotid plaques, pulse wave velocity, or UACR predicted cardiovascular death independently of SCORE. Concerning UACR, the most relevant information was its prognostic value over the SCORE in the subgroup of patients with a SCORE <5%, although with lower UACR threshold than used in the present study.

The recently released ESH-ESC guidelines state that it seems reasonable to search for asymptomatic organ damage in hypertensive patients, not only for the initial stratification of CV risk, but also during follow-up. At the initial evaluation, assessment of organ damage is recommended in low-moderate risk patients, the predominant population in the present study. During the follow-up, UACR can be reliably quantified in a morning urine sample, a test wide available and at low cost, and that can detect treatment-induced changes within a few months. Reduction in UACR has been linked with a reduction in other markers of organ damage, such as LVH. The data of the present study also add information in favor of the prognostic value supporting the use during follow-up. The potential role not only as marker of risk but also as intermediate objective will require further studies in which the treatment goal should be the reduction in UAE by itself. In the meantime, it seems reasonable to take information from changes in UACR to better assess whether treatment is successful.

The results of the study should be considered within their strengths and limitations. The fact that the study was performed in only 1 center had the advantage of a more uniform criteria for monitoring and treating patients, although the criteria were modified over time because of the changes in recommendations provided by the subsequent guidelines throughout the follow-up. On the contrary, the results can be applied only to populations with the profile of low-moderate risk and not generalized to other populations with much more cardiovascular or renal risk.

### Table 3. Cox Proportional Hazard Model With Baseline and Repeated Measures in the Follow-Up Variables Associated With Cardiovascular Events

<table>
<thead>
<tr>
<th>Variables</th>
<th>HRm*</th>
<th>CI 95%</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVH (baseline)</td>
<td>1.21</td>
<td>0.93–1.57</td>
<td>0.15</td>
</tr>
<tr>
<td>EGFR &lt;60 mL/min/1.73m² (baseline)</td>
<td>1.24</td>
<td>0.95–1.61</td>
<td>0.11</td>
</tr>
<tr>
<td>ACEi or ARB treatment (baseline)</td>
<td>1.96</td>
<td>1.46–2.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cardiovascular risk (baseline)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (SCOREc 0–1)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate risk (SCOREc 2–4)</td>
<td>3.01</td>
<td>2.05–4.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High risk (SCOREc &gt;=5)</td>
<td>5.32</td>
<td>3.50–8.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.98</td>
<td>2.77–5.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office SBP (mm Hg) &lt;140 mm Hg</td>
<td>0.85</td>
<td>0.66–1.09</td>
<td>0.20</td>
</tr>
<tr>
<td>(each visit)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL &lt;100 mg/dl (each visit)</td>
<td>0.77</td>
<td>0.59–0.99</td>
<td>0.04</td>
</tr>
<tr>
<td>Microalbuminuria (each visit)</td>
<td>1.49</td>
<td>1.14–1.94</td>
<td>0.003</td>
</tr>
</tbody>
</table>

ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blocker; CI, confidence interval; EGFR, estimated glomerular filtration rate; HRm, multivariate hazard ratio; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; SCOREc: calibrated systemic coronary risk estimation; and SBP, systolic blood pressure.

Figure 3. Survival estimate by evolution of microalbuminuria. Kaplan–Meier of event-free survival of the 4 groups according to the presence or absence of microalbuminuria at baseline and at each examination. Persistent normoalbuminuric (pN), persistent microalbuminuric (pM), regression (R), and progression (P) (see text).
Perspectives

UACR assessment is a valuable marker of cardiovascular risk in a population of hypertensives with low-moderate risk. The present study not only reinforces the potential role of microalbuminuria assessment as a marker to stratify risk in hypertension but also supports the potential use as a proxy of the effect of antihypertensive therapy beyond the changes on BP values. Whether microalbuminuria should be considered an intermediate objective during the follow-up will be tested in further studies.

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Disclosures

The authors declare no conflicts of interest.

References


**Novelty and Significance**

**What Is New?**
- Long-term follow-up study from 1 center in which urinary albumin/creatinine ratio has been measured yearly and the prognostic value over time were assessed.
- The prognostic value of urinary albumin/creatinine ratio has been tested over systemic coronary risk estimation.

**What Is Relevant?**
- Persistence of increased urinary albumin excretion or new development increase the risk for cardiovascular events independent of other cardiovascular risk factors or even systemic coronary risk estimation risk scale.
- The present study not only reinforces the potential role of microalbuminuria assessment as a marker to stratify risk in hypertension, but also supports the potential use as a proxy of the effect of antihypertensive therapy beyond the changes on blood pressure values.
- Microalbuminuria should be tested during the follow-up of patients treated for hypertension.

**Summary**
Urinary albumin assessment is a valuable marker of cardiovascular risk in a population of hypertensives with low-moderate risk and indirectly support the potential use as a proxy of the effect of antihypertensive therapy beyond the changes on blood pressure values.
Prognostic Value of Microalbuminuria During Antihypertensive Treatment in Essential Hypertension
Jose Maria Pascual, Enrique Rodilla, Jose Antonio Costa, Miguel Garcia-Escrich, Carmen Gonzalez and Josep Redon

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流行病学人群（摘要）

原发性高血压降压治疗过程中微量白蛋白尿的预后意义

Prognostic Value of Microalbuminuria During Antihypertensive Treatment in Essential Hypertension

Jose Maria Pascual, Enrique Rodilla, Jose Antonio Costa, Miguel Garcia-Escrivá, Carmen Gonzalez, Josep Redon

陈晨 译 薛秋艳 审校

降压治疗中随时间变化的尿白蛋白排泄是否具有预后意义仍有争论。本文的目的是评估随时间变化的降压治疗中尿白蛋白排泄对心血管风险的预后意义。该研究对2835名既往无心血管疾病的高血压病患者进行随访研究。患者平均年龄为55岁，男性占47%，平均血压138/80 mm Hg，19.1%患者合并糖尿病，校准后系统性冠心病风险因子估计为5或者＞10.6%。通过实施常规降压治疗以维持血压小于140/90 mm Hg，尿蛋白排泄每年评估一次，且用肌酐比值表示，在随访期间，记录致死性或非致死性的心血管事件的发生率。在平均随访4.7年内（17 028例患者-年），已记录294例致死性和首次非致死性的心血管事件（每年每百人中平均1.73人发生心血管病）。独立于血压、有小气泡发生频率值、心血管风险等级及降压治疗，基线时即发生微量白蛋白尿和随访期间的任意时间内发生微量白蛋白尿的事件发生风险均更高，风险比（hazard ratio, HR）分别为1.35（95%可信区间，1.08–1.79）和1.49（95%可信区间，1.14–1.94）。同样，进展的微量白蛋白尿（HR=1.66, CI, 1.04–2.46）或者微量白蛋白尿自始至终保持不变（HR=1.53, 95%可信区间，1.13–2.06）的患者比维持正常白蛋白尿（HR=1.53, 95%可信区间，1.13–2.06）的患者其事件发生率明显更高，事件发生率分别是18%、18%、8%和11%，P值均＜0.001。本研究支持尿蛋白排泄作为心血管疾病风险的评价指标，但也提出将其作为高血压治疗的中间目标。

(Hypertension. 2014;64:1228-1234.)

临床试验（摘要）

奈必洛尔而非美托洛尔可降低NO敏感性高血压患者血压

Nebivolol, But Not Metoprolol, Lowers Blood Pressure in Nitric Oxide–Sensitive Human Hypertension

Luis E. Okamoto, Alfredo Gamboa, Cyndya A. Shihbou, Amy C. Arnold, Leena Choi, Bonnie K. Black, Satish R. Raj, David Robertson, Italo Biaggioni

王翔凌 译 刘蔚 审校

奈必洛尔与其他选择性β1受体阻滞剂不同，其可通过增加一氧化氮（Nitric Oxide, NO）的生物利用度引起血管舒张。奈必洛尔通过此机制对抗血压降低的影响程度尚不清楚，因为正常状态下该作用可能被压力反射缓冲所掩盖。自主神经调节障碍者提供了一个独特的高血压模型，此模型缺乏自主神经调节功能，但对NO增加所致的血压下降敏感。本研究用于验证奈必洛尔降低自主神经调节功能障碍患者血压的机制并非依赖于β受体阻滞的假设。我们将20例合并卧位高血压的自主神经功能障碍患者进行双盲、交叉研究，在不同夜间随机给予单个口服剂量的小安慰剂、奈必洛尔5 mg、美托洛尔50 mg（阳性对照）和西地那非25 mg（阴性对照），自8 pm至8 am每2小时测量一次卧位血压。与安慰剂比较，西地那非和奈必洛尔可降低夜间收缩压（混合效应模型结果为服药后8小时内收缩压最大下降分别为-20±6和-24±9 mm Hg, P＜0.001和P=0.036），而美托洛尔无此作用。亚组分析中，我们将患者分为西地那非反应组（4:00 am血压下降＞20 mm Hg者）和西地那非无反应组。奈必洛尔显著降低西地那非反应组的收缩压水平（-44±13 mm Hg），而西地那非无反应组则无此影响（1±11 mm Hg）。尽管奈必洛尔可降低夜间血压，但与安慰剂相比并未使晨起立位血压耐受性恶化。总而言之，奈必洛尔可不依赖于β1受体阻滞作用而有效降低自主神经调节障碍患者的卧位血压，研究结果证实了奈必洛尔可通过增强NO效应而降压的假设。

(Hypertension. 2014;64:1241-1247.)