Hypertension (HTN) is an established risk factor of cardiovascular and all-cause mortality.\(^1\) However, more than half of all cardiovascular disease (CVD) occurs in individuals with mild HTN or normal blood pressure (BP, pre-HTN), despite a risk reduction with a decrease in BP levels.\(^2,^3\) Further studies have identified other factors that may provide additional important predictive information regarding the risk of CVD. Proteinuria and microalbuminuria are well known independent risk factors for CVD and mortality along with HTN.\(^4–^6\) Moreover, HTN has been closely linked with a greater prevalence of proteinuria and microalbuminuria.\(^7\) The Prevention of Renal and Vascular End stage Disease (PREVEND) study showed that urinary albumin excretion is a predictor of all-cause mortality in the general population,\(^8\) and the relationship was apparent at levels of albuminuria currently considered to be normal.\(^8\) A recent meta-analysis documented that irrespective of the presence or absence of diabetes, CVD risk and mortality were increased with albuminuria at levels lower than that currently used to define microalbuminuria.\(^9\)

In the Framingham Offspring Study, participants of middle-aged nondiabetic without hypertensive individuals, low levels of urinary albumin excretion well below the current microalbuminuria threshold predicted the development of CVD.\(^10\) Furthermore, some prospective studies indicated an association between urinary albumin excretion without threshold effects and cardiovascular mortality in the general population.\(^8,^11\)
However, it remains unclear whether urinary albumin with or without HTN predicts a risk of CVD events and death in the general population. Moreover, there are no reports that compare subjects with HTN to subjects with albuminuria below the microalbuminuria threshold level with regard to the risk of all-cause death and CVD. Recently, we reported in cohort study during a maximum of 11 years of follow-up that low grade albuminuria (below the microalbuminuria level) is an independent risk factor for incident HTN and CVD mortality.\textsuperscript{12}

Thus, the aim of this study was to investigate the effect of HTN and urinary albumin on the risk of CVD and all-cause mortality in a large, predominantly single ethnicity, occupational Korean cohort.

In addition, the risk of death and CVD were analyzed with regard to the degree of albuminuria according to subgroups that were known to have conventional cardiovascular risk factors.

METHODS

Study population

The study population consisted of individuals with urinary albumin/creatinine ratio (UACR, mg/g) measurements who participated in a comprehensive health screening program at Kangbuk Samsung Hospital, Seoul, Korea, from 2002 to 2012 (n = 44,964). For this analysis, 12,311 subjects were excluded for one of more of the following reasons: 4,794 subjects had missing data on smoking status, alcohol consumption, and exercise; 868 subjects had a pre-existing history of malignancy; and 1 subject had an unknown vital status. Further analyses were undertaken after excluding subjects with diabetes (n = 3,435) and subjects with antihypertensive medication (n = 5,874). The total number of eligible individuals for the study was 32,653.

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital. The requirement for informed consent was waived, and deidentified information was retrieved retrospectively.

Measurements

Data on medical history, medication use, and health-related behaviors were collected through a self administered questionnaire. Details regarding alcohol use included the frequency of intake per week. Current smokers were identified, and the weekly frequency of moderate- or vigorous-intensity physical activity was assessed. Body weight was measured with the subject in light clothing and no shoes to the nearest 0.1 kg using a digital scale. Height was measured to the nearest 0.1 cm.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Trained nurses measured sitting BP with a standard mercury sphygmomanometer.

Blood specimens were sampled from the antecubital vein after 12 hours of fasting. Serum levels of glucose, total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high density lipoprotein (HDL) cholesterol were measured using Bayer Reagent Packs (Bayer Diagnostics, Leverkusen, Germany) on an automated chemistry analyzer (Advia 1650 Autoanalyzer; Bayer Diagnostics). Insulin levels were measured with an immunoradiometric assay (Biosource, Nivelles, Belgium) with an intra- and interassay coefficient of variation of 2.1–4.5% and 4.7–12.2%, respectively. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR), calculated as insulin \times glucose/22.5. The serum creatinine (Scr) level was measured by means of the alkaline pizrate (Jaffe) method. We used an estimation of the glomerular filtration rate (GFR) to assess the degree of kidney impairment, which was calculated using the CKD-EPI equation: eGFR = 141 \times \min (Scr/K, 1) \times \max (Scr/K, 1)−1.209 \times 0.993\text{age} \times 1.018 (if female) \times 1.159 (if Black), where Scr is serum creatinine, K is 0.7 for females and 0.9 for males, a is ~0.329 for females and ~0.411 for males, min indicates the minimum of Scr/K or 1, and max indicates the maximum of Scr/K or 1.\textsuperscript{13}

A single morning voided urine sample was used to measure the UACR. The urinary albumin concentration was determined by immunoradiometry (Radio-immunological competition assay, Immunotech Co., Prague, Czech Republic), and the urinary creatinine concentration was measured by a modified Jaffe method. The UACR measured in a spot urine sample has been reported to be highly correlated with the 24-hour urinary albumin excretion level.\textsuperscript{14}

Abdominal ultrasonography (Logic Q700 MB; GE, Milwaukee, WI, USA) using a 3.5 MHz probe was performed in all subjects by experienced clinical radiologists, and fatty liver was diagnosed or excluded based on standard criteria, including hepatorenal echo contrast, liver brightness, and vascular blurring.\textsuperscript{15} HTN was defined as a systolic BP \geq 140 mm Hg, diastolic BP \geq 90 mm Hg, a self-reported history of HTN. Diabetes mellitus was defined as a fasting serum glucose level \geq 126 mg/dl, a self-reported history of diabetes, or the current use of diabetic medication.\textsuperscript{16} Obesity was defined according to those described for Asian populations, and the BMI threshold for obesity was \geq 25 kg/m\textsuperscript{2}.\textsuperscript{17} Receiver operating characteristic curve analyses were performed to find out appropriate UACR cutoff for predicting all-cause and CVD mortality and the cut-point was 5.42 mg/g.

Four groups were then defined as follows: (i) subjects who were below the UACR 5.42 mg/g but without HTN (no HTN/UACR < 5.42); (ii) subjects who were below 5.42 for UACR with HTN (HTN/UACR < 5.42); (iii) subjects at or above 5.42 for UACR without HTN (no HTN/UACR \geq 5.42); and (iv) subjects at or above 5.42 for UACR with HTN (HTN/UACR \geq 5.42).

Ascertainment of mortality

Mortality follow-up between January 1, 2002 and December 31, 2012 was based on the nationwide death certificate data of the Korea National Statistical Office. Deaths among subjects were confirmed by matching the information to death records. Causes of death were coded centrally by trained coders using the ICD-10 classification (International Classification of Diseases, 10th revision) and ICD 00-99 codes were considered to represent cardiovascular death.
Statistical analyses

The χ²-test and Student's t test were used to compare the characteristics of the deceased and alive study participants at baseline. We used receiver operating characteristic curve analysis to identify the optimal UACR cutoff value for predicting all-cause and CVD mortality.

Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cardiovascular mortality, comparing the HTN/UACR < 5.42, no HTN/UACR ≥ 5.42, and the HTN/UACR ≥ 5.42 groups with the reference no HTN/UACR < 5.42 group. The models were initially adjusted for age, sex, treatment center, year of screening exam, smoking status, alcohol intake, regular exercise, and education level (Model 1). In Model 2: the models were further adjusted for BMI, HTN, diabetes, and history of CVD. Model 3 included adjustments for the same factors as Model 2 plus an additional adjustment for eGFR. In addition, the participants were stratified into quartiles according to UACR.

UACR quartiles were categorized as following: Q1: < 3.3 mg/g, Q2: 3.3–4.6 mg/g, Q3: 4.7–7.2 mg/g, and Q4: ≥ 7.3 mg/g. The risk of all-cause mortality and CVD mortality were analyzed with the degree of albuminuria according to sub-groups, which were based on conventional cardiovascular risk factors.

Adjustment or stratification was made for multiple confounders/effect modifiers including age, sex, BMI, eGFR, alcohol intake and exercise, educational attainment (college graduation or higher), smoking status and prior evidence of CVD.

The proportional hazards assumption was checked by examining graphs of estimated log (−log) survival. Statistical analysis was performed using Stata, version 11.2. All reported P-values are two tailed, and P < 0.05 was considered statistically significant.

RESULTS

There were 249 deaths during the follow-up period (Table 1). Table 1 describes the baseline clinical characteristics analyzed according to the vital status at follow-up. Subjects who died were older, and a higher proportion had a history of HTN at baseline. Other conventional cardiovascular risk factors including glucose, triglycerides, and blood pressure, were also higher, and the HDL-C and proportion

Table 1. Baseline characteristics of the cohort according to death at follow-up

| Baseline characteristics | No death | New death | P value |
|-------------------------|----------|-----------|---------|
| Number                  | 32,404   | 249       |         |
| Men (%)                 | 16,701 (51.5) | 178 (48.5) | <0.001 |
| Age (years)             | 43.9 (11.3) | 55.1 (12.4) |         |
| BMI (kg/m²)             | 23.4 (3.1) | 23.4 (3.2) | 0.867   |
| Systolic BP (mm Hg)     | 114.7 (14.5) | 120.9 (16.4) | <0.001 |
| Diastolic BP (mm Hg)    | 74.3 (9.9) | 78.0 (9.8) | <0.001 |
| Higher education (%)a   | 58.5     | 37.1      | <0.001 |
| Regular exercise (%)b   | 18.0     | 17.3      | 0.766   |
| Current smoker          | 27.1     | 37.4      | <0.001 |
| Alcohol intake ≥ 20 g/day (%) | 19.7  | 26.5      | 0.007   |
| Obesity (%)             | 27.1     | 37.4      | <0.001 |
| Hypertension (%)        | 13.9     | 27.7      | <0.001 |
| History of CVD (%)      | 6.8      | 8.4       | 0.317   |
| Insulin (µIU/ml)        | 7.97 (6.24–10.18) | 7.89 (6.38–10.07) | 0.272   |
| Glucose (mg/dl)         | 93.1 (9.4) | 94.0 (10.6) | 0.102   |
| Total cholesterol (mg/dl)| 195.7 (34.9) | 193.5 (35.9) | 0.310   |
| LDL-C (mg/dl)           | 115.4 (31.1) | 110.9 (30.5) | 0.023   |
| HDL-C (mg/dl)           | 56.4 (13.4) | 56.0 (14.3) | 0.679   |
| Triglycerides (mg/dl)   | 100 (70–148) | 109 (81–154) | 0.004   |
| HOMA IR                 | 1.82 (1.37–2.37) | 1.85 (1.43–2.39) | 0.192   |
| Urine ACR mean (mg/g)   | 9.9 (35.0) | 17.9 (93.6) | <0.001 |
| Urine ACR median (mg/g) | 4.65 (3.32–7.32) | 5.42 (3.49–9.53) | <0.001 |

Data are mean (SD), median (interquartile range), or percentage. Abbreviations: ACR, albumin/creatinine ratio; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HDL-C, high density lipoprotein cholesterol; HOMA IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol.

a≥college graduate.
b≥ 3 time per week.
of those performing regular exercise was lower in subjects who died by the end of the follow-up period. At baseline, mean and median UACR were higher in the group who died during follow-up compared to survivors.

Table 2 shows the baseline characteristics across the four previously defined groups based on below or above the 75th percentile for UACR levels and the absence or presence of HTN. Differences in characteristics across the four groups were statistically significant. The median UACR levels were higher in the group that had HTN at baseline compared with the group without HTN.

Table 3 shows the age-adjusted, sex-adjusted, and fully adjusted, including eGFR, HRs for all-cause and CVD mortality according to the four baseline groups. For all-cause mortality, there was a higher HR in the no HTN/UACR ≥ 5.42 and the HTN/UACR ≥ 5.42 groups (HR 1.48, CI 1.02–2.15; HR 1.47, CI 0.94–2.32, respectively) compared with the no HTN/UACR < 5.42 group (reference group).

When HRs for CVD mortality were analyzed, no HTN/UACR ≥ 5.42 and HTN/UACR ≥ 5.42 group showed a similar significantly increased fully adjusted HR compared with the reference group (CVD mortality; HR 5.75; 95% CI 1.54–21.47; HR 5.87; 95% CI 1.36–25.29). However, subjects in the HTN/UACR < 5.42 group did not show statistically significantly increased HRs compared with the reference group (HR 4.13, CI 0.81–20.93). The number of event in CVD was small.

Figure 1 illustrates the Kalpan–Meier curves for all-cause death(A) and CVD death(B) according to UACR < 5.42 or UACR ≥ 5.42 and HTN (hypertension) status.

Although overall mortality rates were low, subjects with a UACR ≥ 5.42 mg/g without or with HTN showed a similar increased in all-cause mortality and CVD mortality about 8 years.

The multivariate-adjusted HRs and CIs for all-cause and cardiovascular mortality according to the UACR quartiles are listed in Supplementary Tables S1 and S2.

When the HR of first quartile group for all-cause mortality was set as the reference, HRs for all-cause mortality tend to increase in proportion to the quartiles of UACR from the second to the fourth quartile group (Supplementary Table S1). However, these associations were not statistically significant.

Similar to associations with CVD mortality, the statistically significant was present in subjects with men, age ≥50 years, eGFR ≥ 90 ml/min and and group with BMI M < 25 kg/m² (Supplementary Table S2).

## DISCUSSION

We describe the effects of HTN and urinary albumin levels on all-cause and cardiovascular mortality in a large number of Koreans participating in a health screening program with a median follow-up of 5.13 years.

Even small changes in the UACR (UACR level > 5.42 mg/g, below microalbuminuria level) showed an incremental association with mortality in those subjects with or without HTN. This trend was independent of eGFR levels. Importantly, for the first time, we showed that above 5.42 in UACR level in whole range of albuminuria increased risk of death and CVD to similar extent even if subject with or without HTN.

In addition, subjects with a UACR > 5.42 and HTN had a 3.27-fold increased risk of CVD mortality compared to those with a UACR < 5.42 mg/g with no HTN.

In general, urinary albumin excretion is classified as: normoalbuminuria (< 30 mg per day or UACR < 30 mg/g), microalbuminuria (30–300 mg per day or UACR 30–300 mg/g, equivalent to 3.4–34 mg/mmol), and macroalbuminuria (>300 mg per day or UACR > 300 mg/g).

Furthermore, these results suggest that urinary albumin, in particular at levels below the microalbuminuria level, might be more attributable to CVD and all-cause mortality than HTN in a healthy, young, occupational cohort. Thus, this study supports the concept that any range of albuminuria as regular examination could be helpful to prevent in organ damage with hypertensive patient.

The 2013 European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) hypertension guidelines recommended that all hypertensive patients have a test for microalbuminuria with a spot urine sample. In addition, the guidelines stressed that a test for microalbuminuria is a cost-effective test for organ damage in hypertensive patients.

Furthermore, some prospective studies indicate that the association between urinary albumin excretion without threshold effects and cardiovascular mortality in general population and in non-diabetic hypertensive patients, microalbuminuria.

A cohort study performed in North America, South America, and Europe that followed individuals ≥ 55 years old for a median of 4.5 years showed that any degree of albuminuria was a risk factor for the occurrence of CV events.

Another multicenter cohort study involving patients with HTN and left ventricular hypertrophy also showed an association between UACR and increased cardiovascular morbidity and mortality with no UACR threshold necessary to demonstrate the increased risk.

Another study suggested that urinary albumin excretion testing improves the accuracy of cardiovascular risk assessment in patients with HTN.

It has also been suggested that albuminuria may be as reliable as cardiac and carotid ultrasound evaluations in predicting cardiovascular risk in hypertensive patients.

Cuspidi et al. reported that combined ultrasound and microalbuminuria screening can improve the accuracy of target organ damage detection by 10-fold compared with routine investigations.

Thus, our study suggests that a UACR > 5.42 mg/g (below the microalbuminuria level) is associated with an increased risk of death and CVD to a similar extent in those with or without HTN. This means that the UACR level, even at levels far below the microalbuminuria level, might be as useful a tool for evaluating risk stratification and target organ damage as is the presence or absence of HTN.

It is well known that overt proteinuria, macroalbuminuria, and microalbuminuria are associated with CVD mortality and other metabolic parameters. The Heart Outcomes Prevention Evaluation (HOPE) study found that there was a continuous association between albuminuria and cardiovascular events starting well below the microalbuminuria cutoff level in high risk patients with CVD.

Dell’Omo et al. suggest the appropriateness of shifting downward the threshold level for diagnosing microalbuminuria in hypertensive patients. That study showed that high-normal
Table 2. Baseline characteristics of study subjects by urineACR quartile

| Characteristics       | Overall   | No HTN/ACR < 75% | HTN/ACR < 75% | No HTN/ACR ≥ 75% | HTN/ACR ≥ 75% | P-value |
|-----------------------|-----------|------------------|---------------|-----------------|---------------|---------|
| N = 32,653            |           |                  |               |                 |               |         |
| Age (years)           | 44.0 (11.3)| 42.2 (10.6)      | 46.7 (10.8)   | 44.8 (11.9)     | 51.1 (11.0)   | <0.001  |
| BMI (kg/m²)           | 23.4 (3.1)| 23.1 (2.9)       | 24.8 (3.1)    | 23.0 (3.3)      | 25.2 (3.3)    | <0.001  |
| Systolic BP (mm Hg)   | 114.7 (14.6)| 110.6 (10.9)    | 133.6 (11.9)  | 112.1 (11.6)    | 139.1 (14.2)  | <0.001  |
| Diastolic BP (mm Hg)  | 74.3 (9.9)| 71.6 (7.9)       | 87.8 (7.7)    | 72.6 (8.2)      | 89.4 (8.8)    | <0.001  |
| Higher education (%)a| 58.3      | 64.7             | 54.7          | 53.6            | 40.7          | <0.001  |
| Regular exercise (%)b| 18.0      | 18.1             | 21.2          | 17.0            | 18.5          | <0.001  |
| Current smoker(%)     | 27.2      | 31.0             | 35.4          | 20.0            | 23.6          | <0.001  |
| Alcohol intake ≥20 g/day (%)| 19.7 | 20.1 | 33.4 | 14.9 | 26.4 | <0.001 |
| Fatty liver (%)       | 26.1      | 23.0             | 38.1          | 24.7            | 43.7          | <0.001  |
| Obesity (%)           | 28.8      | 25.1             | 45.6          | 26.5            | 50.6          | <0.001  |
| History of CVD (%)    | 6.85      | 6.34             | 6.45          | 7.38            | 8.49          | <0.001  |
| Insulin (µIU/ml)      | 2.06 (1.83–2.32) | 2.05 (1.80–2.29) | 2.13 (1.91–2.39)| 2.08 (1.83–2.33)| 2.20 (1.96–2.46)| <0.001 |
| Glucose (mg/dl)       | 93.1 (3.4) | 92.0 (8.8)       | 95.8 (9.8)    | 93.1 (9.5)      | 97.6 (10.1)   | <0.001  |
| Total-cholesterol (mg/dl) | 195.7 (35.0) | 192.8 (33.4) | 203.2 (34.5) | 195.7 (36.0) | 209.5 (36.7) | <0.001  |
| LDL-C (mg/dl)         | 115.3 (31.1) | 114.0 (30.1) | 121.6 (31.4) | 114.1 (32.0) | 124.6 (32.5) | <0.001  |
| HDL-C (mg/dl)         | 56.4 (13.4) | 56.1 (13.3) | 54.0 (12.5) | 57.6 (13.9) | 54.9 (12.4) | <0.001  |
| Triglycerides (mg/dl) | 100 (70–148) | 96 (69–140) | 131 (91–183) | 95 (66–143) | 132 (93–193) | <0.001  |
| HOMA IR               | 1.82 (1.38–2.38) | 1.75 (1.32–2.27) | 2.01 (1.54–2.62) | 1.83 (1.37–2.40) | 2.14 (1.64–2.86) | <0.001  |
| eGFR (ml/min)         | 82.3 (14.3) | 82.6 (13.8) | 78.6 (12.1) | 83.7 (15.4) | 78.2 (13.5) | <0.001  |
| Urine ACR mean (mg/g) | 9.94 (35.83) | 3.56 (1.00) | 3.70 (0.98) | 17.42 (49.60) | 27.78 (73.01) | <0.001  |
| Urine ACR median (mg/g) | 4.66 (3.32–7.34) | 3.54 (2.82–4.34) | 3.73 (2.96–4.49) | 8.18 (6.44–12.74) | 10.35 (7.26–19.70) | <0.001  |

Data are mean (SD), median (interquartile range), or percentage. Abbreviations: ACR, albumin/creatinine ratio; BP, blood pressure; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HTN, hypertension; HDL-C, high density lipoprotein cholesterol; HOMA IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol.

*a ≥ college graduate.

*b ≥ 3 time per week.
Table 3. Risk of all cause and CVD mortality according to baseline urine ACR and HTN

| ACR quartiles (mg/dl) | Person-years | Number of events | Mortality rate (100,000 person-year) | Age-sex adjusted HR (95% CI) | Multivariate HR (95% CI) |
|-----------------------|--------------|------------------|--------------------------------------|-----------------------------|-------------------------|
|                       |              |                  |                                      | Model 1                     | Model 2                 | Model 3                 |
| All cause mortality   |              |                  |                                      |                             |                         |                         |
| No HTN/ACR < 5.42 mg/g| 85828.81     | 101              | 117.7                                | 1.00 (reference)            | 1.00 (reference)        | 1.00 (reference)        |
| HTN/ACR < 5.42 mg/g   | 11055.4      | 23               | 208.0                                | 1.01 (0.64–1.60)            | 1.24 (0.72–2.15)        | 1.24 (0.72–2.15)        |
|                       |              |                  |                                      |                             | 1.22 (0.70–2.10)        |                         |
| No HTN/ACR ≥ 5.42 mg/g| 51696.3      | 79               | 152.8                                | 1.19 (0.88–1.61)            | 1.54 (1.06–2.23)        | 1.54 (1.06–2.23)        |
|                       |              |                  |                                      |                             | 1.48 (1.02–2.15)        |                         |
| HTN/ACR ≥ 5.42 mg/g   | 15182.2      | 46               | 303.0                                | 1.28 (0.89–1.84)            | 1.51 (0.96–2.36)        | 1.51 (0.97–0.37)        |
|                       |              |                  |                                      |                             | 1.47 (0.94–2.32)        |                         |
| CVD mortality         |              |                  |                                      |                             |                         |                         |
| No HTN/ACR < 5.42 mg/g| 85828.8      | 11               | 12.8                                 | 1.00 (reference)            | 1.00 (reference)        | 1.00 (reference)        |
| HTN/ACR < 5.42 mg/g   | 11055.4      | 4                | 36.2                                 | 1.52 (0.48–4.80)            | 4.06 (0.80–20.58)       | 3.92 (0.77–19.89)       |
|                       |              |                  |                                      |                             | 4.13 (0.81–20.93)       |                         |
| No HTN/ACR ≥ 5.42 mg/g| 51696.3      | 11               | 21.3                                 | 1.57 (0.67–3.70)            | 5.46 (1.47–20.29)       | 5.59 (1.50–20.85)       |
|                       |              |                  |                                      |                             | 5.75 (1.54–21.47)       |                         |
| HTN/ACR ≥ 5.42 mg/g   | 15182.18     | 8                | 52.7                                 | 1.98 (0.77–5.09)            | 5.41 (1.26–23.20)       | 5.74 (1.33–24.72)       |
|                       |              |                  |                                      |                             | 5.87 (1.36–25.29)       |                         |

Cox proportional hazard models were used to estimate HR (hazard ratio) and 95 percentage confidence intervals (95% CIs). Model 1: adjustment for age, sex, treatment center, year of screening exam, smoking status, alcohol intake, regular exercise, education level. Model 2: Model 1 plus adjustment for body mass index, HTN, and history of CVD. Model 3: Model 2 + estimated glomerular filtration rate. Abbreviations: ACR, albumin/creatinine ratio; CVD, cardiovascular disease; HTN, hypertension.
albuminuria is associated with cardiovascular risk factors and predicts morbid events in hypertensive subjects. Some studies have raised questions regarding the original definition of microalbuminuria when evaluating the risk of CVD or death.\textsuperscript{5,13,26,27} Thus, in recent years the focus of research has shifted towards the prognostic value of low-grade albuminuria at levels below the microalbuminuria range.\textsuperscript{28}

The Nord-Trøndelag Health Study reported that the lowest UACR level associated with 2.2-fold increased risk for mortality was the 60th percentile (≥6.7 mg/g) during a 4.4-year follow-up of 2,089 subjects without diabetes and with treated HTN.\textsuperscript{29} In individuals with or without DM in the HOPE study, the relative risk of cardiovascular death in the fourth quartile was 1.97 (UACR > 1.62 mg/mmol) compared with the lowest quartile of the UACR.\textsuperscript{5} In general population with cohort study within UACR below 30 mg/g, the hazard risk of HTN in fourth quartile was 1.97(UACR ≥ 7.4 mg/g) and the risk of CVD death increased 3.37-folds compared with the lowest quartile (UACR < 3.4 mg/g).\textsuperscript{15}

Our findings provide further evidence to support the assumption that UACR, even below the microalbuminuria level (UACR cutoff > 5.42 mg/g), with or without HTN, could predict the occurrence of death as well as CVD. This result suggests that the linkage between albuminuria and mortality might not be through elevated blood pressure, which has been known to be closely associated with urinary albumin excretion in general. Thus, our study shows that the risk of death and CVD was significantly increased if the UACR was ≥5.42 mg/g, independent of HTN status. In addition, our study found that albuminuria is superior to HTN status in predicting all-cause and CVD mortality after adjusting for associated cardiovascular risk factors, because of the relatively short follow-up period. Although there were few cardiovascular deaths, albuminuria and HTN could have an additive effect in all-cause and CVD mortality outcome.

The pathophysiological processes that link albuminuria and CVD are unclear.

Increased albumin excretion has been related to endothelial alterations in the glomerular capillaries in patients with essential HTN.\textsuperscript{30} However, the cause of albuminuria in persons without HTN is still uncertain. In patient without heart failure, elevated UACR predicts future hospitalization for heart failure.\textsuperscript{31}

Increased UACR is also associated with left ventricular hypertrophy, a potent risk factor for progression to heart failure.\textsuperscript{32} Also, another researcher showed that adverse hemodynamics may play a role in albuminuria in the absence of HTN or DM.\textsuperscript{32}

In addition, low-grade inflammation can be both a cause and consequence of endothelial dysfunction. Some previous studies have associated markers of low-grade inflammation, such as C-reactive protein, IL-6, and TNF-α, to the occurrence and progression of microalbuminuria and an increased risk for atherosclerotic disease.\textsuperscript{33}

Alternatively, endothelial dysfunction leading simultaneously to albuminuria and subclinical coronary artery disease (CAD) could explain the association.\textsuperscript{34}

The multi-ethnic study of atherosclerosis including 6,774 individuals, asymptomatic individuals demonstrates an increased risk of incident coronary artery calcification (CAC) as well as greater CAC progression among those with microalbuminuria.\textsuperscript{35}

Kramer et al. reported 6,814 participants without clinical CVD that mean CAC scores were higher among participants with high normal urinary albumin excretion, microalbuminuria and macroalbuminuria compared with normal urinary albumin.\textsuperscript{34} This study concluded that higher urinary albumin, including levels below microalbuminuria, may reflect the presence of subclinical CVD among adults without established CVD.\textsuperscript{34}

We showed the pathologic link that increased a risk of CVD and mortality in general population may vary according to the albuminuria with the presence or absence of hypertensive status.

When interpreting our results, several limitations should be considered.

First, urinary albumin excretion was measured on a single voided urine collection, which may not have accurately reflected the true level of albuminuria. However, prior research suggested that a single-void urine UACR correlated highly with the 24-hour urinary albumin excretion with a high specificity and sensitivity; therefore, it can be used to estimate quantitative microalbuminuria.\textsuperscript{14}
Second, we did not address the severity of HTN. Previous studies reported that BP is positively correlated with albuminuria. Thus, the level of the mean and median UACR had some differences.

Third, there is a possibility that the pharmacological therapies used by the subjects are not fully reflected in the medication history. However, prior antihypertensive medication history excluded in our study population. Thus, we excluded the influence of antihypertensive medication.

Fourth, the study was performed in a relatively homogenous population of working individuals who participated in a health screening program, and it is not fully representative of the entire Korean population. However, the number of subjects included in our study is larger than in any previous studies investigating this question.

In conclusion, this study shows that urinary albumin is an important marker for both cardiovascular and all-cause mortality in subjects with or without HTN. Subjects with a UACR $\geq 5.42$ have a similar risk of death and CVD among hypertensive patients if albuminuria defined as UACR (UACR cutoff $= 5.42$ mg/g) is present. This increased risk is independent of age, sex, smoking status, alcohol intake, regular exercise, BMI, HTN, history of CVD, and eGFR. In the general population, the risk of death and CVD increases as the UACR increases in subjects, with or without HTN. Thus, urinary albumin is more attributable to CVD and all-cause mortality than HTN. Urinary albumin measurement might be a valuable tool in subjects with or without HTN to identify those subjects at higher risk for CVD and all-cause mortality.

SUPPLEMENTARY MATERIAL

Supplementary data are available at American Journal of Hypertension online.

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DISCLOSURE

The authors declared no conflicts of interest.

REFERENCES

1. Ford ES. Trends in mortality from all causes and cardiovascular disease among hypertensive and nonhypertensive adults in the United States. Circulation 2011; 123:1737−1744.
2. Fujiyoshi A, Ohkubo T, Miura K, Murakami Y, Nagasawa SI, Okamura T, Ueshima H; Observational Cohorts in Japan (EPOCH-JAPAN) Research Group. Blood pressure categories and long-term risk of cardiovascular disease according to age group in Japanese men and women. Hypertens Res 2012; 35:947−953.
3. Takashima N, Ohkubo T, Miura K, Okamura T, Murakami Y, Fujiyoshi A, Nagasawa ST, Kadota A, Kita Y, Miyagawa N, Hisamatsu T, Hayakawa T, Okayama A, Ueshima H; NIPPPON DATA80 Research Group. Long-term risk of BP values above normal for cardiovascular mortality: a 24-year observation of Japanese aged 30 to 92 years. J Hypertens 2012; 30:2299−2306.
4. Perkovic V, Verdon C, Ninnomiya T, Barzi F, Cass A, Patel A, Jardine M, Gallagher M, Turnbull F, Chalmers J, Craig J, Huxley R. The relationship between proteinuria and coronary risk: a systematic review and meta-analysis. PLoS Med 2008; 5:e207.
5. Gerstein HC, Mann JF, Yi Q, Zimmet B, Dinneen S, Hoogwerf B, Hall JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S; HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, heart failure in diabetic and nondiabetic individuals. JAMA 2001; 286:421−426.
6. Sung KC, Kim BJ, Ryu S. An association of a variety of cardiovascular risk factors with low grade albuminuria in Korean men. Atherosclerosis 2008; 196:320−326.
7. Atkins RC, Briganti EM, Zimmet PZ, Chadban SJ. Association between albuminuria and proteinuria in the general population: the AusDiab Study. Nephrol Dial Transplant 2003; 18:2170−2174.
8. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Velthuisen DJ, Gans RO, Janssen WM, Grobbée 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.
9. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerpink HJ, Lee BJ, Perkins RM, Rossing P, Sairenchi T, Tonelli M, Vassalotti JA, Yamagishi K, Coresh J, de Jong PE, Wen CP, Nelson RG; Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012; 380:1662−1673.
10. Arnljov J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D, Benjamin EJ, D'Agostino RB, Vasan RS. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. Circulation 2005; 112:969−975.
11. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010; 375:2073−2081.
12. Sung KC, Ryu S, Lee JY, Lee SH, Cheong E, Hyun YY, Lee KB, Kim H, Byrne CD. Urine albumin/creatinine ratio below 30 mg/g is a predictor of incident hypertension and cardiovascular mortality. J Am Heart Assoc 2016; 5:e003245.
13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI Chronic Kidney Disease Epidemiology Collaboration. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150:604−612.
14. Bakker AJ. Detection of microalbuminuria. Receiver operating characteristic curve analysis favors albumin-to-creatinine ratio over albumin concentration. Diabetes Care 1999; 22:307−313.
15. Saadé S, Yousoufi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, Mullen KD, Cooper JN, Sheridan MJ. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002; 123:745−750.
16. James PA, Oparil S, Carter BL, Cushman WC, Dinneen SF, Hoogwerf B, Jackson L, Kusek JW, Levey AS, Velmahos GC, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ong JP, Hurley M; Chronic Kidney Disease Epidemiology Collaboration. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150:604−612.
17. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JJ, Donato KA, Frucht CJ, James WP, Liu X, Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic
syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120:1640–1645.

18. Cuspidi C, Meani S, Salerno M, Severgnini B, Fusi V, Valerio C, Catini E, Magrini F, Zanchetti A. Cardiovascular risk stratification according to the 2003 ESH-ESC guidelines in uncomplicated patients with essential hypertension: comparison with the 1999 WHO/ISH guidelines criteria. Blood Press 2004; 13:144–151.

19. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Gillerardi M, Grogger DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waebler B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsiofou C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdal D, Hoes AW, Kirchhof P, Knudt J, Koli P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendler M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendler M, Rolei EA, Ambrosioni E, Anker SD, Bauersachs J, Hiti JB, Caufield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germani C, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovie D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonka J, Popescu BA, Reiner Z, Rydén L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013; 34:2159–2219.

20. Dell’Omo G, Penno G, Giorgi D, Di Bello V, Mariani M, Pedrinelli R. Association between high-normal albuminuria and risk factors for cardiovascular and renal disease in essential hypertensive men. Am J Kidney Dis 2002; 40:1–8.

21. Jensen JS, Borch-Johnsen K, Feldt-Rasmussen B, Appleyard M, Jensen G. Urinary albumin excretion and history of acute myocardial infarction in a cross-sectional population study of 2,613 individuals. J Cardiovasc Risk 1997; 4:121–125.

22. Schmieder RE, Schrader J, Zidek W, Tebbe U, Paar WD, Bramlage P, Pittrow D, Böhm M. Low-grade albuminuria and cardiovascular risk: what is the evidence? Clin Res Cardiol 2007; 96:247–257.

23. Romundstad S, Holmen J, Kvenild K, Hallan H, Ellekjær H. Microalbuminuria and all-cause mortality in 2,089 apparently healthy individuals: a 4.4-year follow-up study. The Nord-Trøndelag Health Study (HUNT), Norway. Am J Kidney Dis 2003; 42:466–473.

24. Leoncini G, Sacchi G, Viazzi F, Ravera M, Parodi D, Ratto E, Vettoretti S, Tomolillo C, De Ferrari G, Pontremoli R. Microalbuminuria identifies overall cardiovascular risk in essential hypertension: an artificial neural network-based approach. J Hypertens 2002; 20:1315–1321.

25. Pedrinelli R, Giampietro O, Carmassi F, Melillo E, Dell’Omo G, Catapano G, Matteucci E, Talarico L, Morale M, De Negri F. Microalbuminuria and endothelial dysfunction in essential hypertension. Lancet 1994; 344:14–18.

26. Wachter K, Ibsen H, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B, Devereux RB, Bevers G, de Faire U, Fyhrlqvist F, Julius S, Kjeldsen SE, Kristiansen K, Lederballe-Pedersen O, Nieminen MS, Oikin PM, Omvik P, Oparil S, Wedel H, Snapinn SM, Aurup P. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. Ann Intern Med 2003; 139:901–906.

27. Festa A, D’Agostino R, Howard G, Mykkänen L, Tracy RP, Haffner SM. Inflammation and microalbuminuria in nondiabetic and type 2 diabetic subjects: The Insulin Resistance Atherosclerosis Study. Kidney Int 2000; 58:1703–1710.

28. Gruden G, Cavallero-Perin P, Bazzan M, Stella S, Vueling A, Pagano G. PAI-1 and factor VII activity are higher in IDDM patients with microalbuminuria. Diabetes 1994; 43:426–429.

29. Tanaka F, Komi R, Makita S, Onoda T, Tanno K, Ohuwa M, Itaki K, Sakata K, Omama S, Yoshida Y, Ogasawara K, Ishibashi Y, Kuribayashi T, Okayama A, Nakamura M; Iwate-Kenco Study Group. Low-grade albuminuria and incidence of cardiovascular disease and all-cause mortality in nondiabetic and normotensive individuals. J Hypertens 2016; 34:506–512; discussion S12.

30. Stühnwer CD, Gall MA, Twisk JW, Knudsen E, Emeis JJ, Parving HH. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. Diabetes 2002; 51:1157–1165.

31. Djouris L, Kocher J, Hunt SC, North KE, Gu CC, Tang W, Arnett DK, Devereux RB. Relation of albuminuria to left ventricular mass (from the HyperGEN Study). Am J Cardiol 2008; 101:212–216.

32. Jackson CE, Solomon SD, Gerstein HC, Zetterstrand S, Olofsson B, Michelson EL, Granger CB, Swedberg K, Pfeffer MA, Yusuf S, McMurray JJ; CHARM Investigators and Committees. Albuminuria in chronic heart failure: prevalence and prognostic importance. Lancet 2009; 374:543–550.

33. Bakker SJ, Ganevoort RT, Stuveling EM, Gans RO, de Zeeuw D. Microalbuminuria and C-reactive protein: similar messengers of cardiovascular risk? Curr Hypertens Rep 2005; 7:379–384.

34. Kramer H, Jacobs DR Jr, Bild D, Post W, Saad MF, Detrano R, Tracy R, Cooper R, Liu K. Urinary albumin excretion and subclinical cardiovascular disease. The Multi-Ethnic Study of Atherosclerosis. Hypertension 2005; 46:38–43.

35. DeFilippis AP, Kramer HJ, Katz R, Wong ND, Bertoni AG, Carr J, Budoff MJ, Blumenthal RS, Nasir K. Association between coronary artery calcification progression and microalbuminuria: the MESA study. JACC Cardiovasc Imaging 2010; 3:595–604.