Association Between High and Very High Albuminuria and Nighttime Blood Pressure: Influence of Diabetes and Chronic Kidney Disease

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Diabetes Care 2016;39:1729–1737 | DOI: 10.2337/dc16-0748

OBJECTIVE

Nighttime blood pressure (BP) and albuminuria are two important and independent predictors of cardiovascular morbidity and mortality. Here, we examined the quantitative differences in nighttime systolic BP (SBP) across albuminuria levels in patients with and without diabetes and chronic kidney disease.

RESEARCH DESIGN AND METHODS

A total of 16,546 patients from the Spanish Ambulatory Blood Pressure Monitoring Registry cohort (mean age 59.6 years, 54.9% men) were analyzed. Patients were classified according to estimated glomerular filtration rate (eGFR), as ≥60 or <60 mL/min/1.73 m^2 (low eGFR), and urine albumin-to-creatinine ratio, as normoalbuminuria (<30 mg/g), high albuminuria (30–300 mg/g), or very high albuminuria (>300 mg/g). Office and 24-h BP were determined with standardized methods and conditions.

RESULTS

High albuminuria was associated with a statistically significant and clinically substantial higher nighttime SBP (6.8 mmHg higher than with normoalbuminuria, $P < 0.001$). This association was particularly striking at very high albuminuria among patients with diabetes and low eGFR (16.5 mmHg, $P < 0.001$). Generalized linear models showed that after full adjustment for demographic, lifestyles, and clinical characteristics, nighttime SBP was 4.8 mmHg higher in patients with high albuminuria than in those with normoalbuminuria ($P < 0.001$), and patients with very high albuminuria had a 6.1 mmHg greater nighttime SBP than those with high albuminuria ($P < 0.001$). These differences were 3.8 and 3.1 mmHg, respectively, among patients without diabetes, and 6.5 and 8 mmHg among patients with diabetes ($P < 0.001$).

CONCLUSIONS

Albuminuria in hypertensive patients is accompanied by quantitatively striking higher nighttime SBP, particularly in those with diabetes with very high albuminuria and low eGFR.

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Received 5 April 2016 and accepted 20 July 2016.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-0748/-/DC1.

Hypertension is the worldwide cause of death as repeatedly shown by the Global Burden of Disease Study in 2002 (1) and 2012 (2). It is also known that nighttime blood pressure (BP) is a stronger predictor of cardiovascular disease (CVD) than daytime BP (3–6). Moreover, it is well established that elevated BP is the most important risk factor for progression of kidney injury toward end-stage renal disease (ESRD) (7,8). Albuminuria (i.e., an increased amount of albumin in the urine) is the most common marker of renal injury in patients with chronic kidney disease (CKD) and can be present with preserved or diminished estimated glomerular filtration rate (eGFR) (9). Importantly, several lines of evidence suggest that albuminuria is associated not only with CKD progression, but also with the development of CVD and ESRD (10–12).

Several studies (13–17) have associated the circadian rhythm of BP to proteinuria/albuminuria in patients with diabetes and/or CKD. Additionally, previous data from our group showed that high albuminuria (30–300 mg/g creatinine) is associated with nighttime systolic BP (SBP) in treated and untreated patients with hypertension and in those with resistant hypertension (18,19). These findings prompted us to analyze the relationship between nighttime BP and very high albuminuria (>300 mg/g creatinine) in patients with hypertension accompanied by CKD or diabetes drawn from the large Spanish Ambulatory Blood Pressure Monitoring (ABPM) Registry (20). We were particularly interested in quantifying the difference in nocturnal BP across albuminuria groups in patients with and without diabetes or CKD, which, to the best of our knowledge, has not been specifically addressed.

RESEARCH DESIGN AND METHODS

Study Population

The Spanish ABPM Registry was initiated to promote the use of ABPM, mostly in primary health care. Details of the Registry characteristics have been reported elsewhere (20). Briefly, physicians and nurses from a selected group of primary care centers and specialized units received specific training in the technique of ABPM and how to use a purpose-built Internet-based platform that receives ABPM registries and relevant clinical information. The general indications for ABPM according to the European Society of Hypertension Guidelines for BP measurement were used (21–23), and included suspected white-coat hypertension, resistant hypertension, assessment of dipping status, assessment of drug treatment efficacy, labile or borderline hypertension, untreated hypertension, and high-risk hypertension. The protocol was approved by various ethics committees of the participating centers in Spain. All patients gave informed consent before ABPM recording. All ABPM reports obtained in real-time, along with corresponding medical information, are uploaded in the Internet-based platform and stored in an external database.

The current study is a cross-sectional analysis of 16,546 patients included in the Registry from December 2009 to December 2014, with valid ABPM readings and complete information for the determination of albuminuria, diabetes, and CKD status, as described below. Every patient underwent the same examinations as any hypertensive patient entering a primary care center (20).

Measurements and Definitions

Office BP was measured twice with calibrated mercury sphygmomanometers or validated oscillometric devices available at the study centers with adequate cuff size, according to European Society of Hypertension/European Society of Cardiology recommendations (21). ABPM was performed after the clinic visit using a validated SpaceLabs 90207 device. The monitor recorded BP at 20-min intervals for the 24-h period. Recordings were performed preferentially on working days, and the patients maintained their usual activities. Valid measurements were those fulfilling ≥80% successful recordings, at one or more valid measurement/hour, and ≥24-h duration. Daytime and nighttime periods were defined individually according to patients' self-reported data on going-to-bed and getting-up times. Hypertension was defined as office SBP/diastolic BP (DBP) ≥140/90 mmHg or current treatment with antihypertensive drugs. Hypertension control was defined for office values as <140/90 mmHg, control of ambulatory BP was defined as mean 24-h BP <130/80 mmHg, and daytime and nighttime BP control as values <135/85 and <120/70 mmHg, respectively (21). Dipping status was defined according to international guidelines (21). Nondipper (or reduced dipper) was defined as the finding of a nocturnal BP fall of <10% of daytime values, and riser (or reverse dipper) was defined as a nocturnal BP rise.

The eGFR value was estimated from serum creatinine levels with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (24). Serum creatinine was measured at local sites and multiplied by 0.95 because it was not standardized to isotope dilution mass spectrometry (25). Urinary albumin excretion was measured at local laboratories by turbidimetry according to current recommended standards and was reported as the albumin-to-creatinine ratio in milligrams per gram creatinine. Two morning urine samples were obtained from every patient, and the average of the two was considered as the value of albuminuria. Laboratory data were obtained within 2 months of the index visit. Patients were initially classified according to eGFR as ≥60 or <60 mL/min/1.73 m^2 (low eGFR), and then according to urine albumin-to-creatinine ratio as microalbuminuria or high albuminuria (30–300 mg/g), and macroalbuminuria or very high albuminuria (>300 mg/g) following Kidney Disease Improving Global Outcomes (26).

Additional information based on interviews and the physical examination of patients at the time of the visit and on data from clinical records was defined and measured in accordance with consensus guidelines of the European Society of Hypertension/European Society of Cardiology in 2007 (22) and 2013 (21), and included the following: age, sex, weight, height, BMI, abdominal circumference, smoking, dyslipidemia, diabetes (defined based on known history of diabetes, use of antidiabetic drugs, or fasting glucose values >126 mg/mL) (27), family history of premature CVD (<55 years of age in men or <65 years of age in women), and associated clinical conditions (including a documented presence of coronary heart disease, cerebrovascular disease, or heart failure). Stratification of the cardiovascular risk of patients was performed following international guidelines (21,22), which classify the 10-year risk of cardiovascular mortality as low risk (<1%),

moderate risk (1–4%), high risk (5–10%), and very high risk (>10%).

Statistical Methods

Differences in sociodemographic and clinical characteristics between albuminuria groups were evaluated by ANOVA for continuous variables and χ^2 test for categorical variables. In particular, we calculated and tested the differences in nighttime and daytime BP among the three albuminuria groups (normoalbuminuria, microalbuminuria, and macroalbuminuria), in the total sample and in the two eGFR-based subgroups. Since of all BP variables, only nighttime SBP is independently associated with high and very high albuminuria, and this variable was the objective of the current study, we focused on nocturnal SBP for further analyses. We also calculated the percentage of SBP circadian patterns (dippers, nondippers, and risers), and the night-to-day SBP ratio according to albuminuria and eGFR groups and diabetes status.

A generalized linear model of the association between nighttime SBP (main variable of interest) and albuminuria (three groups) was built adjusting for age (continuous), sex, BMI (continuous), waist circumference (continuous), smoking status (current, ex-smoker, never), diabetes (yes/no), blood glucose levels, dyslipidemia (yes/no), CVD (yes/no), antihypertensive drug treatment (yes/no), eGFR (continuous), nighttime DBP (continuous), daytime SBP (continuous), daytime DBP (continuous), clinic SBP (continuous), and clinic DBP (continuous). Separate adjusted models were also built for patients with and without diabetes. As a sensitivity analysis, we performed more parsimonious models, excluding adjustment for waist circumference, diabetes status, and clinic BP, thus dealing with possible collinearity among some covariates. Also, these parsimonious models were analyzed separately according to diabetes status. P values <0.05 were considered to be statistically significant. Analyses were performed using SPSS version 17 (IBM, Armonk, NY).

RESULTS

Baseline Characteristics

A total of 16,546 patients (mean age 59.6 years, 54.9% males) were included in this analysis. Most of them (93%) had hypertension. The mean clinic SBP/DBP was 149.6/87.0 mmHg, and mean 24-h SBP/DBP was 129.3/76.1 mmHg. SBP, but not DBP, was significantly higher among patients with albuminuria than in patients with normoalbuminuria ($P < 0.001$). Some 25.3% of the population had diabetes. As presented in Table 1, 84% had normoalbuminuria, 13.7% had high albuminuria (30–300 mg/g), and 2.4% had very high albuminuria (>300 mg/g). Patients with high albuminuria were characterized by significantly older age ($P < 0.001$), and higher BMI ($P < 0.001$) and waist circumference ($P < 0.001$), but these differences were not clinically meaningful. These differences were more marked in patients with very high albuminuria than in patients with normoalbuminuria and high albuminuria. The presence of albuminuria was accompanied by a significantly higher prevalence of cardiovascular risk factors and high/very high cardiovascular risk ($P < 0.001$), with the exception of family history of early CVD. Serum glucose, creatinine, triglyceride, and LDL cholesterol values were significantly higher when albuminuria was elevated ($P < 0.001$), but generally is of little clinical meaning. eGFR measured by CKD-EPI was significantly lower when albuminuria was present, with >40% of patients with high albuminuria and >65% of those with very high albuminuria presenting eGFR <60 mL/min/1.73 m^2.

As can also be seen in Table 1, the percentage of patients with office BP under control was lower when albuminuria was present (P = 0.002), and the same was true for ABPM data during daytime, nighttime, and 24 h ($P < 0.001$). The percentage of the dipper pattern on ABPM was significantly lower, and that of the nondipper pattern was higher in patients with albuminuria ($P < 0.001$). The percentage of risers increased significantly from normoalbuminuria to very high albuminuria ($P < 0.001$). Finally, Table 1 presents the different antihypertensive medications received by the patients. Both the number of drugs and the percentage of most antihypertensive classes were higher in patients with albuminuria, and the use of renoprotective agents (i.e., blockers of the renin-angiotensin system) in patients with albuminuria was slightly >60%.

ABPM Findings According to Presence of CKD or Diabetes

Table 2 shows nighttime and daytime SBP and DBP values in the whole group according to eGFR category and albuminuria status. A significant increase for nighttime and daytime SBP across progressive albuminuria groups (from normoalbuminuria to high and very high albuminuria) in all subjects and eGFR categories was noted (all $P <$ 0.001). In the total sample, DBP showed a variable pattern with significant, albeit clinically minor, increases during the night and a decrease during the day across the albuminuria groups. Only nighttime DBP changes reached statistical significance in eGFR subgroups ($P < 0.001$). In addition, when compared with the normoalbuminuria group, the mean increment in nighttime SBP among patients with very high albuminuria was 14.3 mmHg in the whole group, 12.0 mmHg in the group with eGFR ≥60 mL/min/1.73 m^2, and 13.9 mmHg in the group with eGFR <60 mL/min/1.73 m^2. This compared with 8.9, 7.0, and 10.0 mmHg increments in daytime SBP in the three groups, respectively. Among the untreated and treated patients, the pattern of nighttime and daytime BP values across albuminuria and eGFR groups was similar in magnitude and direction to that in the whole sample, but in general statistical significance was only reached for SBP values (Supplementary Table 1).

Data for patients with and without diabetes are presented in Table 3. As depicted in Table 3, a significant increase for nighttime and daytime SBP across progressive albuminuria groups was observed in patients without diabetes ($P <$ 0.001). In the whole group, the mean increases in nighttime SBP were 8.9 and 5.0 mmHg in patients with very high or high albuminuria, respectively, compared with patients with normoalbuminuria. In the group with eGFR ≥60 mL/min/1.73 m^2, the increases were 5.7 and 3.8 mmHg, respectively, and in the group with eGFR <60 mL/min/1.73 m^2, they were 8.8 and 5.8 mmHg, respectively. For daytime SBP, the differences were smaller, as noted in Table 3. The data for patients with diabetes show a similar behavior for nighttime and daytime SBP, with significant increases (Table 3; $P < 0.001$), but DBP increased only slightly during daytime in patients with CKD stages 3–5. The mean increment in nighttime SBP for the whole group of patients with diabetes was 16.0 mmHg for patients with very high

Table 1—Sample characteristics according to albuminuria status

Variable	Total (*N* = 16,546)	Normoalbuminuria <30 mg/g (*n* = 13,892)	High albuminuria 30–300 mg/g (*n* = 2,259)	Very high albuminuria ≥300 mg/g (*n* = 395)	*P* value
Age (years)	59.6 ± 13.6	59.0 ± 13.6	62.3 ± 13.3	64.5 ± 12.5	<0.001
≥60 years	8,819 (53.3)	7,145 (51.4)	1,399 (61.9)	275 (69.6)	<0.001
BP					
Office BP <140/90 mmHg	3,818 (23.1)	3,258 (23.5)	494 (21.9)	66 (16.7)	0.002
24-h ABPM <130/80 mmHg	7,464 (45.1)	6,495 (46.8)	864 (38.2)	105 (26.6)	<0.001
Daytime ABPM <135/85 mmHg	8,604 (52.0)	7,437 (53.5)	1,027 (45.5)	140 (35.4)	<0.001
Nighttime ABPM <120/70 mmHg	7,012 (42.4)	6,192 (44.6)	739 (32.7)	81 (20.5)	<0.001
Risk factors					
BMI (kg/m^2)	29.3 ± 4.9	29.2 ± 4.9	29.9 ± 4.9	30.2 ± 5.5	<0.001
Obesity (BMI ≥30 kg/m^2)	7,128 (43.1)	5,816 (41.9)	1,108 (49.0)	204 (51.6)	<0.001
Waist circumference (cm)					
Men	101.7 ± 10.5	101.2 ± 10.2	103.7 ± 11.3	105.4 ± 10.6	<0.001
Women	96.1 ± 12.3	95.8 ± 12.2	97.9 ± 12.4	99.1 ± 13.1	<0.001
Abdominal obesity	8,640 (52.2)	7,127 (51.3)	1,280 (56.7)	233 (59.0)	<0.001
Family history of premature CVD	2,695 (16.3)	2,314 (16.7)	334 (14.8)	47 (11.9)	0.005
Diabetes	4,185 (25.3)	3,047 (21.9)	920 (40.7)	218 (55.2)	<0.001
Dyslipidemia	7,788 (47.1)	6,252 (45.0)	1,259 (55.7)	277 (70.1)	<0.001
Cardiovascular disease	2,055 (12.4)	1,425 (10.3)	472 (20.9)	158 (40.0)	<0.001
Cardiovascular risk stratification					
Low to moderate	7,372 (44.6)	6,739 (48.5)	589 (26.1)	44 (11.1)	<0.001
High	5,440 (32.9)	4,379 (31.5)	925 (40.9)	136 (34.4)	<0.001
Very high	3,347 (20.2)	2,415 (17.4)	722 (32.0)	210 (53.2)	
Circadian profile					
Dipper	7,815 (47.2)	6,849 (49.3)	852 (37.7)	114 (28.9)	<0.001
Nondipper	6,509 (39.3)	5,357 (38.6)	979 (43.3)	173 (43.8)	<0.001
Riser	2,222 (13.4)	1,686 (12.1)	428 (18.9)	108 (27.3)	<0.001
Analytical values					
Triglycerides (mmol/L)	132.2 ± 72.6	128.8 ± 68.6	148.4 ± 88.1	161.3 ± 90.1	<0.001
LDL (mmol/L)	127.3 ± 74.6	125.0 ± 74.6	140.4 ± 74.0	136.1 ± 70.1	<0.001
Glucose (mg/dL)	108.1 ± 31.5	105.9 ± 29.0	118.4 ± 39.1	124.9 ± 47.5	<0.001
Creatinine (μmol/L)	0.94 ± 0.36	0.91 ± 0.29	1.04 ± 0.42	1.45 ± 1.10	<0.001
eGFR by CKD-EPI (mL/min/1.73 m^2)	75.8 ± 23.7	77.5 ± 22.5	69.1 ± 26.8	52.6 ± 27.1	<0.001
eGFR by CKD-EPI <60 (mL/min/1.73 m^2)	4,870 (29.4)	3,622 (26.1)	980 (43.4)	268 (67.8)	<0.001
Antihypertensive drugs					
Patients treated	10,906 (65.9)	8,799 (63.3)	1,780 (78.8)	328 (83.0)	<0.001
Number of drugs in treated	2.2 ± 1.1	2.1 ± 1.1	2.5 ± 1.2	2.8 ± 1.4	<0.001
Diuretics	3,747 (34.4)	2,998 (34.1)	626 (35.2)	123 (37.5)	0.143
β-Blockers	1,817 (16.7)	1,456 (16.5)	313 (17.6)	48 (14.6)	0.865
Calcium channel blockers (dihydropyridines)	2,144 (19.7)	1,609 (18.3)	432 (24.3)	103 (31.4)	<0.001
Calcium channel blockers (nondihydropyridines)	343 (3.1)	265 (3.0)	64 (3.6)	14 (4.3)	0.081
ACE inhibitors	2,260 (20.7)	1,841 (20.9)	350 (19.7)	69 (21.0)	0.413
ARBs	3,861 (35.4)	2,986 (33.9)	737 (41.4)	138 (42.1)	<0.001
Direct renin inhibitors	71 (0.7)	44 (0.5)	20 (1.1)	7 (2.1)	<0.001
α-Blockers	612 (5.6)	401 (4.6)	166 (9.3)	45 (13.7)	<0.001

Data are given as the mean ± SD or *n* (%). ARB, angiotensin receptor blocker.

albuminuria versus normoalbuminuria. In the group with eGFR ≥60 mL/min/1.73 m^2, the increase was 13.5 mmHg, and in the group with eGFR <60 mL/min/1.73 m^2, it was 16.5 mmHg. For daytime SBP, the differences were 11.0, 8.9, and 12.5 mmHg, respectively (Table 3). Overall, the increasing trend in nocturnal SBP across albuminuria groups was significantly higher in individuals with diabetes than in those without diabetes, in total and in both eGFR groups ($P < 0.001$). In addition, the proportion of nondipper and riser patients and the night-to-day BP ratio generally increased across albuminuria groups, although more notably in patients with low eGFR or diabetes (all $P < 0.001$) (Tables 2 and 3 and Fig. 1).

Multivariable Analysis of Albuminuria With Nighttime BP

The generalized linear model showed that after full adjustment for demographic characteristics, lifestyles, and clinic variables (including diabetes, blood glucose level, CVD, eGFR, BP medication, and clinic and daytime BP), nighttime SBP was 4.8 mmHg higher in patients with high albuminuria than in those with normoalbuminuria, and patients with very high albuminuria had a 6.1 mmHg greater nighttime SBP than those with high albuminuria (Table 4). These differences were 3.8 and 3.1 mmHg, respectively, among patients without diabetes, and

Table 2—Nighttime and daytime BP values and dipping proportion according to eGFR and albuminuria status

	Total (N = 16,546)				eGFR ≥60 mL/min/1.73 m^2 (n = 11,676)				eGFR <60 mL/min/1.73 m^2 (CKD Stage 3–5) (n = 4,870)			
	Normoalbuminuria <30 mg/g	High albuminuria 30–300 mg/g	Very high albuminuria ≥300 mg/g		Normoalbuminuria <30 mg/g	High albuminuria 30–300 mg/g	Very high albuminuria ≥300 mg/g		Normoalbuminuria <30 mg/g	High albuminuria 30–300 mg/g	Very high albuminuria ≥300 mg/g	
n (%)	13,892 (84.0)	2,259 (13.7)	395 (2.4)	P value	10,270 (88.0)	1,279 (11.0)	127 (1.1)	P value	3,622 (74.4)	980 (20.1)	268 (5.5)	P value
Nighttime SBP, mmHg	119.1 ± 15.0	125.9 ± 18.2	133.4 ± 19.9	<0.001	118.5 ± 14.7	124.6 ± 17.8	130.5 ± 20.1	<0.001	120.9 ± 15.6	127.5 ± 18.7	134.8 ± 19.7	<0.001
Nighttime DBP, mmHg	67.9 ± 10.1	69.9 ± 11.2	70.0 ± 11.0	<0.001	68.3 ± 9.9	69.8 ± 10.8	68.5 ± 10.0	<0.001	67.0 ± 10.4	67.8 ± 11.7	69.5 ± 11.0	<0.001
Daytime SBP, mmHg	131.6 ± 13.4	135.7 ± 16.2	140.5 ± 17.5	<0.001	131.7 ± 13.2	135.3 ± 15.6	138.7 ± 15.5	<0.001	131.4 ± 14.0	136.2 ± 16.9	141.4 ± 18.3	<0.001
Daytime DBP, mmHg	79.1 ± 10.6	78.2 ± 11.5	77.6 ± 11.1	<0.001	80.0 ± 10.3	79.9 ± 11.1	80.1 ± 10.6	0.899	76.6 ± 10.9	76.0 ± 11.6	76.4 ± 11.2	0.384
Dippers, %	49.3	37.7	28.9	<0.001	51.9	41.4	39.4	<0.001	42.0	32.9	23.9	<0.001
Nondippers, %	38.6	43.3	43.8	<0.001	37.9	42.8	37.8	<0.001	40.3	44.1	46.6	<0.001
Risers, %	12.1	18.9	27.3	<0.001	10.2	15.8	22.8	<0.001	17.7	23.1	29.5	<0.001

Data are given as n (%) for categorical variables and mean ± SD for continuous variables.

6.5 and 8 mmHg among patients with diabetes ($P < 0.001$) (Table 4). Multivariable models for daytime BP failed to attain statistical significance (data not shown). When the parsimonious model was used, the aforementioned general pattern was quite similar (Table 4).

CONCLUSIONS

These data demonstrate that the presence of high or very high albuminuria is associated with significant and substantial increases in nighttime SBP, irrespective of the level of eGFR and the existence of diabetes. In particular, nighttime SBP is significantly and substantially higher in the presence of very high albuminuria in patients with CKD and diabetes (16.5 mmHg) when compared with patients with diabetes who have normoalbuminuria. Even after full adjustment for demographic, lifestyle, and clinic covariates (including eGFR, glucose levels, BP medication, and clinic and daytime BP), nighttime SBP remained as a significant, independent, and clinically substantial factor associated with albuminuria, amounting to 14.5 mmHg higher pressure among very high albuminuria patients with diabetes than among their normoalbuminuria counterparts. Daytime SBP was also significantly elevated in patients with albuminuria and particularly in those with diabetes at a lower, albeit still marked, increase (up to 12.5 mmHg). Indeed, of all BP variables, only nighttime SBP was independently associated with increased likelihood of high and very high albuminuria. A similar pattern for the increase in nighttime and daytime SBP with albuminuria status was observed in patients without diabetes, although the differences were much smaller. The presence or absence of antihypertensive treatment did not contribute to change the BP pattern described here. Consistent with our results, several previous studies described an association between albuminuria and circadian ambulatory BP in patients with diabetes or CKD (13–17). However, unlike our study, most of the previous studies had relatively small sample sizes (a few hundred patients), and, more importantly, they focused on nighttime nondipping or isolated nocturnal hypertension, whereas we used nighttime BP as a continuous variable, allowing for the quantification of nocturnal BP differences across albuminuria groups. In addition, we described the existence of a correlation between high albuminuria and nocturnal SBP levels in previous works (18,19), but these relationships were studied specifically in patients with hypertension and in those with resistant hypertension without specific consideration of diabetes or CKD, and were not focused on the quantitative differences in BP according to renal and diabetes status applied in the current study. Thus, to our knowledge, this is the first description of a quantitatively very relevant higher nighttime SBP in patients with high and very high levels of albuminuria compared with normoalbuminuria, particularly in diabetic CKD.

What is the risk of elevated nighttime SBP? Elevated nighttime BP levels are accompanied by the highest cardiovascular risk compared with the elevation of any ABPM component (3–6,28), and the existence of a nondipping status is also characterized by the worst prognosis (29–31). In a previous study (19), we found that the worst profile related to nighttime BP was present in patients exhibiting simultaneously nondipping and nocturnal hypertension. This is also true for BP risers, who present the highest levels of nighttime BP and consequently the highest risk (23).

We also found that nondippers and risers were more frequent in patients with more advanced renal disease and that nocturnal hypertension was associated with high albuminuria. The different behavior of daytime and nighttime DBP compared with SBP indicates the presence of an increase in pulse pressure (the difference between SBP and DBP). In the crosstalk between large and small arteries, this situation allows the transmission of a pulsatile pressure wave facilitating an enhancement of small-vessel damage at the heart, brain, and kidney levels. In the kidney, this event may facilitate the development of albuminuria (32). In this study, we analyzed in a comprehensive and detailed manner the association between nocturnal and daytime ambulatory SBP and DBP on the one hand and albuminuria on the other hand. This was conducted in a large sample of patients with CKD with or without diabetes along their progressive stage.

What is the risk of albuminuria? High, and particularly very high, albuminuria

Table 3—Nighttime and daytime BP values and dipping proportions according to eGFR and albuminuria status in patients without diabetes and in patients with diabetes

	Total				eGFR ≥60 mL/min/1.73 m^2				eGFR <60 mL/min/1.73 m^2 (CKD Stages 3–5)			
	Normoalbuminuria <30 mg/g	High albuminuria 30–300 mg/g	Very high albuminuria ≥300 mg/g	*P* value	Normoalbuminuria <30 mg/g	High albuminuria 30–300 mg/g	Very high albuminuria ≥300 mg/g	*P* value	Normoalbuminuria <30 mg/g	High albuminuria 30–300 mg/g	Very high albuminuria ≥300 mg/g	*P* value
Patients without diabetes												
N	12,361				8,997				3,364			
n (%)	10,845 (87.7)	1,339 (10.8)	177 (1.4)		8,170 (90.8)	776 (8.6)	51 (0.6)		2,675 (79.5)	563 (16.7)	126 (3.7)	
Nighttime SBP, mmHg	118.2 ± 14.6	123.2 ± 17.8	127.1 ± 18.8	<0.001	117.6 ± 14.3	121.4 ± 16.8	123.3 ± 19.0	<0.001	119.9 ± 15.3	125.7 ± 18.8	128.7 ± 18.5	<0.001
Nighttime DBP, mmHg	68.4 ± 10.1	69.8 ± 11.4	70.2 ± 11.5	<0.001	68.7 ± 9.9	70.3 ± 10.7	72.9 ± 9.8	<0.001	67.7 ± 10.5	69.2 ± 12.3	69.1 ± 12.0	<0.001
Daytime SBP, mmHg	131.3 ± 13.3	134.1 ± 15.9	136.5 ± 15.0	<0.001	131.3 ± 13.0	133.5 ± 15.1	133.9 ± 12.3	<0.001	131.1 ± 13.9	135.0 ± 17.0	137.6 ± 15.9	<0.001
Daytime DBP, mmHg	80.1 ± 10.5	80.1 ± 11.5	79.1 ± 11.8	0.343	80.9 ± 10.2	81.5 ± 11.9	83.5 ± 10.2	0.306	77.7 ± 10.9	78.0 ± 11.9	77.4 ± 11.9	0.393
Dippers, %	51.8	42.0	35.0	0.001	54.1	46.9	47.1	<0.001	44.7	35.2	30.2	<0.001
Nondippers, %	37.5	42.6	45.2	0.001	36.9	41.6	37.3	<0.001	39.5	43.9	48.4	<0.001
Risers, %	10.7	15.5	19.8	<0.001	9.0	11.5	15.7	<0.001	15.8	21.0	21.4	<0.001
Patients with diabetes												
N	4,185				2,679				1,506			
N (%)	3,047 (72.8)	920 (22.0)	218 (5.2)		2,100 (78.4)	503 (18.8)	76 (2.8)		947 (62.9)	417 (27.7)	142 (9.4)	
Nighttime SBP, mmHg	122.5 ± 15.9	129.9 ± 18.1	138.5 ± 19.4	<0.001	121.8 ± 15.7	129.7 ± 18.1	135.3 ± 19.5	<0.001	123.7 ± 16.1	130.1 ± 18.2	140.2 ± 19.2	<0.001
Nighttime DBP, mmHg	66.2 ± 9.8	67.6 ± 10.7	69.9 ± 10.5	<0.001	66.8 ± 9.7	69.0 ± 10.8	70.1 ± 11.4	<0.001	65.1 ± 9.9	66.0 ± 10.5	69.7 ± 10.1	<0.001
Daytime SBP, mmHg	132.8 ± 13.9	138.0 ± 16.3	143.8 ± 18.7	<0.001	133.1 ± 13.9	138.1 ± 16.0	142.0 ± 16.6	<0.001	132.3 ± 14.0	137.9 ± 16.6	144.8 ± 19.8	<0.001
Daytime DBP, mmHg	75.4 ± 10.1	75.5 ± 10.9	76.3 ± 10.4	0.446	76.4 ± 10.0	77.3 ± 10.9	77.9 ± 10.2	0.142	73.2 ± 10.0	73.3 ± 10.6	75.5 ± 10.5	0.040
Dippers, %	40.4	31.5	23.9	<0.001	43.2	33.0	34.2	<0.001	34.3	29.7	18.3	<0.001
Nondippers, %	42.2	44.5	42.7	<0.001	42.0	44.5	38.2	<0.001	42.7	44.4	45.1	<0.001
Risers, %	17.3	24.0	33.5	<0.001	14.8	22.5	27.6	<0.001	23.0	25.9	36.6	<0.001

Data are given as *n* (%) for categorical variables and the mean ± SD for continuous variables. Albuminuria is expressed as mg/g.

is a predictor of CVD events and death, as well as of the progression of CKD to ESRD (10,11,33). The progression of albuminuria is observed simultaneously with a progressive decay in eGFR (34). It is well established that albuminuria and diminished eGFR are independently associated with an increased risk for CVD events and death (33,35). Many patients included in this study had both an increase in CVD risk and also an enhanced decay progression of eGFR. This enhanced risk was associated in many patients with the risk attributable to the presence of diabetes. This situation of risk can also be observed during chronic renin-angiotensin system blockade, as we previously described (36). The development of new-onset albuminuria during long-term administration of an ACE inhibitor or angiotensin receptor blocker is accompanied by an increased number of CVD events (36).

Our data suggest the presence of a higher risk in patients with diabetes who have very high albuminuria because of the elevation in nighttime and daytime SBP levels. Hence, it is possible that the simultaneous control of BP, particularly during nighttime and albuminuria, is required to attain the best protection for our patients. Nevertheless, lowering the risk of elevated daytime BP in patients with albuminuria should also be considered when treating these subjects. Clearly, intervention studies are needed to properly address these issues.

What are the consequences of these findings for the prognosis and treatment of patients with albuminuria? It is possible that if we want to improve the prognosis of albuminuria patients, we first need to control the elevated BP, particularly nighttime SBP. A progressive drop in BP estimated in the office is followed by a progressive decrease in CVD events and death, as well as in ESRD (21,37). By contrast, despite its known predictive ability, recent data (38,39) have questioned the preventive capacity of drops in albuminuria. In fact, we probably need to lower the level of albuminuria by >50%, the level at which prevention of CVD events and death can be seen (40), while lower percentage decreases in clinic SBP are accompanied by significant prevention, at least for office BP (41). Finally, these data indicate that,

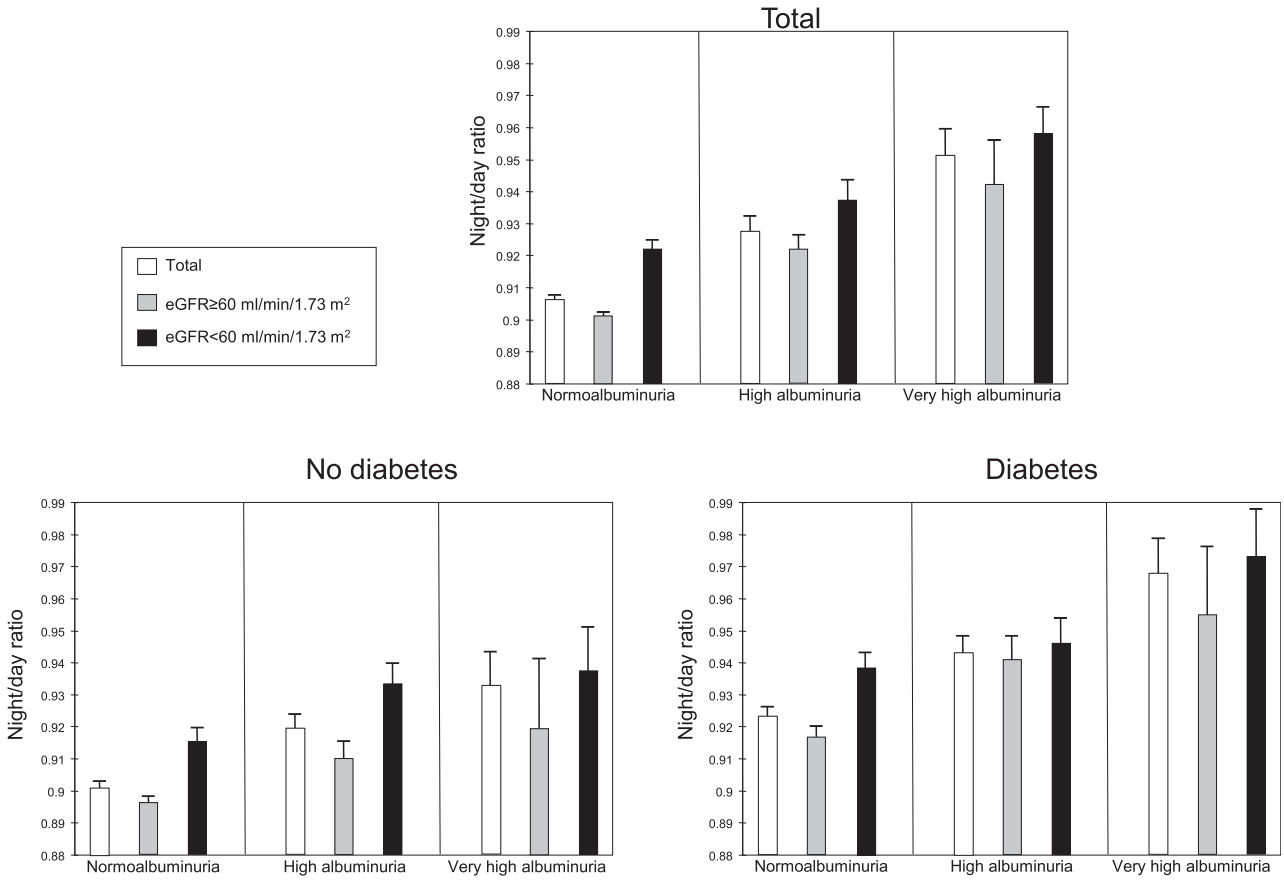

Figure 1—Night-to-day SBP ratio according to albuminuria, eGFR, and diabetes status. Bars indicate 95% CI.

in order to assess the appropriateness of nighttime BP control, ABPM performance is required in patients with albuminuria because elevated nighttime BP could be present in patients with an apparently adequate BP control in the office (42).

Our study has several limitations. There may have been some selection bias from inclusion criteria for conventional ABPM indications; nevertheless, the Spanish ABPM Registry was composed of a large nationwide population sample, providing a real-world view of clinical practice on a large scale, since physicians and patients were recruited across all the geographical communities covered by the national health care system in Spain. Also, the differences in nocturnal

Table 4—Generalized linear model of the association between nighttime SBP and albuminuria according to diabetes status

	Albuminuria groups						
	<30 mg/g		30–300 mg/g		≥300 mg/g		
	Mean	95% CI	Mean	95% CI	Mean	95% CI	*P* value
Full model							
Total							
Nighttime SBP, mmHg	119.4	119.1–119.6	124.2	123.5–124.8	130.3	128.7–131.9	<0.001
Patients without diabetes							
Nighttime SBP, mmHg	118.3	118.0–118.5	122.1	121.3–123.0	125.2	122.8–127.5	<0.001
Patients with diabetes							
Nighttime SBP, mmHg	122.5	121.9–123.1	129.0	127.9–130.1	137.0	134.7–139.3	<0.001
Parsimonious model*							
Total							
Nighttime SBP, mmHg	119.5	119.1–119.7	122.4	122.1–122.6	130.4	130.1–130.6	<0.001
Patients without diabetes							
Nighttime SBP, mmHg	118.8	118.7–118.9	122.8	122.7–122.9	126.8	126.7–126.9	<0.001
Patients with diabetes							
Nighttime SBP, mmHg	122.9	122.7–123.1	128.9	128.7–129.1	135.9	135.7–136.1	<0.001

Models were adjusted for age, sex, eGFR, BMI, waist circumference, tobacco smoking, diabetes (only for the total model), blood glucose, dyslipidemia, CVD, antihypertensive treatment, clinic SBP, clinic DBP, daytime SBP, daytime DBP, and nighttime DBP. *The parsimonious model adjusted for the same variables as the full model except for waist circumference, diabetes status, and clinic BP.

SBP that we found seem to be too high to be explained by selection bias. Another limitation is the cross-sectional analysis of data, which does not allow causal assessment of the relationship studied. However, it seems reasonable to think of microvascular damage as linking to nighttime SBP and high or very high albuminuria, but a prospective study targeting nighttime SBP would be required to fully corroborate this. Also, despite exhaustive adjustments and stratifications used, we recognize that we have no data showing the additive risk of nocturnal BP and albuminuria and eGFR. Finally, we lacked data on sleep quality and duration, which may have influenced our results. As a positive aspect of our study, we would highlight the large number of individuals enrolled, all of them from real clinical practice, which could provide helpful descriptive information.

Acknowledgments. The authors thank all participants of the Spanish Ambulatory Blood Pressure Monitoring Registry. Their names are available at www.cardiorisc.com.

Funding. Specific funding for this study analysis was obtained from FIS grants PI10/01011, PI11/02432, PI13/02321, PIE13/00045, PI14/01841, and CP15/0129; and also from Fundación Senefro, El Fondo Europeo de Desarrollo Regional, and by Cátedra Universidad Autónoma de Madrid de Epidemiología y Control del Riesgo Cardiovascular. The Spanish Ambulatory Blood Pressure Monitoring Registry was initiated and is maintained by an unrestricted grant from Lacer Laboratories, Spain, and the Spanish Society of Hypertension.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. G.R.-H., L.M.R., and J.R.B. contributed to the study concept, design, and supervision; the acquisition, analysis, and interpretation of the data; and the drafting and critical revision of the manuscript for important intellectual content. A.d.l.S., P.S., M.G., J.S., and E.V. contributed to the acquisition, analysis, and interpretation of the data and to critical revision of the manuscript for important intellectual content. J.J.d.l.C. contributed to administrative, technical, and material support for the study; to the acquisition, analysis, and interpretation of the data; and to critical revision of the manuscript for important intellectual content. L.M.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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