Diabetes Care 39.10 (2016): 1729-1737

DOI: http://dx.doi.org/10.2337/dc16-0748

Title: Association between high and very high albuminuria and nighttime blood pressure: influence of diabetes and chronic kidney disease

Authors: Gema Ruiz-Hurtado[1*], PhD; Luis M. Ruilope[1,2*], MD, PhD; Alex de la Sierra[3], MD, PhD; Pantelis Sarafidis[4], MD, PhD; Juan J. de la Cruz[2], ScD; Manuel Gorostidi[5], MD, PhD; Julián Segura[1], MD, PhD; Ernest Vinyoles[6], MD, PhD; José R. Banegas[2], MD, PhD.

[1]Hypertension Unit, Institute of Research i+12, Hospital Universitario 12 de Octubre, Madrid, Spain. [2]Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autónoma de Madrid/IdiPAZ and CIBER in Epidemiology and Public Health (CIBERESP), Madrid, Spain. [3]Department of Internal Medicine. Hospital Mutua Terrassa. University of Barcelona, Barcelona, Spain. [4]Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, Greece. [5]Department of Nephrology, Hospital Universitario Central de Asturias, RedinRen, Oviedo, Spain. [6]CAP la Mina, University of Barcelona, Barcelona, Spain

*Corresponding author: Luis M Ruilope, email: ruilope@ad-hocbox.com and Gema Ruiz-Hurtado, email: gemaruiz@h12o.es; Unidad de Hipertensión. Instituto de Investigación i+12, Hospital Universitario 12 de Octubre, Avenida de Córdoba s/n, 28041, Madrid. Phone: +34 913908764. Fax: +34 915765644.

Running title: Nighttime BP and very high albuminuria

Word count (not including references, tables and figures): 3621

Number of Tables: 4

Number of Figures: 1

Abstract

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

16,546 patients from the Spanish Ambulatory BP 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 mL/min/1.73m^2 or <60 mL/min/1.73m^2 (low eGFR), and to 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 hours 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 in 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 non-diabetic patients, and 6.5 and 8 mmHg among diabetic patients (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.

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 towards 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 have associated the circadian rhythm of BP to proteinuria/albuminuria in patients with diabetes and/or CKD (13-17). 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 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 present 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 determination of albuminuria, diabetes and CKD status, as described below. Every patient underwen the same examinations as any hypertensive patient entering a primary care centers (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-minute intervals for the 24-hour period. Recordings were performed preferentially on working days, and the patients maintained their usual activities. Valid measurements were those fulfilling ≥80% successful recordings, at ≥1 valid measurement/hour, and ≥24-hour duration. Daytime and nighttime periods were defined individually according to patients' self-reported data of going-to-bed and getting-up times. Hypertension was defined as office systolic/diastolic BP (SBP/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-hour 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 a nocturnal BP raise.

The eGFR value was estimated from serum creatinine levels with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) 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 albumin-creatinine ratio (ACR) in mg/g of creatinine. Two morning urine samples were obtained from in 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 micro or high

albuminuria (30–300 mg/g), and macro or very high albuminuria (>300 mg/g) following KDIGO (26).

Additional information based on interviews and physical examination of patients at the time of the visit and on data from clinical records was defined and measured in accordance with consensus European Society of Hypertension/European Society of Cardiology (ESH/ESC) 2007(22) and 2013 (21) guidelines, and included the following: age, sex, weight, height, body mass index (BMI), abdominal circumference, smoking, dyslipidemia, diabetes (defined based on known history of diabetes, use of antidiabetic drugs or fasting glucose values above 126 mg/mL (27)), family history of premature cardiovascular disease (aged <55 years in men or <65 years in women), and associated clinical conditions (including documented presence of coronary heart disease, cerebrovascular disease, or heart failure). Stratification of cardiovascular risk of patients was performed following international guidelines (21, 22), which classifies 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 analysis of variance (ANOVA) for continuous variables and χ^2 test for categorical variables. In particular, we calculated and tested differences in nighttime and daytime BP between the 3 albuminuria groups (normo, micro, and macro), in the total sample and in the 2 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 present 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/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 (3 groups) was built adjusting for age (continuous), sex, BMI (continuous), waist circumference (continuous), smoking (current, ex-smoker, never), diabetes (yes/no), blood glucose levels, dyslipidemia (yes/no), cardiovascular disease (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 of <0.05 was considered statistically significant. Analyses were performed using the SPSS version 17 (IBM, Armonk, NY) computer software program.

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%) were hypertensive. 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 albuminuric than normoalbuminuric patients (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 normo 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, triglycerides and LDL cholesterol values were significantly higher when albuminuria was elevated (P<0.001), but generally of little clinical meaning. eGFR measured by CKD-EPI was significantly lower when albuminuria was present, with more than 40% of patients with high albuminuria and more than 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 hours (P<0.001). The percentage of dipper pattern on ABPM was significantly lower and that of nondipper higher in albuminuric patients (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 albuminuric patients, and the use of renoprotective agents (i.e. blockers of the renin-angiotensin-system) in patients with albuminuria was slightly over 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 eGFR $\geq$60 ml/min/1.73 m^2 group, and 13.9 mmHg in the eGFR <60 ml/min/1.73 m^2 group. This compared with 8.9, 7.0, and 10.0 mmHg increments in daytime SBP in the 3 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 the table, a significant increase for nighttime and daytime SBP across progressive albuminuria groups was observed in nondiabetic patients ($P<0.001$). In the whole group the mean increase in nighttime SBP was 8.9 mmHg and 5.0 mmHg in patients with very high or high albuminuria, respectively, compared with normoalbuminuric patients. In the eGFR $\geq$60 ml/min/1.73 m^2 group the increases were 5.7 and 3.8 mmHg, respectively, and in the 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. Data for diabetes patients, and shows a similar behavior for nighttime and daytime SBP, with significant increases (Table 3; $P<0.001$), but DBP only slightly increased during daytime in CKD stage 3-5. The mean increment in nighttime SBP for the whole group of diabetic patients was 16.0 mmHg for patients with very high vs. normoalbuminuria. In the eGFR ≥60 ml/min/1.73 m^2 group, the increase was 13.5 mmHg, and in the eGFR <60 ml/min/1.73 m^2 group 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 the total and in both eGFR groups (P<0.001). In addition, the proportion of nondipper and riser patients and the night/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 Figure 1).

Multivariable analysis of albuminuria with nighttime blood pressure

The generalized linear model showed that after full adjustment for demographic characteristics, lifestyles, and clinic variables (including diabetes, blood glucose, cardiovascular disease, 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 non-diabetic patients, and 6.5 and 8 mmHg among diabetic patients (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 systolic BP, 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 normoalbuminuric diabetes patients. 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 increase in nighttime and daytime SBP with albuminuria status was observed in non-diabetic patients, 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 night-time non-dipping or isolated nocturnal hypertension, whereas we used nighttime BP as a continuous variable, allowing for 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 hypertensive and resistant hypertensive patients 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 present study. Thus, to our knowledge, this is the first description of a quantitatively very relevant higher nighttime systolic BP 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 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 as 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 pulsatile pressure wave facilitating an enhancement of small vessel

damage at the cardiac, brain and kidney level. 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, 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 is a predictor of CVD events and death as well as of the progression of CKD to ESRD (10, 11, 33). 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 mellitus. This situation of risk can also be observed during chronic renin-angiotensin system (RAS) blockade, as we previously described (36). The development of new-onset albuminuria during chronic administration of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) is accompanied by an increased number of CVD events (36).

Our data suggest the presence of a higher risk in diabetic patients with very high albuminuria because of the elevation in nighttime and daytime SBP. Hence, it is possible that 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 albuminuria patients? 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 figure of albuminuria to see a prevention in CVD events and death (40), while lower percentage decreases of clinic systolic BP are accompanied by a significant prevention, at least for office BP (41). Finally, these data indicate that, 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 performed on 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 healthcare system in Spain. Also, the differences in nocturnal SBP 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 linking 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 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. We thank all participants of the Spanish ABPM Registry. Their names are available at www.cardiorisc.com. The Spanish ABPM Registry was initiated and is maintained by an unrestricted grant from Lacer Laboratories, Spain and the Spanish Society of Hypertension.

Funding. Specific funding for this study analysis was obtained from FIS grants PI10/01011 PI11/02432, PI13/02321, PIE13/00045, PI14/01841, CP15/0129, and also from Fundación SENEFRO, Fondos FEDER, and by Cátedra UAM de Epidemiología y Control del Riesgo Cardiovascular.

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

Author Contributions. LM.R. 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. LM.R, G.R-H and JR.B: study concept, design, drafting of the manuscript and study supervision. G.R-H, LM.R., A. de la S., P.S., JJ. de la Cruz, M.G., J.S., E.V., JR.B.: acquisition, analysis, interpretation of data and critical revision of the manuscript for

important intellectual contents. JJ de la Cruz for administrative, technical or material support.

Figure Legend.

Figure 1. Systolic blood pressure night/day ratio according to albuminuria, eGFR and diabetes status. eGFR: estimated glomerular filtration rate. Bars indicate 95% confidence intervals.

References

1. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ, Group CRAC: Selected major risk factors and global and regional burden of disease. Lancet 2002;360:1347-1360

2. Lim SS, Vos T, Flaxman AD, et al: A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2224-2260

3. Staessen JA, Thijs L, Fagard R, et al: Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. JAMA 1999;282:539-546

4. Dolan E, Stanton A, Thijs L, et al: Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. Hypertension 2005;46:156-161

5. Kikuya M, Ohkubo T, Asayama K, et al: Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality: the Ohasama study. Hypertension 2005;45:240-245

6. Sega R, Facchetti R, Bombelli M, et al: Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation 2005;111:1777-1783

7. Klag MJ, Whelton PK, Randall BL, et al: Blood pressure and end-stage renal disease in men. N Engl J Med 1996;334:13-18

8. Tozawa M, Iseki K, Iseki C, Kinjo K, Ikemiya Y, Takishita S: Blood pressure predicts risk of developing end-stage renal disease in men and women. Hypertension 2003;41:1341-1345

9. Levey AS, de Jong PE, Coresh J, et al: The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011;80:17-28

10. Bakris GL, Molitch M: Microalbuminuria as a risk predictor in diabetes: the continuing saga. Diabetes Care 2014;37:867-875

11. Hallan SI, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR: Combining GFR and albuminuria to classify CKD improves prediction of ESRD. J Am Soc Nephrol 2009;20:1069-1077

12. Sarafidis PA, Bakris GL: Microalbuminuria and chronic kidney disease as risk factors for cardiovascular disease. Nephrol Dial Transplant 2006;21:2366-2374

13. Oh SW, Han SY, Han KH, et al: Morning hypertension and night non-dipping in patients with diabetes and chronic kidney disease. Hypertens Res 2015;38:889-894

14. Wang C, Zhang J, Liu X, et al: Reversed dipper blood-pressure pattern is closely related to severe renal and cardiovascular damage in patients with chronic kidney disease. PLoS One 2013;8:e55419

15. Afsar B: The relationship between self-reported nocturnal sleep duration, daytime sleepiness and 24-h urinary albumin and protein excretion in patients with newly diagnosed type 2 diabetes. Prim Care Diabetes 2013;7:39-44

16. Ohashi Y, Otani T, Tai R, et al: Associations of proteinuria, fluid volume imbalance, and body mass index with circadian ambulatory blood pressure in chronic kidney disease patients. Kidney Blood Press Res 2012;36:231-241

17. Ogedegbe G, Spruill TM, Sarpong DF, et al: Correlates of isolated nocturnal hypertension and target organ damage in a population-based cohort of African Americans: the Jackson Heart Study. Am J Hypertens 2013;26:1011-1016

18. Oliveras A, Armario P, Martell-Clarós N, Ruilope LM, de la Sierra A, Registry SSoH-RH: Urinary albumin excretion is associated with nocturnal systolic blood pressure in resistant hypertensives. Hypertension 2011;57:556-560

19. de la Sierra A, Gorostidi M, Banegas JR, Segura J, de la Cruz JJ, Ruilope LM: Nocturnal hypertension or nondipping: which is better associated with the cardiovascular risk profile? Am J Hypertens 2014;27:680-687

20. Gorostidi M, Banegas JR, de la Sierra A, Vinyoles E, Segura J, Ruilope LM: Ambulatory blood pressure monitoring in daily clinical practice - the Spanish ABPM Registry experience. Eur J Clin Invest 2016;46:92-98

21. Mancia G, Fagard R, Narkiewicz K, et al: 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

22. Mancia G, De Backer G, Dominiczak A, et al: 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. J Hypertens 2007;25:1751-1762

23. O'Brien E, Parati G, Stergiou G, et al: European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens 2013;31:1731-1768

24. Levey AS, Stevens LA, Schmid CH, et al: A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-612

25. Skali H, Uno H, Levey AS, Inker LA, Pfeffer MA, Solomon SD: Prognostic assessment of estimated glomerular filtration rate by the new Chronic Kidney Disease Epidemiology Collaboration equation in comparison with the Modification of Diet in Renal Disease Study equation. Am Heart J 2011;162:548-554

26. Group. KDIGOW: KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. Suppl. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf (2013).

27. Association AD: 2. Classification and Diagnosis of Diabetes. Diabetes Care 2016;39 Suppl 1:S13-22

28. de la Sierra A, Banegas JR, Segura J, Gorostidi M, Ruilope LM, Investigators CE: Ambulatory blood pressure monitoring and development of cardiovascular events in high-risk patients included in the Spanish ABPM registry: the CARDIORISC Event study. J Hypertens 2012;30:713-719

29. Ohkubo T, Hozawa A, Yamaguchi J, et al: Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. J Hypertens 2002;20:2183-2189

30. Brotman DJ, Davidson MB, Boumitri M, Vidt DG: Impaired diurnal blood pressure variation and all-cause mortality. Am J Hypertens 2008;21:92-97

31. de la Sierra A, Redon J, Banegas JR, et al: Prevalence and factors associated with circadian blood pressure patterns in hypertensive patients. Hypertension 2009;53:466-472

32. Laurent S, Boutouyrie P: The structural factor of hypertension: large and small artery alterations. Circ Res 2015;116:1007-1021

33. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, Matsushita K, Wen CP: Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet 2013;382:339-352

34. Segura J, Campo C, Ruilope LM: Effect of proteinuria and glomerular filtration rate on cardiovascular risk in essential hypertension. Kidney Int Suppl 2004:S45-49

35. Matsushita K, van der Velde M, Astor BC, et al: 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

36. Cerezo C, Ruilope LM, Segura J, et al: Microalbuminuria breakthrough under chronic renin-angiotensin-aldosterone system suppression. J Hypertens 2012;30:204-209

37. James PA, Oparil S, Carter BL, et al: 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-520

38. Bakris GL, Sarafidis PA, Weir MR, et al: Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. Lancet 2010;375:1173-1181

39. Parving HH, Brenner BM, McMurray JJ, et al: Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med 2012;367:2204-2213

40. Schmieder RE, Mann JF, Schumacher H, et al: Changes in albuminuria predict mortality and morbidity in patients with vascular disease. J Am Soc Nephrol 2011;22:1353-1364

41. Ninomiya T, Perkovic V, Turnbull F, et al: Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. BMJ 2013;347:f5680

42. Banegas JR, Ruilope LM, de la Sierra A, et al: High prevalence of masked uncontrolled hypertension in people with treated hypertension. Eur Heart J 2014;35:3304-3312

Table 1. Sample characteristics according to albuminuria status.

Variable	TOTAL	Normo albuminuria <30 mg/g	High albuminuria 30-300 mg/g	Very high albuminuria ≥300 mg/g	P
N	16546	13892	2259	395	
Age (years)	59.6±13.6	59.0±13.6	62.3±13.3	64.5±12.5	<0.001
≥ 60 years	8819(53.3)	7145(51.4)	1399(61.9)	275(69.6)	<0.001
Blood pressure					
Office BP <140/90 mmHg	3818(23.1)	3258(23.5)	494(21.9)	66(16.7)	0.002
24 hour-ABPM <130/80 mmHg	7464(45.1)	6495(46.8)	864(38.2)	105(26.6)	<0.001
Daytime ABPM <135/85 mmHg	8604(52.0)	7437(53.5)	1027(45.5)	140(35.4)	<0.001
Nighttime ABPM <120/70 mmHg	7012(42.4)	6192(44.6)	739(32.7)	81(20.5)	<0.001
Risk factors					
Body mass index (BMI in 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)	7128(43.1)	5816(41.9)	1108(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	8640(52.2)	7127(51.3)	1280(56.7)	233(59.0)	<0.001
Family history of premature cardiovascular disease	2695(16.3)	2314(16.7)	334(14.8)	47(11.9)	0.005
Diabetes mellitus	4185(25.3)	3047(21.9)	920(40.7)	218(55.2)	<0.001
Dyslipidemia	7788(47.1)	6252(45.0)	1259(55.7)	277(70.1)	<0.001
Cardiovacular disease	2055(12.4)	1425(10.3)	472(20.9)	158(40.0)	<0.001
Cardiovascular risk stratification					
Low-moderate	7372(44.6)	6739(48.5)	589(26.1)	44(11.1)	<0.001
High	5440(32.9)	4379(31.5)	925(40.9)	136(34.4)	<0.001
Very high	3347(20.2)	2415(17.4)	722(32.0)	210(53.2)	
Circadian profile					
Dipper	7815(47.2)	6849(49.3)	852(37.7)	114(28.9)	<0.001
Nondipper	6509(39.3)	5357(38.6)	979(43.3)	173(43.8)	<0.001
Riser	2222(13.4)	1686(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)	4870(29.4)	3622(26.1)	980(43.4)	268(67.8)	<0.001
Antihypertensive drugs					
Patients treated	10906(65.9)	8799(63.3)	1780(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	3747(34.4)	2998(34.1)	626(35.2)	123(37.5)	0.143
β-blockers	1817(16.7)	1456(16.5)	313(17.6)	48(14.6)	0.865
Calcium channel blockers (Dihydropyridines)	2144(19.7)	1609(18.3)	432(24.3)	103(31.4)	<0.001
Calcium channel blockers (non-dihydropyridines)	343(3.1)	265(3.0)	64(3.6)	14(4.3)	0.081
ACE inhibitors	2260(20.7)	1841(20.9)	350 (19.7)	69(21.0)	0.413
ARBs	3861(35.4)	2986(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 mean ± SD or n (%).

Table 2. Nighttime and daytime blood pressure values and dipping proportion according to estimated glomerular filtration rate and albuminuria status.

	Total				eGFR ≥60 ml/min/1.73 m^2				eGFR <60 ml/min/1.73 m^2 (CKD Stage3-5)			
N	16546				11676				4870			
	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 (%)	13892(84.0)	2259(13.7)	395(2.4)		10270(88.0)	1279(11.0)	127(1.1)		3622(74.4)	980(20.1)	268(5.5)	
Nighttime SBP, mmHg	119.1±15.0	125.9±18.2	133.4±19.9	P<0.001	118.5±14.7	124.6±17.8	130.5±20.1	P<0.001	120.9±15.6	127.5±18.7	134.8±19.7	P<0.001
Nighttime DBP, mmHg	67.9±10.1	69.9±11.2	70.0±11.0	P<0.001	68.3±9.9	69.8±10.8	68.5±10.0	P<0.001	67.0±10.4	67.8±11.7	69.5±11.0	P<0.001
Daytime SBP, mmHg	131.6±13.4	135.7±16.2	140.5±17.5	P<0.001	131.7±13.2	135.3±15.6	138.7±15.5	P<0.001	131.4±14.0	136.2±16.9	141.4±18.3	P<0.001
Daytime DBP, mmHg	79.1±10.6	78.2±11.5	77.6±11.1	P<0.001	80.0±10.3	79.9±11.1	80.1±10.6	P=0.899	76.6±10.9	76.0±11.6	76.4±11.2	P=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 (percentage) for categorical variables and mean ± SD for continuous variables. SBP, systolic blood pressure. DBP, diastolic blood pressure. eGFR: estimated glomerular filtration rate. CKD, chronic kidney disease.

Table 3. Nighttime and daytime blood pressure values and dipping proportions according to estimated glomerular filtration rate and albuminuria status in non-diabetic patients and in diabetic patients.

	Total				eGFR ≥60 ml/min/1.73 m^2				eGFR <60 ml/min/1.73 m^2 (CKD Stage3-5)			
	Normo-albuminuria <30 mg/g	High albuminuria 30-300 mg/g	Very high albuminuria ≥300 mg/g	P	Normo-albuminuria <30 mg/g	High albuminuria 30-300 mg/g	Very high albuminuria ≥300 mg/g	P	Normo-albuminuria <30 mg/g	High albuminuria 30-300 mg/g	Very high albuminuria ≥300 mg/g	P
Non-diabetic patients												
N		12361				8997				3364		
N (%)	10845(87.7)	1339(10.8)	177(1.4)		8170(90.8)	776(8.6)	51(0.6)		2675(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
Diabetic patients												
N		4185				2679				1506		
N (%)	3047(72.8)	920(22.0)	218(5.2)		2100(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 (percentage) for categorical variables and mean ± SD for continuous variables. Albuminuria is expressed as mg/g. SBP, systolic blood pressure. DBP, diastolic blood pressure. eGFR: estimated glomerular filtration rate. CKD, chronic kidney disease.

Table 4. Generalized linear model of the association between nighttime systolic blood pressure 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
Non diabetic patients							
Nighttime SBP, mmHg	118.3	118.0-118.5	122.1	121.3-123.0	125.2	122.8-127.5	<0.001
Diabetic patients							
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
Non diabetic patients							
Nighttime SBP, mmHg	118.8	118-7-118.9	122.8	122.7-122.9	126.8	126.7-126.9	<0.001
Diabetic patients							
Nighttime SBP, mmHg	122.9	122.7-123.1	128.9	128-7-129.1	135.9	135.7-136.1	<0.001

SBP, systolic blood pressure. 95%, 95% confidence interval. Models were adjusted for age, sex, estimated glomerular filtration rate, body mass index, waist circumference, tobacco smoking, diabetes (only for the total model), blood glucose, dyslipidemia, cardiovascular disease, antihypertensive treatment, clinic systolic BP, clinic diastolic BP, daytime systolic BP, daytime diastolic BP, and nighttime diastolic BP. The parsimonious model adjusted for the same variables as the full model except for waist circumference, diabetes status, and clinic BP.