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ORIGINAL ARTICLE

# Abnormalities in ambulatory blood pressure monitoring in hypertensive patients with diabetes

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**Our aim was to assess the ambulatory blood pressure monitoring (ABPM) characteristics or patterns in hypertensive patients with diabetes compared with non-diabetic hypertensives. We performed a cross-sectional analysis of a 68 045 patient database from the Spanish Society of Hypertension ABPM Registry, a nation-wide network of >1200 primary-care physicians performing ABPM under standardized conditions in daily practice. We identified 12 600 (18.5%) hypertensive patients with diabetes. When compared with patients without diabetes, diabetic hypertensives exhibited higher systolic blood pressure (BP) levels in every ABPM period (daytime 135.4 *vs.* 131.8, and nighttime 126.0 *vs.* 121.0 mm Hg, $P<0.001$ for both) despite they were receiving more antihypertensive drugs (mean number 1.71 *vs.* 1.23, $P<0.001$). Consequently, diabetic patients suffered from lack of control of BP more frequently than non-diabetic subjects particularly during the night (65.5% *vs.* 57.4%, $P<0.001$). Prevalence of a non-dipping BP profile (64.2% *vs.* 51.6%, $P<0.001$) was higher in diabetic patients. In the other hand, prevalence of 'white-coat' hypertension in diabetic patients was 33.0%. We conclude that there was a remarkably high prevalence of alterations in ABPM in patients with diabetes. Abnormalities in systolic BP, particularly during the night, and in circadian BP pattern could be linked with the excess of BP-related cardiovascular risk of diabetes. A wider use of ABPM in diabetic patients should be considered.**
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**Keywords:** ambulatory blood pressure monitoring; circadian profile; diabetes; hypertension control

## INTRODUCTION

Hypertension affects the majority of patients with diabetes and constitutes a major risk factor for vascular complications.[1] Ambulatory blood pressure monitoring (ABPM) provides a high-quality approach in estimating the true levels of blood pressure (BP).[2] Several population- and patient-based studies have showed the benefits of ABPM in exploring the relationship between BP and cardiovascular events.[2,3] A series of reports dealing with diabetic patients have also shown a close correlation between ambulatory BP and diabetic complications.[4,5] Evidences are available for the entire cardiorenal continuum of diabetic damage from the prediction of microalbuminuria by early changes in nocturnal BP in type 1 patients[6] to the effect of a riser pattern on mortality in patients with type 2 diabetes.[7] Nevertheless, information about the ABPM characteristics of large cohorts of diabetic hypertensives attending primary care centers is scarce. We aimed to assess such characteristics in comparison with non-diabetic hypertensives by using the Spanish Society of Hypertension ABPM Registry.

## METHODS

### The Spanish Society of Hypertension ABPM registry

The methods of the Spanish Society of Hypertension ABPM Registry have been reported previously.[8,9] Briefly, >1200 primary care physicians perform ABPM under standardized conditions. They send the registries together with corresponding clinical data through a web platform (http://www.cardiorisc.com) and receive a result report on real time. The protocol was approved by a series of Ethics Committees from different sites of Spain and patients gave an informed consent.

### Patients

Inclusion criteria were a diagnosis of hypertension, age ⩾18 years and a conventional indication for ABPM.[10] Briefly, indications for ABPM were a suspected 'white-coat' hypertension, assessment of drug treatment efficacy, assessment of dipper status, resistant hypertension and high-risk hypertension. Diagnosis of hypertension was established following the Spanish Society of Hypertension guidelines,[11] which, for diagnosis and classification purposes, adopt the 2003 recommendations of the European Society of Hypertension/European Society of Cardiology (ESH/ESC).[12] In summary, the diagnosis of

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hypertension was based on a series of BP measurements, taken on separate occasions, showing values $\geqslant$140/90 mm Hg. Exclusion criteria for entering in this study were an arm circumference above 42 cm and highly irregular arrhythmias.

### ABPM assessment

More than 900 Spacelabs 90207 devices (Spacelabs, Redmond, Washington, DC, USA) were used for 24-h ABPM. The monitors recorded BP every 20 min during the 24 h. The vast majority of registries were performed on working days and the patients were instructed to maintain their usual activities. Cuffs of large-adult size were used when arm circumference was between 35 and 42 cm. Daytime and nighttime periods were defined in each case according to the patient self-reported data of going-to-bed and waking-up hours. Quality controls were performed to exclude registries not fulfilling any of pre-specified criteria, which were (1) 24-h duration, (2) 1 BP measurement per hour at least, (3) 14 BP recordings during the activity period at least and (4) 7 BP recordings during the rest period at least.[10,13]

### Variables

Clinical information was collected via an electronic case record form. This included age, gender, weight, height, waist circumference, duration of hypertension, known cardiovascular risk factors, such as smoking habit, dyslipidemia and family history of premature cardiovascular disease at age $<$55 years in men or $<$65 years in women, data about target organ damage and previous cardiovascular events, and number and type of antihypertensive drugs if the patient was under pharmacological treatment. Definitions for variables were those of the 2003 ESH/ESC guidelines.[12] Diabetes diagnosis was performed following the American Diabetes Association criteria of having a fasting plasma glucose $\geqslant$126 mg dl$^{-1}$, a 2-h value in an oral glucose tolerance test $\geqslant$200 mg dl$^{-1}$ or a random plasma glucose concentration $\geqslant$200 mg dl$^{-1}$ when symptoms are present.[1] Office BP was recorded according the recommendations of the 2003 ESH/ESC guidelines. In summary, two BP determinations were performed in the sitting position after a 5-min resting period with a calibrated mercury sphygmomanometer or a validated automatic oscillometric device. Appropriate size of cuff (large-adult) was used when arm circumference was 35–42 cm. The reference value was the average of the two measurements.

### Definitions of control

Office BP was considered as controlled when the reference value was $<$140/90 mm Hg. Control of ambulatory BP was considered for the three conventional periods of ABPM when average BP levels were $<$135/85 mm Hg (daytime), $<$120/70 mm Hg (nighttime) and $<$130/80 mm Hg (24 h).[13] These office and daytime BP thresholds were used to establish the diagnoses of office resistant control or 'white-coat' (office BP$\geqslant$140/90 mm Hg and daytime ambulatory BP$<$135/85 mm Hg) and isolated office control or masked hypertension (office BP$<$140/90 mm Hg and daytime ambulatory BP$\geqslant$135/85 mm Hg). A parallel analysis with clinic BP$<$130/80 mm Hg and daytime ambulatory BP$<$125/75 mm Hg was also performed.

### Definitions of circadian patterns

A normal dipping pattern (dipper) was diagnosed when the reduction in the average systolic BP during the night period was $>$10% of mean systolic BP during the day. When this proportion was $>$20% the patient was classified as extreme dipper. An abnormal dipping pattern (non-dipper) was diagnosed when night average systolic BP levels were $<$10% with respect to day values. When mean night systolic BP was higher than day one the patient was classified as riser. Night-to-day ratio of systolic BP (mean nighttime systolic BP $\div$ mean daytime systolic BP) was also used to assess circadian profiles.

### Data analysis

Qualitative variables are expressed as number and percentages and quantitative variables as mean (s.d.). Differences between groups were sought using $\chi^2$ test for qualitative variables and Student's *t*-test for quantitative data. Numerical variables were adjusted for age, sex, body mass index and the presence of established cardiovascular disease by multivariate analysis of variance, and categorical variables were adjusted for the same confounding factors by multiple logistic regression. A value of $P<0.05$ was considered to indicate statistical significance. All analyses were two-tailed. The SPSS for Windows version 13.0 software (SPSS, Chicago, IL, USA) was used for statistical analysis.

## RESULTS

The basic characteristics of patients included in our database have been reported previously.[8,9] In brief, we deal with patients of 58.5 years of age, 53.1% male, with a high prevalence of overweight and obesity (45.1% and 35.8%, respectively), and of accompanying cardiovascular risk factors, but a relatively low prevalence of established cardiovascular disease.

Data from the comparison between patients with or without diabetes are shown in Table 1. Diabetic subjects were older, more frequently male, and exhibited higher prevalences of accompanying risk factors and vascular disease. Patients with diabetes were receiving a higher number of antihypertensive drugs per day.

Table 2 shows data from office BP and ABPM. Office systolic BP was higher and office diastolic BP was lower in patients with diabetes than in non-diabetic individuals. Ambulatory systolic BP levels were higher in diabetic patients with respect to that from non-diabetic subjects in every ABPM period being differences wider during the night. Consequently, lack of control of daytime BP (51.5% *vs.* 49.0%) and nighttime BP (65.5% *vs.* 57.4%) was more frequent within diabetic patients than in their counterparts.

Figure 1 shows the distribution of diabetic patients according to clinic and daytime ambulatory BP. Approximately 15% showed concordant control of office and ambulatory BP and nearly 50% showed concordant lack of control. The prevalence of office resistant control ('white-coat') was 33.0% and that of isolated office control (masked hypertension) was 4.9%. When this figure was analyzed with the other cutoff values, clinic BP 130/80 mm Hg and daytime BP 125/75 mm Hg, prevalence of concordant control, concordant lack of control, 'white-coat' and masked hypertension were 3.7%, 77.6%, 15.4% and 3.3%, respectively.

Figure 2 shows the prevalences of the circadian patterns. A non-dipping BP was observed in 64.2% of diabetic patients whereas this abnormality was present in 51.6% of their counterparts. This was mainly because of the difference in the prevalence of the riser pattern as shown in the four-category distribution of the circadian profiles, 21% of patients with diabetes suffered from a riser pattern of BP. Subanalysis of circadian profiles was performed by weight status and by the presence or absence of established cardiovascular disease. The diabetes condition conferred a worse circadian pattern independently of a body mass index $<$ or $\geqslant$30 kg m$^{-2}$ or the presence/absence of cardiovascular disease. Table 3 shows the night-to-day ratio of systolic BP for all these subgroups.

## DISCUSSION

To our knowledge this is the largest study to date evaluating ABPM in hypertensive patients with diabetes. More than 50% of these subjects had their daytime BP uncontrolled and two of three patients had nocturnal hypertension and/or a blunted circadian pattern of BP. One of five diabetic patients showed a riser profile of nocturnal BP. These abnormalities were more frequent in diabetic subjects than in their diabetes-free counterparts. On the other hand, 33% of patients with diabetes showed the so-called 'white-coat' hypertension.

Assessment of control rates of hypertension using ABPM offers a much better figure than that based in office measurements.[8] In our series, 20.3% of patients with diabetes showed clinic BP levels $<$140/90 mm Hg whereas 48.5% of patients had daytime ambulatory BP $<$135/85 mm Hg. Nevertheless, the burden of uncontrolled

**Table 1 Comparison between diabetic and non-diabetic patients. General characteristics**

| *Variable* | *Patients with diabetes* | *Patients without diabetes* | *Significance*[a] |
|---|---|---|---|
| *Basic characteristics* | | | |
| Number | 12 600 | 55 445 | |
| Age (years) | 63.8 ± 11.5 | 57.3 ± 14.1 | <0.001 |
| Male subjects (%) | 55.4 | 52.6 | <0.001 |
| Duration of hypertension (years) | 7.20 ± 8.01 | 5.57 ± 6.84 | <0.001 |
| BMI ($kg\,m^{-2}$) | 30.1 ± 4.92 | 28.6 ± 4.52 | <0.001 |
| Overweight, BMI 25 to $<30\,kg\,m^{-2}$ (%) | 40.6 | 46.2 | <0.001 |
| Obesity, BMI $\geqslant 30\,kg\,m^{-2}$ (%) | 47.0 | 33.3 | <0.001 |
| Fasting glucose ($mg\,dl^{-1}$) | 142.4 ± 43.2 | 97.2 ± 14.2 | <0.001 |
| *Accompanying risk factors*[b] | | | |
| Family with premature vascular disease (%) | 13.3 | 12.6 | 0.045 |
| Smoking (%) | 14.2 | 17.3 | <0.001 |
| Dyslipidaemia (%) | 59.3 | 33.2 | <0.001 |
| Abdominal obesity (%) | 52.0 | 39.3 | <0.001 |
| *Target organ damage*[b] | | | |
| Any manifestation of subclinical damage (%) | 25.0 | 10.9 | <0.001 |
| *Established vascular disease*[b] | | | |
| Coronary heart disease (%) | 11.3 | 4.6 | <0.001 |
| Cerebrovascular disease (%) | 6.5 | 3.4 | <0.001 |
| Congestive heart failure | 3.3 | 1.5 | <0.001 |
| Renal disease (%) | 3.8 | 1.3 | <0.001 |
| Any cardiovascular disease | 21.6 | 9.9 | <0.001 |
| *Antihypertensive treatment* | | | |
| Non-drug treatment (%) | 21.0 | 39.5 | <0.001 |
| Monotherapy (%) | 20.0 | 23.4 | <0.001 |
| Receiving a two-drug combination (%) | 25.1 | 20.2 | <0.001 |
| Receiving a three-drug combination (%) | 20.2 | 11.4 | <0.001 |
| Receiving four or more drugs (%) | 13.6 | 5.6 | <0.001 |
| Mean number of antihypertensive drugs | 1.71 ± 1.43 | 1.25 ± 1.27 | <0.001 |
| *Type of drug* | | | |
| ACE inhibitors (%) | 21.7 | 10.0 | <0.001 |
| ARBs (%) | 28.8 | 16.1 | <0.001 |
| Diuretics (%) | 40.0 | 26.5 | <0.001 |
| Calcium antagonists (%) | 26.7 | 14.7 | <0.001 |
| β-blockers (%) | 19.7 | 16.4 | <0.001 |
| α-blockers (%) | 10.4 | 4.9 | <0.001 |
| Other (%) | 1.0 | 0.5 | <0.001 |

Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin II receptor blockers; BP, blood pressure; BMI, body mass index.
Quantitative variables are expressed as mean ± s.d. Qualitative variables are expressed as percentages.
[a]Differences between groups were sought using $\chi^2$ test for qualitative variables and Student's *t*-test for quantitative data. Numerical variables were age, sex and BMI adjusted by multivariate analysis of variance, and categorical variables were age, sex and BMI adjusted by multiple logistic regression.
[b]Definitions of concomitant risk factors and established vascular diseases were that of the 2003 European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension.[12]

ambulatory hypertension was enormous. Almost 52% of diabetic patients had daytime BP $\geqslant$135/85 mm Hg and two of three cases had nighttime hypertension. When a more strict threshold of control was applied (daytime BP < 125/75 mm Hg) the figure of lack of control was >80%. We had previously observed the finding of a worse control rate during the night than day in our general sample of high-risk hypertensives.[9] Diabetic patients in our study, as in many others, showed a worse cardiovascular risk profile with respect to that observed in patients without diabetes. It has been suggested that a high night-to-day ratio of BP could be a marker of vascular damage or disease.[14] Moreover, the traditional management of hypertension with office-based measurement of BP could lead to higher control rates during the activity period. This has been related to the fact that many antihypertensive drugs do not encompass a complete 24-h period.[15]

The unfavorable control rates of ambulatory BP showed by diabetic patients with respect to those in non-diabetic subjects were observed in spite of diabetic patients were receiving more antihypertensive treatment. Vascular hypertrophy and atherosclerosis could justify the apparent paradox of receiving a more intense treatment to obtain a poorer control rate of hypertension. Premature drug treatment when BP is in the high normal range, as recommended by the guidelines for management of hypertension,[12] should improve the chances of obtaining adequate goals by primary prevention of subclinical vascular damage.

One of the main indications for ABPM is the study of the 'white-coat' phenomenon.[2,10–13] In our series the prevalence of 'white-coat' hypertension (isolated clinic hypertension in untreated patients or office resistant control when treated) was 33%. The prevalence of 'white-coat' hypertension in other studies dealing with diabetic patients ranged between 14 and 51%.[16] Disparities between studies may be related to differences concerning sampling criteria and definition of 'white-coat' hypertension.

Studies about prognosis of 'white-coat' hypertension in diabetic patients offered conflicting results. Whereas a 4-year follow-up study did not find worse outcomes within cases of 'white-coat' hypertension than in normotensive patients,[17] a cross-sectional analysis described diabetic patients with 'white-coat' hypertension as having an increased risk for diabetic retinopathy and nephropathy.[16] Differences between studies probably reflect that 'white-coat' hypertension confers lower dangers than sustained hypertension but higher risks than true normotension.

The 'white-coat' phenomenon in diabetic patients must be interpreted with caution because the majority of studies used, as we did, the standard definition of an office BP $\geqslant$140/90 mm Hg and a daytime ambulatory BP < 135/85 mm Hg. Clinic BP goal in diabetes is <130/80 mm Hg but a similar threshold for the ambulatory BP goal is lacking. Nevertheless, the 130/80-target has been recently questioned in the 2009 reappraisal of European guidelines on hypertension management.[18] With respect to ambulatory BP, those levels defined as optimal by the American Heart Association Scientific Statement about BP measurement[13] could serve as goals in diabetic patients whereas specific data are available.

Prevalence of masked hypertension was low in our series because the main inclusion criterion was a previous diagnosis of hypertension and an established indication for ABPM. Prevalence of masked hypertension in series evaluating normotensive patients with diabetes was 25–50%[19–22] or >40% in diabetic hypertensives showing adequate control of BP.[23] These studies have shown that masked hypertension conferred unfavorable outcomes, thus evaluation of ambulatory BP may be indicated in normotensive diabetic patients[21] and in hypertensive cases with controlled office BP.

**Table 2 Comparison between diabetic and non-diabetic patients. Clinic blood pressure and ambulatory blood pressure monitoring data**

| *Variable* | *Patients with diabetes (n 12 600)* | *Patients without diabetes (n 55 445)* | *Significance*[a] |
|---|---|---|---|
| Clinic systolic BP (mm Hg) | 151.0 ± 20.8 | 147.7 ± 19.0 | <0.001 |
| Clinic diastolic BP (mm Hg) | 84.4 ± 12.6 | 86.7 ± 12.4 | <0.001 |
| Daytime systolic BP (mm Hg) | 135.4 ± 15.9 | 131.8 ± 14.6 | <0.001 |
| Daytime diastolic BP (mm Hg) | 76.6 ± 10.4 | 79.0 ± 10.8 | <0.001 |
| Nighttime systolic BP (mm Hg) | 126.0 ± 18.2 | 121.0 ± 15.9 | <0.001 |
| Nighttime diastolic BP (mm Hg) | 67.4 ± 10.4 | 68.6 ± 10.4 | <0.001 |
| 24-h systolic BP (mm Hg) | 133.0 ± 15.7 | 129.0 ± 14.2 | <0.001 |
| 24-h diastolic BP (mm Hg) | 74.2 ± 9.9 | 76.3 ± 10.3 | <0.001 |
| Clinic BP ⩾ 140/90 mm Hg (%) | 79.7 | 76.7 | <0.001 |
| Mean daytime BP ⩾ 135/85 mm Hg (%) | 51.5 | 49.0 | <0.001 |
| Mean nighttime BP ⩾ 120/70 mm Hg (%) | 65.5 | 57.4 | <0.001 |
| Mean 24-h BP ⩾ 130/80 mm Hg (%) | 40.7 | 44.6 | <0.001 |

Abbreviations: BP, blood pressure; BMI, body mass index.
Quantitative variables are expressed as mean ± s.d. Qualitative variables are expressed as percentages.
[a]Differences between groups were sought using Student's *t*-test for quantitative data and $\chi^2$ test for qualitative variables. Numerical variables were age, sex, BMI and presence of cardiovascular adjusted by multivariate analysis of variance , and categorical variables were age, sex, BMI and presence of cardiovascular disease adjusted by multiple logistic regression.

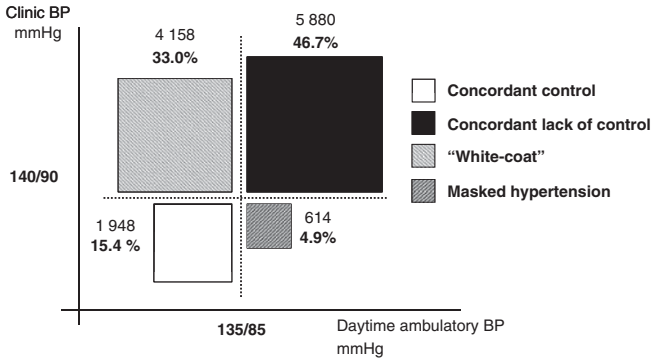


**Figure 1** Distribution of 12 600 hypertensive patients with diabetes according to clinic and ambulatory blood pressure (BP). The term 'white-coat' refers to isolated clinic hypertension in untreated patients and to office resistant control in treated patients. 'Concordant lack of control' should be interpreted as true hypertension in the case of untreated subjects and 'masked hypertension' should be interpreted as isolated office control in treated subjects.

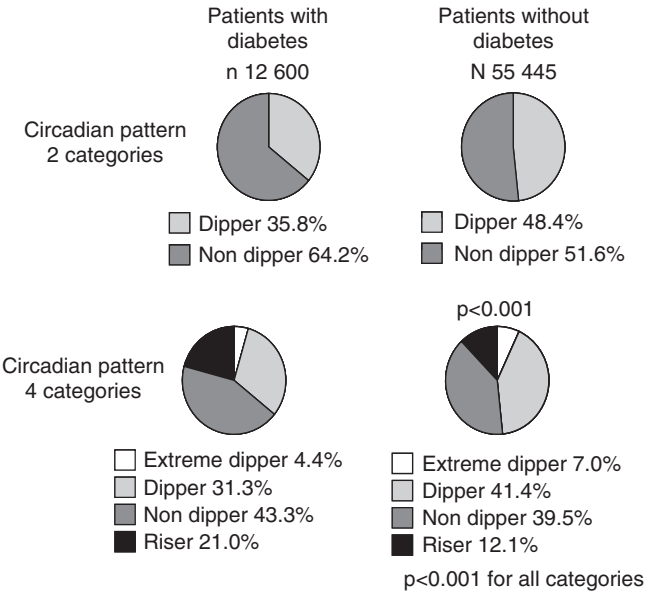


**Figure 2** Prevalence of circadian patterns of blood pressure in hypertensive patients with and without diabetes.

Prevalence of abnormalities in circadian pattern was remarkably high in our series of diabetic hypertensives. Two of 3 cases were non-dippers and the extreme form of this pattern, the riser profile, was present in 21% of diabetic patients. The diabetes condition seemed to have a pivotal role in the circadian profile of BP. As showed in Table 3, diabetics suffered from the most unfavorable night-to-day ratios independently of obesity or cardiovascular disease status, two well-recognized figures of worsened circadian patterns. Furthermore, non-obese diabetics showed a higher night-to-day ratio than non-diabetic obese, and diabetics free of established cardiovascular disease also showed a higher ratio than non-diabetics with cardiovascular disease. Cases with diabetes also showed a worse conventional cardiovascular risk profile (Table 1) than that observed in non-diabetic patients. In our experience, the burden of cardiovascular risk was the main determinant for a blunted nocturnal BP decrease.[24,25] The contribution of the absence of a nocturnal BP fall is controversial in patients with diabetes. Absolute BP levels, particularly at night, probably have a higher predictive value for vascular damage than the BP dipper/non-dipper status.[26–28] Nevertheless, a recent article has reported that type 2 diabetics with a riser profile of BP showed 88% mortality during a follow-up of 9 years meanwhile mortality in the non-risers was 45%.[7]

This study has some limitations that deserve discussion. First, the cross-sectional design precludes conclusions about prognosis but the large number of patients included makes our data valuable in estimating prevalences of abnormalities in ambulatory BP in hypertensive patients with diabetes. Second, only two BP readings from a unique visit were used to assess office BP. More readings of clinic BP lead to lower estimates because of habituation and regression to the mean. This procedure could only change results about 'white-coat' and masked hypertension. Data about lack of control in ambulatory BP levels and estimates of circadian patterns are not influenced by the methodology of clinic BP measurement. Third, we had no information about diabetes control, that is, hemoglobin A1c, and metabolic control could have a role in BP control. Fourth, a conventional indication of ABPM could lead to a selection bias, which produced

**Table 3 Comparisons of night-to-day of systolic BP between diabetic and non-diabetic patients according BMI and cardiovascular disease status**

| | *Diabetics* | *Non-diabetics* | P |
|---|---|---|---|
| *Comparisons according BMI status* | | | |
| BMI $\geqslant 30.0\,kg\,m^{-2}$ | 0.936 ± 0.090 | 0.916 ± 0.083 | <0.001 |
| BMI $< 30.0\,kg\,m^{-2}$ | 0.933 ± 0.090 | 0.904 ± 0.087 | <0.001 |
| | *P* diabetics obese *vs.* non-obese=0.136 | *P* non-diabetics obese *vs.* non-obese <0.001 | |
| *Comparisons according the presence or absence of CV disease* | | | |
| With any CV disease | 0.956 ± 0.094 | 0.924 ± 0.088 | <0.001 |
| Without CV disease | 0.941 ± 0.094 | 0.904 ± 0.084 | <0.001 |
| | *P* diabetics with *vs.* without CV disease <0.001 | *P* non-diabetics with *vs.* without CV disease <0.001 | |

Abbreviations: BMI, body mass index; CV cardiovascular.
Night-to-day ratio is presented as mean ± s.d. Differences between groups were sought using Student's *t*-test.

an overestimation of 'white-coat' hypertension and an underestimation of masked hypertension. Fifth, the limitations of reproducibility of a single 24-h ABPM, as performed in our study, are well known, but the application of repeated ABPM sessions or 48-h ABPM to improve the quality of data is not feasible in large-scale studies. Furthermore, studies demonstrating the relationship between ambulatory BP and cardiovascular outcomes have usually been based on a single 24-h ABPM. Despite these limitations, our data are of value for approaching to prevalences of abnormalities that hypertensive patients with diabetes show in ambulatory BP because the large sample size.

In conclusion, hypertensive patients with diabetes showed a remarkably high prevalence of alterations in ABPM. Abnormalities in systolic BP, particularly during the night, and in circadian BP pattern could be linked with the excess of BP-related cardiorenal risk of diabetes. These observations support the recommendation for a wider use of ABPM in diabetic patients.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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