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High prevalence of masked uncontrolled hypertension in people with treated hypertension

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Aim There are limited data on the quality of treated blood pressure (BP) control during normal daily life, and in particular, the prevalence of 'masked uncontrolled hypertension' (MUCH) in people with treated and seemingly well-controlled BP is unknown. This is important because masked hypertension in 'treatment naïve' patients is associated with a high risk of cardiovascular events. We therefore conducted the first study to define the prevalence and characteristics of MUCH among a large sample of hypertensive patients in routine clinical practice in whom BP was treated and controlled to recommended clinic BP goals.

Methods and results We analysed data from the Spanish Society of Hypertension ambulatory blood pressure monitoring (ABPM) Registry and identified patients with treated and controlled BP according to current international guidelines (clinic BP $<$140/90 mmHg). Masked uncontrolled hypertension was diagnosed in these patients if despite controlled clinic BP, the mean 24-h ABPM average remained elevated (24-h systolic BP $\geq$130 mmHg and/or 24-h diastolic BP $\geq$80 mmHg). From 62 788 patients with treated BP in the Spanish registry, we identified 14 840 with treated and controlled clinic BP, of whom 4608 patients (31.1%) had MUCH according to 24-h ABPM criteria (mean age 59.4 years, 59.7% men). The prevalence of MUCH was significantly higher in males, patients with borderline clinic BP (130–9/80–9 mmHg), and patients at high cardiovascular risk (smokers, diabetes, obesity). Masked uncontrolled hypertension was most often because of poor control of nocturnal BP, with the proportion of patients in whom MUCH was solely attributable to an elevated nocturnal BP almost double that solely attributable to daytime BP elevation (24.3 vs. 12.9%, $P < 0.001$).

Conclusion The prevalence of masked suboptimal BP control in patients with treated and well-controlled clinic BP is high. Clinic BP monitoring alone is thus inadequate to optimize BP control because many patients have an elevated nocturnal BP. These findings suggest that ABPM should become more routine to confirm BP control, especially in higher risk groups and/or those with borderline control of clinic BP.

Keywords Ambulatory blood pressure monitoring • Masked • Uncontrolled hypertension • MUCH • Guidelines

Introduction

Masked hypertension (MH) is a term used to define people who have a normal seated clinic blood pressure (BP) but an elevated out-of-office BP, as determined by ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM). Masked hypertension is the opposite of the more commonly recognized 'white coat hypertension'. Patients with MH are now known to be at particularly high risk of developing cardiovascular disease (CVD) because they often remain undetected and untreated.[1,2]

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Most studies on the prevalence of MH have primarily focused on 'treatment naïve' patients, prior to the diagnosis of hypertension, and many of them based the measurements on HBPM or daytime ABPM, or were of small size.[2,3–10] This daytime definition of MH would not include people whose sole abnormality is an elevation in nocturnal BP, which some studies suggest is the strongest predictor of CVD risk compared with daytime or 24-h mean pressures.[11–13] Furthermore, few studies have established the prevalence of the equivalent of MH, i.e. 'masked uncontrolled hypertension', which we have termed MUCH, in patients with treated hypertension. We use MUCH to describe treated patients in whom BP levels are suboptimally controlled according to ABPM, but who are considered controlled to clinic BP targets by current treatment guidelines recommendations (<140/90 mmHg), which universally recommend the use of seated clinic BP to monitor BP control.[14–16] MUCH has gone unrecognized because few studies have used 24-h ABPM[8,17] to determine the prevalence of suboptimal BP control in seemingly well-treated patients, and there are no such studies in large cohorts of treated patients attending usual clinical practice.

The normal range for ABPM values has been defined based on data from prospective studies.[14,18–20] For the diagnosis of hypertension, the recent UK NICE guidelines[15] defined a daytime mean ABPM of ≥135/85 mmHg as being equivalent to the usual seated clinic BP threshold of ≥140/90 mmHg. However, ABPM also yields values for nocturnal pressures, and previous studies have suggested an ABPM-based diagnostic threshold for nocturnal hypertension as ≥120/70 and ≥130/80 mmHg for the 24-h BP average.[14,18,19]

Despite the recognized potential for clinic BP alone to both over- and underdiagnose hypertension, to date, no guidelines have recommended the routine use of ABPM to monitor the quality of BP control because there are very little data on the quality of BP control in routine clinical practice.

The Spanish ABPM registry[21,22] was established to evaluate the utility of the wider use of ABPM, and we have used this large, well-characterized population of hypertensive patients specifically to determine the frequency of MUCH in patients with treated hypertension. To our knowledge, this is the first large-scale study to evaluate and report the prevalence and characteristics of MUCH in people with seemingly well-treated hypertension.

Methods

Study design and participants

The Spanish ABPM Registry was established by the distribution of >1000 ambulatory BP monitors (Spacelabs90207, Spacelabs, Inc., Redmond, WA, USA) for routine use by primary care physicians and physicians from specialist units across Spain. Details of physicians' recruitment and characteristics of the registry have been previously reported.[13,21,22]

Briefly, physicians and nurses received training in the use of ABPM. The data from the ABPM device and the corresponding medical charts were linked via an Internet-based platform to ABPM registries, enabling physicians to receive ABPM reports in real time, and these registries were stored in the database of an external clinical research organization. Consistency and quality of the information is centrally checked through the platform and using protocolized actions. International practice guidelines were used to establish general indications for ABPM.[14,18,19] The registry continues to expand and has received data from ~1500 patients per month, since the first patient was recruited in June 2004. Studies from the Registry have been approved by a series of ethics committees (Hospital Universitario 12 de Octubre, Madrid, Spain; Hospital Clinic, Barcelona, Spain), and all patients gave informed consent.

In December 2010, we identified 99 884 hypertensive patients included in the Registry, of whom 62 788 were treated with anti-hypertensive medications and had complete information regarding seated clinic BP measurements, clinical characteristics, and ABPM data of good quality. From these, we identified 14 840 patients who had controlled clinic BP values, i.e. <140/90 mmHg. Masked uncontrolled hypertension was diagnosed in these patients according to international guideline consensus criteria for MH (normal seated clinic BP <140/90 and 24-h ambulatory systolic BP ≥130 and/or diastolic BP ≥80 mmHg).[2,14,18,19]

Blood pressure measurements

Blood pressure was measured at the clinic with a calibrated mercury sphygmomanometer or a validated semi-automatic oscillometric device, after 5 min of rest in a sitting position. Clinic BP values were calculated as the mean of two readings. Thereafter, 24-h ABPM was performed using an automated non-invasive oscillometric device (SpaceLabs 90207), programmed to register BP at 20-min intervals for the 24-h period. Appropriate cuff sizes were used. The ABPM recordings were performed on working days and the patients were instructed to maintain their usual activities, and to keep the arm extended and immobile at the time of each cuff inflation. Valid ABPM recordings had to fulfil a series of pre-established criteria, including successful recording of ≥80% of systolic BP (SBP) and diastolic BP (DBP) during both the daytime and nocturnal periods, and at least one BP measurement per hour. Daytime and nocturnal periods were defined according to the patient's self-reported data of going-to-bed and waking times.

Study variables

Variables collected for each patient were based on interviews and physical examination at the time of visit and on data drawn from clinical records and defined and measured in accordance with international guidelines.[14] The variables included age, gender, weight and height [obesity defined as body mass index (weight in kg/height in meters squared) ≥30 kg/m^2], duration of hypertension, known cardiovascular risk factors such as tobacco smoking and diabetes mellitus (American Diabetes Association criteria),[23] biochemical values of creatinine and lipid profile, target organ damage (TOD) including urinary albumin excretion (UAE), left ventricular hypertrophy (LVH) (electrocardiographic Sokolow-Lyon voltage >38 and/or Cornell duration/voltage index >2440 mm/ms), and radiological evidence of carotid plaque, and clinical CVD (coronary heart disease, congestive heart failure, or cerebrovascular disease). Renal disease was diagnosed when serum creatinine was >1.5 mg/dL in men and >1.4 mg/dL in women and/or when proteinuria was present. Details of anti-hypertensive treatment (e.g. drug class, number of drugs, and time of administration) were also recorded. Cardiovascular risk was stratified using the 2007 European Society of Hypertension/European Society of Cardiology guidelines, at work at the time of this study, based on clinical BP category, the presence of other risk factors, TOD, or previous CVD for patients with well-controlled office BP.[14]

Statistical analysis

Data are presented as frequencies and percentages for qualitative variables and as mean ± standard deviation [or median (interquartile range)] for quantitative variables. Differences in study variables between groups were assessed with the Pearson χ^2 for qualitative variables and Student's *t*-test (or Mann–Whitney test) for quantitative data.

Table 1 Clinical features in treated clinically controlled hypertensive patients with and without masked uncontrolled hypertension

Variables	Clinic and 24-h BP control hypertensive patients ($n = 10232$)	MUCH hypertensive patients ($n = 4608$)	*P*-value*
Age, years	60.4 ± 13.3	59.4 ± 13.4	<0.001
Gender, *n* (%) men	4922 (48.1)	2753 (59.7)	<0.001
Duration of hypertension, years	5 (2–10)	5 (2–10)	0.167
Body mass index, kg/m^2	29.5 ± 5.0	29.2 ± 4.7	<0.001
Tobacco smoking, *n* (%)	1406 (13.7)	872 (18.9)	<0.001
Diabetes, *n* (%)	1960 (19.2)	1047 (22.7)	<0.001
Total cholesterol, mg/dL	198.0 ± 39.3	199.1 ± 39.3	0.346
LDL cholesterol, mg/dL	119.9 ± 35.6	122.0 ± 35.1	0.062
HDL cholesterol, mg/dL	52.9 ± 14.5	52.0 ± 17.7	0.084
Triglycerides, mg/dL	128.6 ± 57.2	132.8 ± 66.2	0.048
Creatinine, mg/dL	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.211
LVH, *n* (%)	865 (8.5)	431 (9.4)	0.073
UAE, mg/g	5.2 (2.0–16.8)	6.4 (2.7–19.2)	0.011
Carotid plaque, *n* (%)	607 (5.9)	234 (5.1)	0.037
Target organ damage, *n* (%)	1761 (17.2)	846 (18.4)	0.089
Previous CVD, *n* (%)	1782 (17.4)	751 (16.3)	0.394
High/very high CVD risk, *n* (%)	3612 (35.3)	1893 (41.1)	<0.001
Number of AH drugs	2.0 ± 1.1	2.0 ± 1.1	0.924
On only one AH drug, *n* (%)	4038 (39.5)	1876 (40.7)	0.151

Clinic and 24-h BP controlled hypertensive patients: clinic BP <140/90 mmHg and 24-h BP <130/80 mmHg. MUCH: clinic BP <140/90 mmHg and 24-h BP ≥130/80 mmHg. LVH, left ventricular hypertrophy; UAE, urinary albumin excretion; CVD cardiovascular disease; AH, anti-hypertensive; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Values are mean ± SD or median (inter-quartile range), or *n* (%).
**P*-values for association between MUCH patients and patients with both clinic and 24-h BP controlled.

Patients with MUCH were classified according to whether they presented only-daytime BP elevated (threshold ≥135/85 mmHg),[14,18,19] only-nocturnal BP elevated (threshold ≥120/70 mmHg),[14,18,19] or both. The first two groups were compared using the Pearson χ^2 test.

Since the reproducibility of ABPM data has been poorly studied,[24] and could have affected the reliability of the reported prevalence of MUCH, we also examined the reproducibility of MUCH and MUCH subtypes in a sample of patients who underwent a second ABPM, using the χ^2 test and linear kappa coefficient for testing agreement between both sessions.

Logistic regression analysis was used to assess factors independently associated with the following outcomes: MUCH (vs. both clinic and 24-h BP controlled), and isolated nocturnal MUCH (vs. isolated daytime MUCH). Covariates included age, gender, hypertension duration, cardiovascular risk factors (BMI, obesity, smoking, diabetes, total and LDL cholesterol, triglycerides, creatinine), TOD (LVH, UAE, carotid plaque, and TOD as a whole), CVD risk, previous CVD, renal disease, number of anti-hypertensive drugs used (1 vs. 2 or more), clinic SBP and DBP, and 24-h SBP and DBP. All variables were modelled as categorical (dichotomous) except age, BMI, hypertension duration, blood cholesterol, triglycerides, creatinine, UAE, and BP (continuous). Factors with significance at $P \leq 0.20$ in univariate analyses (Wald χ^2 test) were introduced into a multivariable logistic regression model using the stepwise forward method for variable selection. Then, with the variables selected and those that were considered clinically relevant, a final model was fitted. Goodness-of-fit of models was evaluated with the Hosmer–Lemeshow test. We excluded 'CV risk'[14] as a covariate in multivariable analyses because it showed co-linearity with other covariates and impeded robust modelling. The SPSS for Windows version 19.0 software was used for statistical analysis.

Results

Sample characteristics

There were 4608 patients with MUCH despite optimal clinic BP control (mean age 59.4 years, 59.7% men), and 10 232 patients were identified as having optimal BP control, i.e. with both office and 24-h BP controlled. When compared with the optimal BP control group, MUCH patients were more likely to be male and had a worse CVD risk profile, including higher proportion of smokers, diabetes, higher levels of triglycerides, greater proportion of high estimated CVD risk, and marginally but not significantly higher levels of LDL cholesterol ($P = 0.06$) and higher proportion of TOD ($P = 0.09$) (*Table 1*).

The percentage of MUCH receiving monotherapy did not significantly differ from those optimally controlled (*Table 1*). Most MUCH patients took their anti-hypertensive medication only in the morning (76.6 vs. 76.2% in those optimally controlled), 12.5% only in the evening/night, and 10.9% in both the morning and the evening/night. The percentage of MUCH vs. optimal control patients taking specific drug classes were diuretics 7.6 and 8%, respectively ($P = 0.594$), beta-blockers 12.1 and 17.2% ($P < 0.01$), angiotensin-

converting enzyme inhibitors (ACEi) 25.5 and 24.7% ($P = 0.541$), angiotensin-receptor blockers (ARB) 19.9 and 19.8% ($P = 0.932$), calcium-channel blockers 9.6 and 6.5% ($P < 0.01$), and alpha-blockers 1.4 and 1.1% ($P = 0.327$).

Mean daytime and nocturnal ambulatory BP were higher in those with MUCH when compared with the optimal control group (*Table 2*). The absolute difference in nocturnal SBP between both groups was 17.4 mmHg (126.8 vs. 109.4 mmHg, respectively), and 17.8 mmHg in daytime SBP (136.5 vs. 118.7 mmHg, respectively). The corresponding absolute difference in DBP was ~10 mmHg for both daytime and nocturnal BP (*Table 2*).

Prevalence of masked uncontrolled hypertension

The proportion of MUCH among treated hypertensive patients well controlled in the clinic was 31.1% (95% confidence interval 30.4–31.8%). The prevalence of MUCH was significantly higher in males, patients aged <65 years, smokers, those with diabetes, or those at high cardiovascular risk than their counterparts (*Table 3*). However, the difference in the prevalence of MUCH according to obesity status, TOD, or previous CVD were only marginally significant or not clinically relevant (absolute differences <4 mmHg). Notably, the prevalence of MUCH was clearly higher when the clinic BP was closer to the BP control threshold, i.e. in those with borderline control according to clinic BP (*Table 3*).

The prevalence of MUCH was not significantly different between patients on one drug vs. those on ≥2 drugs (31.7 vs. 30.6%, $P = 0.151$), and either according to the time of drug administration (*Table 3*). Lastly, the prevalence of MUCH was significantly lower in patients taking only beta-blockers (24.6%) and higher in those on only calcium-channel blockers (40.8%) or only alpha-blockers (37.1%) (*Table 3*).

Table 2 Differences in office, daytime, and nocturnal BP, as well as circadian pattern distribution, in treated well-controlled hypertensive patients with and without masked uncontrolled hypertension

Variables	Clinic and 24-h BP control hypertensive patients ($n = 10\,232$)	MUCH hypertensive patients ($n = 4608$)	*P*-value*
Office systolic BP	125.7 ± 10.1	129.1 ± 8.8	<0.001
Office diastolic BP	76.0 ± 8.3	78.1 ± 8.4	<0.001
24-h systolic BP	116.2 ± 7.9	134.2 ± 10.3	–
24-h diastolic BP	69.1 ± 6.8	79.9 ± 8.3	–
Daytime systolic BP	118.7 ± 8.4	136.5 ± 10.4	<0.001
Daytime diastolic BP	71.6 ± 7.4	82.4 ± 9.0	<0.001
Nocturnal systolic BP	109.4 ± 10.7	126.8 ± 14.7	<0.001
Nocturnal diastolic BP	62.2 ± 7.4	72.6 ± 8.8	<0.001

Values are in millimetres of mercury (mean ± SD), or %. BP, blood pressure.
*P-values for association between MUCH patients and patients with both clinic and 24-h BP controlled.

Table 3 Prevalence of masked uncontrolled hypertension in treated and controlled hypertensive patients according to demographics, cardiovascular risk factors, target organ damage, cardiovascular disease status, and anti-hypertensive medication

Group	*n*	%	95% confidence interval
Total ($n = 14840$)	4608	31.1	30.4–31.8%
Clinic blood pressure, mmHg			
<120/<80	359	15.4	14.4–16.4
120–9/<80	639	26.1	24.8–27.4
130–9/80–9	3610	36.7	35.3–38.1
P		<0.001	
Gender			
Male	2753	35.9	34.8–37.0
Female	1855	25.9	24.9–26.9
P		<0.001	
Age			
<45 years	640	33.7	31.6–35.9
45–64 years	2306	32.1	31.0–33.2
≥65 years	1662	28.8	27.6–30.0
P		<0.001	
Obesity			
Yes	1719	29.3	28.1–30.5
No	2889	32.2	31.2–33.2
P		<0.001	
Tobacco smoking			
Yes	872	38.3	36.3–40.3
No	3736	29.7	28.9–30.5
P		<0.001	
Diabetes			
Yes	1047	34.8	33.1–36.5
No	3561	30.1	29.3–30.9
P		<0.001	
Target organ damage			
Yes	846	32.5	30.7–34.3
No	3762	30.8	30.0–31.6
P		0.089	
Previous cardiovascular disease			
Yes	751	29.6	27.8–31.4
No	3857	31.3	30.4–32.1
P		0.094	
Cardiovascular risk			
High/very high	1893	34.4	33.1–35.7
Low/moderate	2715	29.1	28.2–30.0
P		<0.001	
Number of anti-hypertensive drugs			
One	1876	31.7	30.4–33.0
≥2	2732	30.6	29.3–31.9

Continued

Table 3 *Continued*

Group	n	%	95% confidence interval
P		0.151	
Drug class on monotherapy			
Diuretic	190	30.6	28.3–32.9
Beta-blocker	302	24.6	22.2–27.0
ACEi	633	32.4	30.1–34.7
ARB	496	31.8	29.3–34.3
Calcium-channel blocker	185	40.8	36.2–45.4
Alpha blocker	35	37.1	28.5–45.7
Time of drug administration			
Only in the morning	3529	31.2	30.3–32.1
Only in the evening or night	576	30.7	29.9–31.5
In the morning and evening/ night	498	30.9	29.4–32.0
P		0.898	

MUCH: clinic BP <140/90 mmHg and 24-h BP ≥130/80 mmHg. ACEi, angiotensin-converting enzyme inhibitor. ARB, angiotensin-receptor blocker.

Contribution of elevated daytime and nocturnal blood pressure to masked uncontrolled hypertension

Although 60% of MUCH patients had both uncontrolled daytime and nocturnal BP, the proportion of patients with only-nocturnal BP elevated was almost double than that with only-daytime elevated BP (24.3 vs. 12.9%; $P < 0.001$) (*Table 4*). A few (126 or 2.7%) of the patients with MUCH had both daytime and nocturnal BP controlled, but they all had a mean 24-h BP >130/80 mmHg.

Reproducibility of masked uncontrolled hypertension

In 231 patients with treated hypertension and MUCH, two ABPM recordings were available, separated by a median time between the two visits of 1 month (inter-quartile range 0.5–8 months). Of these, 202 (87.4%; 95% confidence interval, 83.5–91.5%) continued to fulfil the criteria for MUCH in the second ABPM session, and all of the 66 patients with a third ABPM available persisted as MUCH patients. Consequently, the concordance in the prevalence of MUCH between the two ABPM sessions was very good ($\kappa = 0.85$).

Furthermore, no statistically significant differences in the prevalence of MUCH subtypes were observed between ABPM sessions 1 and 2 ($P = 0.913$). Moreover, the MUCH classification remained unchanged in 58 of 63 (92.1%) with only-nocturnal MUCH, 23 of 29 (79.3%) with only-daytime MUCH, and 116 of 133(87.2%) of those with daytime-nocturnal MUCH (*Figure 1*). The clinical characteristics of the small reproducibility sample (mean age, 57.9 years; mean BMI, 29 kg/m^2; median duration since hypertension diagnosis, 3 years; and CVD risk, 41.6%) resembled those of the total 4608 patients with MUCH (*Table 1*). Likewise, the distribution of MUCH subtype in both samples was quite similar: 27.3 and 24.3%, respectively, had a nocturnal-MUCH subtype, and 12.6 and 12.9% had a daytime subtype (*Table 4* and *Figure 1*).

Multivariable analyses of MUCH

The multivariable odds ratio of having MUCH in people with treated and well-controlled clinic BP was significantly inversely related to age, and higher in males, those with a longer duration of hypertension, obesity, smokers, those with diabetes, and in those with a clinic BP closer to the control threshold (140/90 mmHg) (*Table 5*; goodness-of-fit Hosmer–Lemeshow, $P = 0.109$). In addition, the odds of having only-nocturnal MUCH was significantly higher among older patients, those with obesity, TOD or previous CVD than in patients with only-daytime MUCH (odds ratios of 1.031, 1.570, 1.863, and 1.969, respectively; all $P < 0.01$), and marginally but not significantly higher in patients with diabetes (OR 1.33; 95% CI 0.94–1.65, $P = 0.10$).

Discussion

The results of this study suggest that almost one-third of people who are considered to have adequate BP control by conventional clinic criteria do not have their BP controlled when assessed by ABPM. We have used the term 'masked uncontrolled hypertension' or 'MUCH' to describe this cohort of patients. Importantly, over one in three patients with borderline clinic BP have MUCH and therefore have a BP that is not adequately controlled. The frequency of MUCH was especially high in patients with major cardiometabolic risk factors or who smoke, all of which identify people who are at higher CVD risk who would benefit most from optimal BP control.

These findings were observed in a large European population of people cared for in usual clinical practice, and the prevalence of MUCH was consistent across the status of cardiovascular risk factors, TOD, CVD, and anti-hypertensive medication. Our results also suggest a good short-term reproducibility of MUCH as defined by ABPM, which adds to the scarce literature on the reproducibility of ABPM-defined MH.[24] Moreover, our results suggest a good reproducibility of nocturnal and daytime MUCH subtypes. We did not analyse possible changes in treatment over time in these analyses; however, the median time between the two visits was only 1 month and thus treatment changes were unlikely.

Thus, our findings suggest that based on the currently recommended use of clinic BP to monitor BP control, physicians will substantially overestimate the number of patients who are truly controlled, leaving many higher-risk patients at excess risk.

Importance of nocturnal masked uncontrolled hypertension

We found that suboptimal nocturnal BP control accounted for more cases of MUCH than suboptimal daytime BP control. Indeed, about one-quarter of MUCH cases had only the nocturnal BP elevated (vs. 13% with elevated daytime BP). Remarkably, nocturnal SBP/DBP was almost 20/10 mmHg higher in MUCH patients when compared with those patients in whom both clinic BP and ABPM readings were controlled. Such difference seems to be too high to be explained by methodological aspects of ABPM measurement (e.g. frequent inflation of the cuff). We speculate that the

Table 4 Differences in daytime and nocturnal blood pressure control rate in patients with masked uncontrolled hypertension

Daytime blood pressure	Nocturnal blood pressure		Total
	Controlled (<120/70 mmHg)	Uncontrolled (≥120/70 mmHg)	
Controlled (<135/85 mmHg)	Both BP controlled[a] (24-h MUCH)	Isolated daytime control (nocturnal-MUCH)	
	126	1122	1248
	2.7% (2.2–3.2)	24.3% (23.1–25.5%)	25.0% (23.7–26.2%)
Uncontrolled (≥135/85 mmHg)	Isolated nocturnal control (daytime-MUCH)	Both uncontrolled (daytime/nocturnal MUCH)	
	595	2765	3360
	12.9% (11.9–13.9%)	60.0% (58.6–61.4%)	75.0% (73.7–76.3%)
Total	721	3887	4608
	13.3% (12.3–14.3%)	86.7% (85.7–87.7%)	100%

Numbers are *n*, % (95% confidence interval).
[a]Patients with both daytime and nocturnal BP on target, yet having 24-h BP >130/80 mmHg.

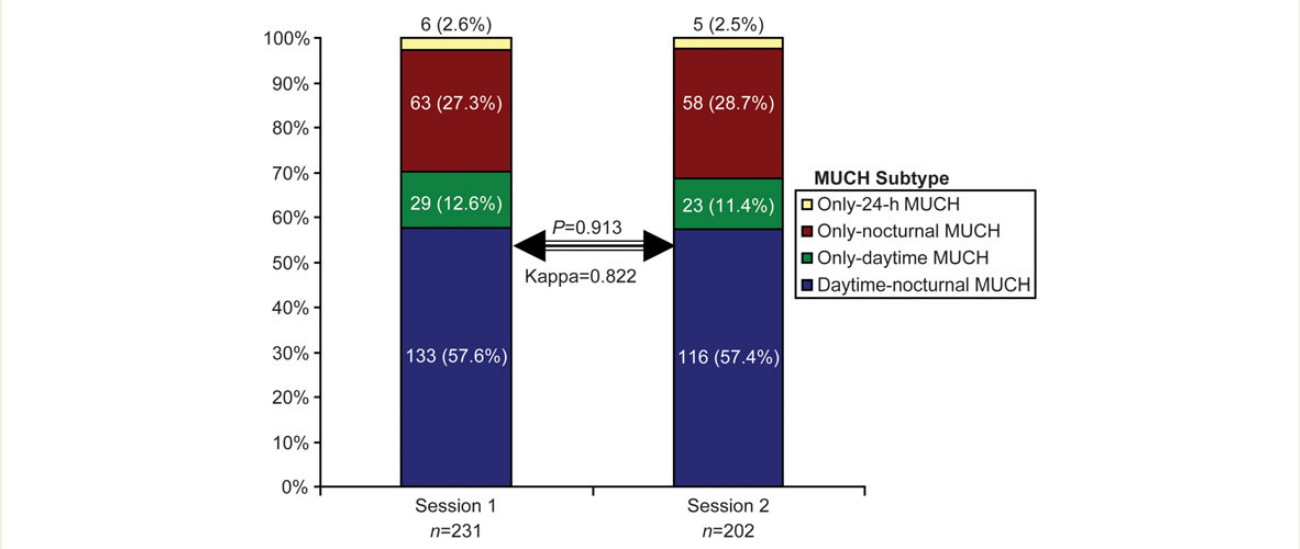

Figure 1 Percentage distribution of subtypes of masked uncontrolled hypertension (MUCH) in a sample of treated and controlled hypertensive patients in two ambulatory blood pressure monitoring sessions. Kappa: concordance for the categorization of patients into the masked uncontrolled hypertension subtypes. Masked uncontrolled hypertension: clinic blood pressure <140/90 mmHg and 24-h blood pressure ≥130/80 mmHg. Only-24-h masked uncontrolled hypertension: daytime blood pressure <135/85 mmHg, nocturnal blood pressure <120/70 mmHg, and 24-h blood pressure ≥130/80 mmHg. Only-nocturnal masked uncontrolled hypertension: nocturnal blood pressure ≥120/70 mmHg and daytime blood pressure <135/85 mmHg. Only-daytime masked uncontrolled hypertension: daytime blood pressure ≥135/85 mmHg and nocturnal blood pressure <120/70 mmHg. Daytime–nocturnal masked uncontrolled hypertension: daytime blood pressure ≥135/85 mmHg and nocturnal blood pressure ≥120/70 mmHg.

predominance of nocturnal MUCH could be related to some physiological mechanisms involving sympathetic activity and sleep apnoea.[25,26] Moreover, we found the classification of nocturnal MUCH to be reproducible in the short term, and that factors related to older age, obesity, diabetes, TOD, and the presence of CVD might play a role, as they were significantly associated with isolated elevation of nocturnal BP. However, further research is clearly needed. Whatever the explanation, the fact that MUCH is most often because of nocturnal hypertension is important because nocturnal BP has been strongly linked to CVD morbidity and mortality and nocturnal hypertension can only be detected by ABPM.[14,18–20]

Comparison with other studies

The frequency of MH in HBPM studies ranges from 9 to 37%, and 9 to 21% based on ABPM.[6] However, HBPM cannot properly assess BP during sleep, and nocturnal BP is a stronger risk factor for TOD and CVD.[11–13] This does not mean that HBPM is not a valid alternative to ABPM in the diagnosis of MH, and some authors have indicated

Table 5 Clinical variables associated with masked uncontrolled hypertension in treated well-controlled hypertensive patients, by multiple logistic regression

Variable	Odds ratio	95% confidence interval	*P*-value
Age, years	0.996	0.993–0.999	0.012
Gender (male vs. female)	1.529	1.422–1.645	<0.001
Duration of hypertension, years	1.015	1.010–1.020	<0.001
Obesity (yes vs. no)	1.196	1.110–1.287	<0.001
Tobacco smoking (yes vs. no)	1.387	1.258–1.530	<0.001
Diabetes (yes vs. no)	1.249	1.142–1.366	<0.001
Clinic systolic blood pressure, mmHg	1.037	1.032–1.041	<0.001
Clinic diastolic blood pressure, mmHg	1.017	1.011–1.022	<0.001

MUCH: office blood pressure <140/90 mmHg and 24-h blood pressure ≥130/80 mmHg.

that both ABPM and HBPM appear to be appropriate for the detection of MH.[27] But the fact remains that daytime BP measurements alone are insufficient to detect all MH cases. In untreated hypertensive patients, the prevalence of MH ranges from 9 to 14%.[6] Interestingly, in our untreated patients the prevalence of MH was 33.6%, a quite similar proportion to that of MUCH. But in general in patients with treated hypertension, the prevalence is less known. The present study thus adds new evidence on the importance of MUCH, particularly nocturnal-MUCH in a large population of already treated hypertensive patients attended in clinical practice. We did not find any significant association between the number of drugs taken and the prevalence of MUCH, consistent with some studies,[9] but at odds with others.[10] We found no statistically significant or clinically relevant associations between MUCH and time of drug administration either. Nevertheless, it cannot be ruled out that redistribution of the time of anti-hypertensive drug therapy would improve BP control, thus reducing the prevalence of MUCH and CVD risk. Interestingly, the frequency of MUCH appeared higher in those receiving calcium-channel blockers, but we caution against reading too much into this because this could be confounding by indication. Indeed, it should be noted that this is not a randomized clinical trial, but an observational registry, and thus results concerning the type and timing of anti-hypertensive medication related to MUCH must be interpreted with caution. New studies done in adequately selected patients randomized to different drug-treatment schedules would help address this issue more properly. Finally, irrespective of the type or timing of treatment, the clinic BP was controlled in these patients and therefore the physician would have been content with the existing treatment.

Clinical profile of MUCH patients

The demographic and clinical characteristics of patients with MH and MUCH are poorly defined,[2] indeed, no large study has ever previously focused on patients with MUCH. Available 24-h ABPM-based studies have identified high-normal clinic BP, age, smoking, obesity, diabetes, proteinuria, and high CVD risk associated with MH.[3–6,28]

We have identified the clinical profile of MUCH patients as more likely to be male or obese, smokers, or those with diabetes. Unfortunately, pathophysiological mechanisms responsible for MH are still unknown. Nevertheless, it is notable that clinic heart rate was marginally higher in MUCH patients than in controlled patients (73.2 and 72.6 b.p.m., respectively, $P = 0.009$), and in particular there was a statistical trend in MUCH patients with diabetes (74.2 vs. 73.3, $P = 0.08$). This may suggest an increased sympathetic activity in some patients with MUCH, consistent with findings reported in detail by Grassi *et al.*[25]

Clinical and public health implications

Since over one-third of the patients with borderline clinic BP control have MUCH, currently recommended methods of BP measurement seem to be insufficient to manage such patients with treated hypertension, and therefore primary care physicians should consider the more routine use of ABPM in patients with borderline clinic BP. At the very least, those with borderline clinic BP and high CVD risk should be considered for ABPM.

Defining patients with MUCH could have important public health implications because this represents millions of people at a population level and such patients are more likely to have major CVD risk factors and have the most to gain in absolute terms with regard to benefits from improved BP control. Although the prognosis for MUCH is presently unknown, it is well recognized that its counterpart, i.e. MH in seemingly normotensive untreated patients is associated with a poor prognosis.[1,2,6,7,29]

Study strengths and limitations

A key strength of this study is that it was performed on a large nationwide population sample—the first time that the prevalence of MUCH has been assessed in such a large single cohort of hypertensive patients (62 788 treated and 14 840 with a treated clinic BP <140/90 mmHg). Even though any registry study has inherent potential sources of bias associated, and there may be some selection bias from inclusion criteria for conventional ABPM indications, it is important to note that Spanish ABPM registry provides a real-world view of clinical practice, at scale, for several reasons: (i) both primary care physicians and specialist referral units were represented, (ii) physicians and patients were recruited across the 17 autonomous communities covered by the national healthcare system in Spain, and (iii) ~90% of treated and controlled hypertensive patients in Spain have a

BP 130–9/85–9 mmHg or were at high added risk according to European guidelines,[14,30] situations that were consistent with clinical indications for ABPM as defined by the Registry. Thus, the registry used here was very inclusive.

The current study must be interpreted within the context of its potential limitations: (i) 'normal clinic BP' was based on the recording of only two seated clinic BP measurements at a single visit. Nevertheless, in a study of HBPM with treated hypertensive patients, no variation in the frequency of MH was observed with the number of clinical measurements (three or six);[31] (ii) the BP levels we chose for defining normality in ambulatory BP are those most commonly used and evidence-based,[14,15] but possibly conservative and may change in the future. Lower BP thresholds, such as the recently proposed population-based outcome-driven thresholds[32] would yield an even greater prevalence of MUCH than that we have reported here; (iii) the multivariable regression model was intended only to identify factors independently associated with MUCH, and their results should be interpreted with caution; (iv) we have no way of assessing patients' concordance with their anti-hypertensive treatment; and (v) pulse wave velocity, maybe the most important marker of TOD regarding risk prediction,[33] was not included in this study. Nevertheless, it could be helpful in future work to evaluate potential mechanisms for our findings.

Conclusions

In conclusion, MUCH in people with seemingly well-controlled clinic BP is high and seems to be reproducible on repeat ABPM measures. The characteristics of such patients (male, longer duration of hypertension, obesity, smoking history, and diabetes) indicates that this is a higher-risk group with most to gain from improved BP. An important determinant of MUCH is poorer control of nocturnal BP, which can never be appreciated from clinic readings alone. Moreover, nocturnal BP is increasingly recognized as a strong predictor of risk in many studies of ABPM. Thus, the present study suggests that reliance on clinic BP alone is often inadequate to optimize BP control because many patients (especially higher-risk patients), have an elevated nocturnal BP. Our data suggest that ABPM should be used more widely to monitor BP control, especially in higher-risk groups. However, further studies that assess the impact of such a strategy on clinical outcomes and define the cost-effectiveness of such an approach are needed.

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Authors' contributions

J.R.B., L.M.R., and B.W. conceived and designed the study. J.R.B., L.M.R., J.D., and B.W. developed the analytic approach and drafted the manuscript. J.J.d.l.C. did the statistical analyses. All authors contributed to data interpretation and critical revision of the paper.

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Conflict of interest: Members of the Spanish ABPM Registry, including some authors of this paper (J.R.B., L.M.R., A.d.l.S, M.G., J.S.), have participated in educational meetings focused on spreading the use and importance of ABPM. Some of these meetings have been funded by Lacer Laboratories, Spain. B.W. works in academic collaboration with HealthStats of Singapore which manufactures a device for ABPM.

References

1. Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognosis of masked hypertension and white coat hypertension detected by 24-h ambulatory blood pressure monitoring: 10 year follow-up from the Ohasama study. *J Am Coll Cardiol* 2005;**46**:508–515.
2. Mancia G, Bombelli M, Seravalle G, Grassi G. Diagnosis and management of patients with white-coat and masked hypertension. *Nat Rev Cardiol* 2011;**8**:686–693.
3. Longo D, Dorigatti F, Palatini P. Masked hypertension in adults. *Blood Press Monit* 2005;**10**:307–310.
4. Mancia G, Facchetti R, Bombelli M, Grassi G, Sega R. Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension* 2006;**47**:846–853.
5. Pickering TG, Eguchi K, Kario K. Masked hypertension: a review. *Hypertens Res* 2007;**30**:479–488.
6. Bobrie G, Clerson P, Ménard J, Postel-Vinay N, Chatellier G, Plouin PF. Masked hypertension: a systematic review. *J Hypertens* 2008;**26**:1715–1725.
7. Verberk WJ, Kessels AG, de Leeuw PW. Prevalence, causes, and consequences of masked hypertension: a meta-analysis. *Am J Hypertens* 2008;**21**:969–975.
8. Viera AJ, Hinderliter AL, Kshirsagar AV, Fine J, Dominik R. Reproducibility of masked hypertension in adults with untreated borderline office blood pressure: comparison of ambulatory and home monitoring. *Am J Hypertens* 2010;**23**:1190–1197.
9. Andalib A, Akhtari S, Rigal R, Curnew G, Leclerc JM, Vaillancourt M, Tardiff JC. Determinants of masked hypertension in hypertensive patients treated in a primary care setting. *Intern Med J* 2012;**42**:260–266.
10. Park SJ, Park JB, Choi DJ, Youn HJ, Park CG, Ahn YK, Shin JH, Kim DW, Rim SJ, Bae JH, Park HY; on behalf of the Korean Hypertension Research Network. Detection of masked hypertension and the 'mask effect' in patients with well-controlled office blood pressure. *Circ J* 2011;**75**:357–365.
11. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin Outcome Study. *Hypertension* 2005;**46**:156–161.
12. Verdecchia P, Angeli F, Mazzotta G, Garofoli M, Ramundo E, Gentile G, Ambrosio G, Reboldi G. Day-night and early-morning surge in blood pressure in hypertension. Prognostic implications. *Hypertension* 2012;**60**:34–42.
13. De la Sierra A, Banegas JR, Segura J, Gorostidi M, Ruilope LM; CARDIORISC Event Investigators. 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.
14. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B; Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology. 2007 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). *J Hypertens* 2007;**25**:1105–1187.

15. Hypertension: clinical management of primary hypertension in adults. Available at: **http://guidance.nice.org.uk/cg127** (2 January 2011).
16. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Rydén L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;**34**:2159–2219.
17. Schillaci G, Verdecchia P, Sacchi N, Bruni B, Benemio G, Pede S, Porcellati C. Clinical relevance of office underestimation of usual blood pressure in treated hypertension. *Am J Hypertens* 2000;**13**(5 Pt 1):523–528.
18. O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P; on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens* 2005;**23**:697–701.
19. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Roccella EJ. Recommendations for blood pressure measurement in humans and experimental animals. Part 1: blood pressure measurement in humans a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005;**45**:142–161.
20. Ohkubo T, Imai Y, Tsuji I, Nagai K, Ito S, Satoh H, Hisamichi S. Reference values for 24-hour ambulatory blood pressure monitoring based on a prognostic criterion: the Ohasama Study. *Hypertension* 1998;**32**:255–259.
21. Banegas JR, Segura J, Sobrino J, Rodríguez-Artalejo F, de la Sierra A, de la Cruz JJ, Gorostidi M, Sarría A, Ruilope LM; Spanish Society of Hypertension Ambulatory Blood Pressure Monitoring Registry Investigators. Effectiveness of blood pressure control outside the medical setting. *Hypertension* 2007;**49**:62–68.
22. Gorostidi M, Sobrino J, Segura J, Sierra C, De la Sierra A, Hernández del Rey R, Vinyoles E, Galcerán JM, López-Eady MD, Marín R, Banegas JR, Sarría A, Coca A, Ruilope LM; on behalf of the Spanish Society of Hypertension ABPM Registry investigators. Ambulatory blood pressure monitoring in hypertensive patients with high cardiovascular risk: a cross-sectional analysis of a 20,000-patient database in Spain. *J Hypertens* 2007;**25**:977–984.
23. American Diabetes Association. Executive summary: standards of medical care in diabetes-2011. *Diabetes Care* 2011;**34**(Suppl 1):S4–S10.
24. Ben-Dov IZ, Ben-Arie L, Mekler J, Bursztyn M. Reproducibility of white-coat and masked hypertension in ambulatory BP monitoring. *Int J Cardiol* 2007;**117**:355–359.
25. Grassi G, Seravalle G, Trevano FQ, Dell'oro R, Bolla G, Cuspidi C, Arenare F, Mancia G. Neurogenic abnormalities in masked hypertension. *Hypertension* 2007;**50**:537–542.
26. Drager LF, Diegues-Silva L, Diniz PM, Bortolotto LA, Pedrosa RP, Couto RB, Marcondes B, Giorgi DM, Lorenzi-Filho G, Krieger EM. Obstructive sleep apnea, masked hypertension, and arterial stiffness in men. *Am J Hypertens* 2010;**23**:249–254.
27. Stergiou GS, Salgami EV, Tzamouranis DG, Roussias LG. Masked hypertension assessed by ambulatory blood pressure versus home blood pressure monitoring: is it the same phenomenon? *Am J Hypertens* 2005;**18**:772–778.
28. Mallion JM, Clerson P, Bobrie G, Genes N, Vaisse B, Chatellier G. Predictive factors for masked hypertension within a population of controlled hypertensives. *J Hypertens* 2006;**24**:2365–2370.
29. Hansen TW, Kikuya M, Thijs L, Björklund-Bodegård K, Kuznetsova T, Ohkubo T, Richart T, Torp-Pedersen C, Lind L, Jeppesen J, Ibsen H, Imai Y, Staessen JA; IDACO Investigators. Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: a meta-analysis of 7,030 individuals. *J Hypertens* 2007;**25**:1554–1564.
30. Rodriguez-Roca GC, Llisterri-Caro JL, Barrios-Alonso V, Alonso-Moreno FJ, Lou-Arnal S, Prieto-Diaz MA, Sanchez-Ruiz T, Dura-Belinchon R, Santos-Rodriguez JA, Divison-Garrote JA, Gonzalez-Segura D, Banegas-Banegas JR; Working Group of Arterial Hypertension of the Spanish Society of Primary Care Physicians (group HTA/SEMERGEN); PRESCAP 2006 Investigators. Cardiovascular risk and blood pressure control in a Spanish hypertensive population attended in a Primary Care setting. Data from the PRESCAP 2006 study. *Blood Press* 2009;**18**:117–125.
31. Mallion JM, Genès N, Vaur L, Clerson P, Vaïsse B, Bobrie G, Chatellier G. Detection of masked hypertension by home blood pressure measurement: is the number of measurements an important issue? *Blood Press Monit* 2004;**9**:301–305.
32. Kikuya M, Hansen TW, Thijs L, Björklund-Bodegård K, Kuznetsova T, Ohkubo T, Richart T, Torp-Pedersen C, Lind L, Ibsen H, Imai Y, Staessen JA; International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes Investigators. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-year cardiovascular risk. *Circulation* 2007;**115**:2145–2152.
33. Sehestedt T, Jeppesen J, Hansen TW, Wachtell K, Ibsen H, Torp-Pedersen C, Hildebrandt P, Olsen MH. Risk prediction is improved by adding markers of subclinical organ damage to SCORE. *Eur Heart J* 2010;**31**:883–891.