Phenotypes of Masked Hypertension:

Isolated Ambulatory, Isolated Home and Dual Masked Hypertension

Short title: Ambulatory and Home masked hypertension

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CONFLICTS OF INTEREST

GS: Conducted validation studies of BP monitors of various manufacturers and advised manufacturers on device and software development. RM: Received BP monitoring equipment for research purposes from Omron and Lloyds Pharmacies. The other authors report no conflicts.

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ABSTRACT

Objectives: Masked hypertension (MH) is defined as normal office blood pressure (OBP) and elevated ambulatory (ABP) or home blood pressure (HBP). This study assessed MH identified by each of these two methods.

Methods: A retrospective analysis of cross-sectional data in treated and untreated adults from Greece, Finland and UK who had OBP, HBP and 24-hour ABP measurements was performed. Dual MH was defined as normal OBP and elevated HBP and ABP, Isolated Ambulatory MH as normal OBP and HBP and elevated ABP and Isolated Home MH as normal OBP and ABP and elevated HBP.

Results: Of 1,971 subjects analyzed, 445 (23%) had MH on ABP and/or HBP (age 57.1±10.8 years, males 55%, treated 49%). Among subjects with any MH, 215 had Dual MH (48%), 132 Isolated Ambulatory MH (30%) and 98 Isolated Home MH (22%). Moreover, 55% had high-normal, 35% normal and 10% optimal OBP. In logistic regression analysis Isolated Ambulatory MH was predicted by younger age (OR 0.35, $p<0.01$ per 10 years increase), while Isolated Home MH was predicted by older age (OR 2.05, $p<0.01$ per 10 years increase).

Conclusions: MH diagnosed by ABP and not HBP monitoring or the reverse is not uncommon. Age appears to be the most important determinant of Isolated Ambulatory or Home MH, with the former being more common in younger subjects and the latter in older ones. Only half of subjects with MH have high-normal OBP, while the rest have lower levels.

Keywords: ambulatory blood pressure; home blood pressure; masked hypertension; masked uncontrolled hypertension; partial masked hypertension

INTRODUCTION

Untreated and treated individuals with masked hypertension (MH) phenomenon defined as normal office and elevated out-of-office blood pressure (BP) have similar cardiovascular risk as those with uncontrolled hypertension and are missed when BP is evaluated only in the office [1-7]. Thus, current guidelines in the US and Europe recommend that out-of-office BP evaluation is mandatory for treatment decisions in most cases with suspected or treated hypertension, particularly when office BP (OBP) is close to the hypertension threshold [8,9]. Interestingly, outcome studies have shown that out-of-office BP assessed using self-home (HBP) or ambulatory monitoring (ABP) provides similar prognostic information about the increased risk associated with the MH phenomenon [1-6]. Current guidelines recommend that either HBP or ABP monitoring can be used for detecting the MH phenomenon among both untreated and treated patients, and these two out-of-office BP measurement methods are regarded as rather interchangeable for clinical practice [8,9].

HBP and ABP monitoring are similar methods in that they both provide multiple BP measurements away from the office setting in the usual environment of each individual [10,11]. On the other hand, there are important differences between the two methods, as HBP measurements are taken only in the sitting posture, only at home, and during days, weeks or months, whereas ABP measurements are taken in the sitting, standing and lying posture, at home, at work and even during sleep, and usually within 24 hours [10,11]. Thus, despite the current recommendation that these methods are interchangeable and the same threshold should be used for hypertension diagnosis based on HBP or daytime ABP measurement [8,9],

different conditions and behavior of individuals during routine daily activities might lead to disagreement between the two methods in defining the daytime BP level and thereby the diagnosis of daytime hypertension [12]. This analysis of a large European sample investigated the prevalence of MH detected by only ABP, or only HBP monitoring, or both, and the predictors of these MH phenotypes.

METHODS

This is a retrospective analysis of cross-sectional data in treated and untreated adults evaluated with OBP, HBP and ABP measurements, which were collected in the context of prospective trials using similar measurement protocols and according to current guidelines. Subjects aged ≥18 years on stable antihypertensive drug treatment for at least 4 weeks or untreated were recruited in 3 centers (Athens, Greece; Birmingham, UK; Turku, Finland) [12]. OBP, HBP and 24-hour ABP measurements were taken within 10-21 days, with random order of HBP and ABP monitoring according to device availability and patients' preference.

BP Measurements

At each visit 2-6 OBP measurements were taken (depending on the center) after at least 5 minutes sitting rest using a standard mercury sphygmomanometer or validated automated upper arm-cuff devices and appropriate cuff sizes according to each individual's arm circumference [12]. Average OBP of the first 2-3 readings of the first 1-3 visits performed within 10-21 days (2-9 BP readings) was used in the analysis [12]. Eligible participants had OBP measurements in ≥1 visit and ≥2 readings [12].

HBP measurements were taken in the morning (6-12 am, before drug intake if treated) and the evening (6-12 pm) for 7 days within 1-2 weeks. Measurements were taken after a 2-5-minute sitting rest and 1-minute interval between measurements using validated electronic upper arm-cuff devices with cuff size appropriate to each individual's arm circumference [12]. Subjects with at least 12 valid HBP readings were included. Average HBP of 12-28

readings collected in 3-7 days was calculated per participant [12]. Eligible participants had HBP monitoring in ≥3 days and ≥12 readings [12].

ABP was monitored on a routine workday using validated oscillometric devices [12]. Measurements were scheduled at 15-30-minute intervals during daytime and 20-60-minute intervals during night-time. Day and night periods were defined according to the individual patients' diaries, apart from the Birmingham study that used fixed night-time period (11 pm-7 am). Average 24-hour and daytime ABP was calculated [12]. Eligible participants had ≥14 daytime and ≥7 nighttime ABP readings [12].

Definitions

MH was defined as normal OBP (<140/90 mmHg) and elevated HBP (≥135/85 mmHg), or ABP (24-hour average ≥130/80 mmHg), or both (*Any MH*). According to the presence of elevated HBP and/or ABP, subjects with MH were classified into 3 categories: (i) *Dual MH*: OBP <140/90 mmHg and HBP ≥135/85 mmHg and 24-hour ABP ≥130/80 mmHg; (ii) *Isolated Ambulatory MH*: OBP <140/90 mmHg and HBP <135/85 mmHg and 24-hour ABP ≥130/80 mmHg; (iii) *Isolated Home MH*: OBP <140/90 mmHg and HBP ≥135/85 mmHg and 24-hour ABP <130/80 mmHg.

Statistical analysis

The Kolmogorov-Smirnov test was used to assess normality following which continuous variables were compared using one-way analysis of variance (ANOVA) or Kruskal-Wallis test as appropriate. Chi-squared test was used to compare categorical variables. Determinants

of MH phenotypes were assessed using multivariate binary logistic regression analysis. Independent variables were age, gender, body mass index, diabetes mellitus, cardiovascular disease, hypercholesterolemia, antihypertensive drug treatment status, smoking status, alcohol consumption and high normal OBP status (systolic/diastolic 130-139/85-89 mmHg). Sensitivity analyses were performed by using awake-ABP ≥135/85 mmHg (instead of 24-hour ABP ≥130/80 mmHg) to define ambulatory hypertension and by redefining the MH diagnosis criteria (BP thresholds set at 5 mmHg lower for OBP and 5 mmHg higher for HBP and ABP) aiming to exclude from the analysis subjects with BP levels close to the diagnostic BP thresholds implying diagnostic uncertainty. The IBM SPSS Statistics 25 (SPSS Inc., Chicago, IL, USA) software was used. Results are expressed as mean±standard deviation (SD). A two-sided probability value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 2,383 subjects were included in the 3 centers' datasets of whom 1,971 (83%) with valid data for all the three BP measurement methods were analyzed. Mean age was 53.8±11.4 years, 52.6% were males and 32% treated for hypertension. Details of the participants' characteristics have been reported [12].

A total of 445 subjects (23%) had Any MH (normal OBP and elevated 24-hour ABP or HBP or both) and were included in the subsequent analyses. Mean age was 57.1±10.8 years (range 21-86), 245 (55.1%) were men and 217 (48.8%) were treated for hypertension **(Table 1)**. Of subjects with MH, 55% had high-normal OBP (130-139/85-89 mmHg), 35% normal OBP (120-129/80-84 mmHg) and 10% optimal OBP (<120/80 mmHg) **(Table 1)**. There was no difference between the untreated and treated MH group in the proportion of subjects with OBP within the high-normal, normal or optimal range (53%, 50% and 44% for untreated vs. 47%, 50% and 56% for treated group respectively; P=NS).

Among subjects with MH, 215 (48%) had Dual MH, 132 (30%) had Isolated Ambulatory MH and 98 (22%) had Isolated Home MH (**Figure 1**). In multivariate logistic regression analysis **(Table 2)** (i) history of cardiovascular disease independently increased the odds of Dual MH phenotype (odds ratio [OR] 2.30, $p<0.05$), (ii) high-normal OBP (versus lower) independently increased the odds of Dual MH phenotype (OR 2.48, $p<0.01$) and decreased the odds of Isolated Ambulatory MH (OR 0.39, $p<0.01$), (iii) female gender independently increased the odds of Isolated Ambulatory MH (OR 1.96, $p<0.01$) and (iv) older age independently decreased the odds of Isolated Ambulatory MH (OR 0.67, per 10 years

increase, p<0.01) and increased the odds of Isolated Home MH (OR 1.42, per 10 years increase, p<0.01).

When subjects with MH were divided into age subgroups <50 years, 50-65 and >65 years (120, 202 and 123 subjects respectively), Isolated Ambulatory MH appeared to be at least two-fold more common than Isolated Home MH in younger subjects and the reverse was the case in the older group, whereas there was no difference in the prevalence of Dual MH among these age subgroups (about 50%) **(Figure 2).**

In a secondary analysis using awake-ABP ≥135/85 mmHg (instead of 24-hour ABP ≥130/80 mmHg) to define ambulatory hypertension, similar results were found with 430 (22%) of the participants having any MH, and of subjects with any MH 201 (47%) with Dual MH, 117 (27%) Isolated Ambulatory MH and 112 (26%) Isolated Home MH. Predictors of MH phenotypes were comparable with the main analysis.

In a sensitivity analysis performed by redefining the MH diagnostic criteria in order to eliminate from the analysis subjects with BP values close to the diagnostic thresholds implying diagnostic uncertainty, BP thresholds were set 5 mmHg lower for OBP (135/85 mmHg) and 5 mmHg higher for HBP and 24-hour ABP (140/90 mmHg and 135/85 mmHg, respectively) and the MH definitions were modified accordingly. In this analysis 126 subjects (6%) had any MH (Dual MH 29%; Isolated Ambulatory MH 38%, Isolated Home MH 33%). In logistic regression analysis, only age was found to significantly influence the odds of MH phenotypes. Older age (per 10 year increase) independently decreased the odds of Isolated

Ambulatory MH (OR 0.35, $p<0.01$) and independently increased the odds of Isolated Home MH (OR 2.05, $p<0.01$).

DISCUSSION

This analysis of a large dataset of untreated and treated subjects from three European centers assessed with OBP, HBP and ABP measurements using similar protocols and according to current guidelines investigated the implications of using HBP and ABP in detecting MH. Main findings are: (i) About half of subjects with Any MH (ambulatory or home) have both ambulatory and home (Dual) MH (48%), and the rest (52%) have either Isolated MH (Ambulatory or Home), irrespective of the treatment status; (ii) Age seems to be the most important determinant of Isolated MH, with Isolated Ambulatory MH being much more common in younger subjects and Isolated Home MH much more common in older ones (Dual MH did not appear to be age-dependent); (iii) About half of subjects with any MH phenotype have OBP values within the high-normal BP range (55%), and the rest (45%) have OBP <130/80 mmHg, irrespective of the treatment status.

These data are important for clinical practice because MH detected either by ABP or HBP monitoring appears to convey similar prognostic information [3,5,6]. More importantly,
In the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) outcome study with 12 years follow-up, isolated elevation of office, or home, or ambulatory BP was associated with increased risk compared to subjects with low BP by all methods [6]. In the same line, an analysis from the Ohasama outcome study in Japan with 17 years follow-up showed that Isolated Ambulatory or Home MH is associated with the same risk of stroke as Dual MH [3]. Thus, it was concluded that both HBP and ABP measurements are needed to evaluate the cardiovascular risk accurately [3,6].

The fact that fewer than half of individuals with MH have this diagnosis confirmed by both ABP and HBP is supported by previous smaller studies with different design [3,13,14]. In 2005 Stergiou et al. [13] investigated 438 untreated or treated individuals attending a hypertension clinic and identified 79 subjects with MH, of whom 35 (44%) had Dual MH and 44 (56%) Isolated MH (N=27/17 for awake ABP/HBP). The Ohasama general population study [3] identified 280 subjects with MH, of whom 100 (36%) had Dual MH and 180 (64%) Isolated MH (24-hour ABP or HBP). Anstey et al. [14] in a community-based study in 333 untreated adults reported MH in 73 subjects, of whom 23 had Dual MH (32%) and 50 (68%) Isolated MH (N=36/14 for 24-hour ABP/HBP).

Disagreement between ABP and HBP monitoring has also been reported in diagnosing white coat hypertension (WCH). In a sub-analysis of the PAMELA general population study, Mancia et al. reported that among 391 subjects with any WCH, 58% had ‘partial’ WCH (on ABP and not HBP monitoring, or the reverse) [15]. More importantly, ‘partial’ WCH was associated with higher risk of cardiovascular and all-cause mortality than true WCH (identified by both ABM and HBP monitoring), but lower than of subjects with sustained hypertension [15].

The present results showing disagreement between HBP and ABP measurements in detecting MH challenge the current recommendation that these methods are interchangeable for clinical practice [8,9]. Factors responsible for this disagreement might be: (i) The imperfect reproducibility of both HBP and ABP measurement; (ii) The fact that in many of the cases

with disagreement the BP difference away from the threshold might be small and clinically irrelevant; (iii) Inherent differences between the two out-of-office BP measurement methods providing different information on the BP profile and behavior which differ among individuals with different condition and activities.

Several studies have shown that the reproducibility of both ABP and HBP is superior to that of OBP, yet this is still imperfect and diagnostic disagreement of repeated ABP or HBP is not uncommon [16]. However, studies which have evaluated ABP and HBP reported similar levels of diagnostic disagreement between them as with repeated HBP or repeated ABP [17]. These findings lead to the conclusion that the imperfect reproducibility of both methods is the main reason for their diagnostic disagreement, and therefore these methods should be regarded as interchangeable for hypertension diagnosis. Another factor to be considered in examining the diagnostic disagreement between HBP and ABP is that in many of these cases, the deviation from the BP threshold is small (<5 mmHg) and therefore the disagreement is clinically irrelevant. We have recently examined this issue in the same dataset as in the present study and demonstrated that most of the diagnostic disagreement between HBP and ABP measurements is either too small (arithmetic) or uncertain (BP too close to threshold) [12]. However, in an appreciable minority of cases (8.2%) there was considerable disagreement between the two methods which is most likely due to methodological and patient-related factors [12]. In the present analysis we performed a sensitivity analysis by excluding borderline cases, which largely reduced the prevalence of Any MH. However, again 70% of these cases had Isolated MH (ABP or HBP) and age was a major determinant with Isolated Ambulatory MH being much more common in younger subjects and Isolated Home MH in older ones. Thus, even after excluding uncertain cases, a consistent pattern of

disagreement between HBP and ABP remains, which is probably due to inherent differences between the two methods.

Several factors appeared to independently influence the prevelance of different MH phenotypes, including cardiovascular disease history, high-normal OBP, female gender and older age. However, in a sensitivity analysis performed by redefining the MH diagnostic criteria in order to eliminate from the analysis subjects with BP values close to the diagnostic thresholds implying diagnostic uncertainty, only age remained a significant predictor.

The issue of the influence of age on the relationship between BP measurements obtained by different methods has been rather neglected. Several factors during routine daily activities, which differ in younger compared to older individuals, may be responsible for differences between ABP and HBP measurements in different age groups. Daytime ABP might be selectively increased by more intense physical activity (work, younger people), or mental activity (job strain), or might be selectively reduced due to sedentary lifestyle (retirement, old age, musculoskeletal issues) and orthostatic hypotension (old age). On the other hand, HBP might be selectively increased when self-measurements induce anxiety, which is probably more common in the elderly. Thus, older patients might have lower daytime ABP than HBP and younger ones the reverse. Several studies have compared OBP with ABP and/or HBP measurements in different age groups [18-21]. An analysis of 642 untreated subjects aged 5-78 years who had OBP, ABP and HBP measurements showed higher daytime ABP than HBP in children, no difference after the age of 30 years, and lower daytime ABP than HBP after the age of 60 years [21]. These data might have predicted the findings of the

present study showing that Isolated Ambulatory MH is common in younger people and Isolated Home MH in older ones.

REFERENCES

1. Stergiou GS, Asayama K, Thijs L, Kollias A, Niiranen TJ, Hozawa A, et al. Prognosis of white-coat and masked hypertension: International Database of HOme blood pressure in relation to Cardiovascular Outcome. Hypertension 2014; **63**:675-682.
2. Banegas JR, Ruilope LM, de la Sierra A, Vinyoles E, Gorostidi M, de la Cruz JJ, et al. Relationship between Clinic and Ambulatory Blood-Pressure Measurements and Mortality. N Engl J Med 2018; **378**:1509-1520.
3. Satoh M, Asayama K, Kikuya M, Inoue R, Metoki H, Hosaka M, et al. Long-term stroke risk due to partial white-coat or masked hypertension based on home and ambulatory blood pressure measurements: The Ohasama Study. Hypertension 2016; **67**:48-55.
4. Palla M, Saber H, Konda S, Briasoulis A. Masked hypertension and cardiovascular outcomes: an updated systematic review and meta-analysis. Integr Blood Press Control 2018; **11**:11-24.
5. Pierdomenico SD, Pierdomenico AM, Coccina F, Clement DL, De Buyzere ML, De Bacquer DA, et al. Prognostic value of masked uncontrolled hypertension. Hypertension 2018; **72**:862-869.
6. 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.
7. Cuspidi C, Facchetti R, Quarti-Trevano F, Sala C, Tadic M, Grassi G, et al. Incident Left Ventricular Hypertrophy in Masked Hypertension. Hypertension 2019; **74**:56-62.

8. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018; **71**:1269-1324.
9. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens 2018; **36**:1953-2041.
10. Stergiou GS, Parati G, Vlachopoulos C, Achimastos A, Andreadis E, Asmar R, et al. Methodology and technology for peripheral and central blood pressure and blood pressure variability measurement: current status and future directions - Position statement of the European Society of Hypertension Working Group on blood pressure monitoring and cardiovascular variability. J Hypertens 2016; **34**:1665-1677.
11. Muntner P, Einhorn PT, Cushman WC, Whelton PK, Bello NA, Drawz PE, et al. Blood Pressure Assessment in Adults in Clinical Practice and Clinic-Based Research: JACC Scientific Expert Panel. J Am Coll Cardiol 2019; **73**:317-335.
12. Ntineri A, Niiranen TJ, McManus RJ, Lindroos A, Jula A, Schwartz C, et al. Ambulatory versus home blood pressure monitoring: frequency and determinants of blood pressure difference and diagnostic disagreement. J Hypertens 2019; In press.

13. 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**:772–8.
14. Anstey DE, Muntner P, Bello NA, Pugliese DN, Yano Y, Kronish IM, et al. Diagnosing masked hypertension using ambulatory blood pressure monitoring, home blood pressure monitoring, or both? Hypertension 2018; **72**:1200-1207.
15. Mancia G, Bombelli M, Brambilla G, Facchetti R, Sega R, Toso E, et al. Long-term prognostic value of white coat hypertension: an insight from diagnostic use of both ambulatory and home blood pressure measurements. Hypertension 2013; **62**:168-174.
16. Stergiou GS, Baibas NM, Gantzarou AP, Skeva II, Kalkana CB, Roussias LG, et al. Reproducibility of home, ambulatory, and clinic blood pressure: implications for the design of trials for the assessment of antihypertensive drug efficacy. Am J Hypertens 2002; **15**:101-104.
17. Stergiou GS, Ntineri A. The optimal schedule for self-home blood pressure monitoring. J Hypertens 2015; **33**:693-697.
18. Ishikawa J, Ishikawa Y, Edmondson D, Pickering TG, Schwartz JE. Age and the difference between awake ambulatory blood pressure and office blood pressure: a meta-analysis. Blood Press Monit 2011; **16**:159-167.
19. Conen D, Aeschbacher S, Thijs L, Li Y, Boggia J, Asayama K, et al. Age-specific differences between conventional and ambulatory daytime blood pressure values. Hypertension 2014; **64**:1073-1079.
20. Ntineri A, Stergiou GS, Thijs L, Asayama K, Boggia J, Boubouchairopoulou N, et al. Relationship between office and home blood pressure with increasing age: The

International Database of HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO). Hypertens Res 2016; **39**:612-617.

21. Stergiou GS, Ntineri A, Kollias A, Destounis A, Nasothimiou E, Roussias L. Changing relationship among clinic, home, and ambulatory blood pressure with increasing age. J Am Soc Hypertens 2015; **9**:544-552.

Legend to Figure 1

Prevalence of masked hypertension (MH) phenotypes.

Legend to Figure 2

Prevalence of masked hypertension (MH) phenotypes in different age subgroups.