Hypertension Research (2019) 42:1816–1823
https://doi.org/10.1038/s41440-019-0298-3

ARTICLE

Blood pressure cutoffs for white-coat and masked effects in a large population undergoing home blood pressure monitoring

Audes D. M. Feitosa[1,2,3] · Marco A. Mota-Gomes[4,5] · Weimar S. Barroso[6] · Roberto D. Miranda[7] · Eduardo C. D. Barbosa[8] · Rodrigo P. Pedrosa[2,3] · Paula C. Oliveira[9] · Camila L. D. M. Feitosa[2] · Andréa A. Brandão[10] · José L. Lima-Filho[1] · Andrei C. Sposito[11] · Antonio Coca[12] · Wilson Nadruz[1,11]

Received: 23 March 2019 / Revised: 8 May 2019 / Accepted: 11 June 2019 / Published online: 2 July 2019

Abstract

The values used to define the presence of white-coat or masked blood pressure (BP) effects are arbitrary. The aim of this study was to investigate the accuracy of several cutoff points based on the difference between office and home BP (ΔBP) values to detect white-coat uncontrolled (WUCH) and masked uncontrolled (MUCH) hypertension, which are phenotypes with adverse prognoses, in a large cohort of treated hypertensive patients. This multicenter cross-sectional study included 6,049 treated hypertensive patients (40% males, mean age 59.1 ± 14.4 years) who underwent office and home BP monitoring. We compared the sensitivity, specificity, area under curve (AUC), and positive (PPV) and negative (NPV) predictive values of several ΔBP cutoffs to detect WUCH and MUCH. The 15/9 mmHg cutoff, which reflects a 1.0 standard deviation of the ΔBP, showed the best AUC (0.783, 95% CI = 0.772–0.794) for the detection of WUCH, particularly in individuals with office grade 1 hypertension (AUC = 0.811, 95% CI = 0.793–0.829). The −1/−1 mmHg cutoff, which considers all individuals who had lower systolic or diastolic BP levels in the office than at home, had the highest AUC (0.822, 95% CI = 0.808–0.836) for the detection of MUCH. Both cutoff values also had the best performances for identifying all patients with higher and lower office-than-home BP grades. In conclusion, the 15/9 and −1/−1 mmHg cutoffs showed the best performance for the detection of treated hypertensive patients with WUCH and MUCH, respectively, and therefore might be markers of significant white-coat and masked effects and could be useful for identifying preferential targets for more routine home BP measures.

Keywords Home blood pressure · White-coat hypertension · Masked hypertension

Introduction

Hypertension is a major risk factor for cardiovascular events, including stroke and myocardial infarction [1, 2].

Supplementary information The online version of this article (https://doi.org/10.1038/s41440-019-0298-3) contains supplementary material, which is available to authorized users.

✉ Wilson Nadruz
wilnj@fcm.unicamp.br

1 Laboratory of Immunopathology Keizo Asami, Federal University of Pernambuco, Recife, PE, Brazil

2 Pronto Socorro Cardiológico de Pernambuco (PROCAPE), University of Pernambuco, Recife, PE, Brazil

3 MCor, Memorial São José Hospital–Rede D´Or São Luiz, Recife, PE, Brazil

4 Department of Internal Medicine, State University of Health Sciences of Alagoas, Maceió, AL, Brazil

5 CESMAC University Center, Maceió, AL, Brazil

6 Hypertension League, Federal University of Goiás, Goiânia, GO, Brazil

7 Geriatrics Division, Federal University of São Paulo, São Paulo, SP, Brazil

8 Hypertension League of Porto Alegre, Porto Alegre, RS, Brazil

9 RealCor, Royal Portuguese Hospital of Charity in Pernambuco, Recife, PE, Brazil

10 School of Medicine, State University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil

11 Department of Internal Medicine, School of Medical Sciences, State University of Campinas, São Paulo, SP, Brazil

12 Hypertension and Vascular Risk Unit, Department of Internal Medicine, Hospital Clínic (IDIBAPS) Effect, University of Barcelona, Barcelona, Spain

The management of hypertension depends on accurate blood pressure (BP) measurement so that antihypertensive treatment can be appropriately recommended [3]. BP is frequently assessed at the office, but this measure usually over/underestimates the true BP values [4, 5], resulting in phenotypes with worse prognosis compared with controlled hypertension among treated hypertensive patients, such as white-coat (high office and normal out-of-office BP) uncontrolled (WUCH) and masked (normal office and high out-of-office BP) uncontrolled (MUCH) hypertension [6–8].

The difference between office and out-of-office BP measures, which, depending on the direction, can be defined as a white-coat or masked effect and may reflect an inherent characteristic of BP in the examined individual because office-induced increases or decreases in BP usually persist in subsequent measures [9–12]. The magnitude of this difference can be marked and relevant to patient management [12, 13]. For instance, people with significant white-coat effects are recommended to have more routine out-of-office BP measures as an adjuvant strategy to monitor the therapeutic response [14]. However, there is no consensus value to define the presence of significant white-coat or masked effects in treated hypertensive patients because although several BP cutoffs have been suggested, their clinical relevance has not been established [13, 15–19]. The main objective of the present study was to investigate the sensitivity, specificity and accuracy of several cutoff points for the difference between office and home BP measures (ΔBP) to detect WUCH and MUCH in a large multicenter sample of patients using BP-lowering medications who underwent home BP monitoring. In addition, we tested the performance of the cutoffs for the identification of patients with higher and lower office-than-home BP grades.

Methods

Design

This cross-sectional study included individuals aged 18 years or older from two independent populations. The first population comprised 5777 individuals (2838 using and 2939 not using BP-lowering medications) from two Brazilian cardiology centers who underwent home BP monitoring exams between March 2005 and February 2018 [20, 21]. The second population comprised 5793 individuals (3211 using and 2582 not using BP-lowering medications) from 46 Brazilian centers who performed home BP monitoring and used an online platform (www.telemrpa.com) between May 2017 and November 2018. For the main analysis in this study, we evaluated 6049 participants using BP-lowering medications who were merged from the two studied populations. In addition, we also evaluated the 5521 participants merged from the two studied populations who were not using BP-lowering medications. The protocol conformed to the ethics guidelines in the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the Oswaldo Cruz University Hospital/PROCAPE Complex and by the Federal University of Goiás, which waived the requirement for informed consent.

BP measurements, hypertension phenotypes and clinical variables

Office BP was defined as the mean of two clinical BP readings taken after at least 3 min of rest in a medical office. On the following day, participants started to measure their BP at home. Three home BP measurements were obtained in the morning and in the evening after at least 3 min of rest for 4 consecutive days. Home BP values were defined as the average of both the morning (11.6 ± 1.1 readings) and evening (11.3 ± 1.4 readings) measurements. Devices from Omron (Omron Healthcare, Japan), Microlife (Microlife, UK) and Geratherm (Geratherm Medical AG, Germany) were used to perform the BP measurements, and the same device was used for all office and home BP measurements in each participant.

Hypertension phenotypes among treated participants were defined as follows: controlled hypertension [office systolic BP (SBP) < 140 mmHg and diastolic BP (DBP) < 90 mmHg and home SBP < 135 mmHg and DBP < 85 mmHg], WUCH (office SBP ≥ 140 mmHg or DBP ≥ 90 mmHg and home SBP < 135 mmHg and DBP < 85 mmHg), MUCH (office SBP < 140 mmHg and DBP < 90 mmHg and home SBP ≥ 135 mmHg or DBP ≥ 85 mmHg) and sustained uncontrolled hypertension (SUCH) (office SBP ≥ 140 or DBP ≥ 90 mmHg and home SBP ≥ 135 or DBP ≥ 85 mmHg) [20, 22]. The corresponding terms among untreated participants were normotension, white-coat hypertension, masked hypertension, and sustained hypertension, respectively.

Hypertension in the office was defined as grade 1 if the SBP = 140–159 or the DBP = 90–99 mmHg, grade 2 if the SBP = 160–179 or the DBP = 100–109 mmHg and grade 3 if the SBP was ≥180 or the DBP was ≥110 mmHg [22], while hypertension at home was defined as grade 1 if the SBP = 135–154 or the DBP = 85–94 mmHg, grade 2 if the SBP = 155–174 or the DBP = 95–104 mmHg and grade 3 if the SBP was ≥175 or the DBP was ≥105 mmHg [14].

Data on sex, age and body mass index were gathered from all participants. Information on the use of specific antihypertensive medications was available for 4091 individuals (68% of the participants who were using BP-lowering medications).

BP cutoffs for white-coat and masked effect

The differences between office and home SBP (ΔSBP) and DBP (ΔDBP) measurements among participants using BP-lowering medications were used to build cutoffs to identify white-coat (office BP higher than home BP) and masked (office BP higher than home BP) effects. Seven cutoffs for the white-coat effect were selected: (a) ΔSBP ≥ 30 mmHg or ΔDBP ≥ 18 mmHg [reflecting 2.0 standard deviations (SD) of ΔSBP or ΔDBP]; b) ΔSBP ≥ 20 mmHg or ΔDBP ≥ 15 mmHg [16]; (c) ΔSBP ≥ 20 mmHg or ΔDBP ≥ 10 mmHg [13, 15]; (d) ΔSBP ≥ 15 mmHg or ΔDBP ≥ 9 mmHg (reflecting 1.0 SD of ΔSBP or ΔDBP); (e) ΔSBP ≥ 14 mmHg or ΔDBP ≥ 8 mmHg [based on receiver operating characteristic (ROC) curve cutoff points for ΔSBP or ΔDBP that showed the best association with WUCH in our sample]; (f) ΔSBP ≥ 12 mmHg (reflecting the mean ΔSBP plus 0.2 SD of ΔSBP) [17]; and (g) ΔSBP ≥ 10 mmHg [19]. Seven cutoffs for the masked effect were selected: (a) ΔSBP ≤ −15 mmHg or ΔDBP ≤ −9 mmHg (reflecting −1.0 SD of ΔSBP or ΔDBP); (b) SBP ≤ −8 mmHg or DBP ≤ −4 mmHg (reflecting the mean ΔSBP minus 1.1 SD of ΔSBP or mean ΔDBP minus 1.1 SD of ΔDBP) [17]; c) ΔSBP ≤ −8 mmHg (reflecting the mean ΔSBP minus 1.1 SD of ΔSBP) [17]; (d) ΔSBP ≤ −6 mmHg or ΔDBP ≤ −3 mmHg (reflecting the mean ΔSBP minus 1 SD of ΔSBP or the mean ΔDBP minus 1 SD of ΔDBP) [23]; (e) ΔSBP ≤ −6 mmHg (reflecting the mean ΔSBP minus 1 SD of ΔSBP) [23]; (f) ΔSBP ≤ −5 mmHg or ΔDBP ≤ −2 mmHg (based on the ROC curve cutoff points for ΔSBP or ΔDBP that showed the best association with MUCH in our sample; and g) ΔSBP ≤ −1 mmHg or ΔDBP ≤ −1 mmHg [17, 18, 23].

Statistical analysis

Continuous and categorical variables are expressed as the mean ± SD and the number of subjects and proportion, respectively. In the primary analyses, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) derived from ROC curves with the studied cutoffs for detecting WUCH or MUCH among treated hypertensive participants were calculated. The tests of equality of the AUCs from the ROC curves were performed with the Stata *roccomp* command, using a chi-square test. In the secondary analyses, we compared the performance of the cutoffs to detect: (a) all treated hypertensive participants with significant decreases in BP grade at home, i.e., the sum of the participants with WUCH and those with SUCH who had a hypertension grade at the office higher than that at home and (b) all treated hypertensive participants with significant increases in BP grade at home, i.e., the sum of the participants with MUCH and those with SUCH who had higher hypertension grades at home than at the office. For the sensitivity analyses, we repeated the primary analysis as follows: (1) in all treated hypertensive participants stratified by sex; (2) in the subsample of participants with available information on anti-hypertensive drug class use ($n = 4091$); and (3) in the sample of individuals who were not taking antihypertensive medications ($n = 5521$). P-values < 0.05 were considered statistically significant. The statistical analysis was performed using Stata software version 14.1 (Stata Corp LP, College Station, TX, USA).

Results

The clinical characteristics of the treated hypertensive participants ($n = 6049$) are shown in Table 1. These individuals were 40% male and 59.1 ± 14.4 years old and had a body mass index of 28.9 ± 5.1 kg/m^2. The office SBP, office DBP, home SBP and home DBP values were 138.2 ± 21.1, 82.9 ± 12.2, 128.9 ± 16.3 and 77.2 ± 10.3 mmHg, respectively, resulting in ΔSBP and ΔDBP values of 9.2 ± 15.3 and 5.7 ± 8.8 mmHg, respectively (Table 1 and Supplementary Fig. 1). The numbers and percentages of participants with controlled hypertension, WUCH, MUCH and SUCH were 2063 (43%), 1140 (19%), 537 (9%), and 1769 (29%), respectively (Table 1).

White-coat effect

The distribution of treated hypertensive participants according to the 7 cutoffs for the white-coat effect (ΔSBP/ΔDBP = 30/18, 20/15, 20/10, 15/9, or 14/8 mmHg, and ΔSBP = 12 or 10 mmHg) is shown in Supplementary Table 1. Table 2 shows the sensitivity, specificity, PPV, NPV and AUC for the studied cutoffs for the detection of WUCH. The 15/9 mmHg cutoff resulted in the highest AUC (0.783, 95% CI = 0.772–0.794) for the detection of WUCH, followed by the 14/8 mmHg (AUC = 0.778, 95% CI = 0.768–0.788; $p = 0.046$ compared with the 15/9 mmHg cutoff) and 20/10 mmHg (AUC = 0.769, 95% CI = 0.756–0.783; $p = 0.004$ compared with the 15/9 mmHg cutoff) cutoffs. The sensitivity and specificity of the 15/9 mmHg cutoff were 89.7 (95% CI = 87.8–91.4) and 66.9 (95% CI = 65.6–68.3), respectively.

Most (81%) of the participants with WUCH had office grade 1 hypertension. In this subpopulation, the 15/9 mmHg cutoff resulted in the highest numerical AUC for the detection of WUCH (0.811, 95% CI = 0.793–0.829), with a sensitivity of 87.4 (95% CI = 85.1–89.4) and a specificity of 74.9 (95% CI = 71.9–77.7). In contrast, the studied cutoffs showed poor performance among participants with office BP grades 2 and 3 hypertension due to the low specificity for the detection of WUCH (Supplementary Table 2).

We further tested the ability of the studied cutoffs to identify all treated hypertensive individuals with significant decreases in BP grades at home ($n = 1739$). The sum of participants with WUCH and those with SUCH who had a hypertension grade at the office higher than at home was calculated (Table 3). In this analysis, the 15/9 mmHg cutoff resulted in the highest AUC (0.833, 95% CI = 0.823–0.842; p-value at least ≤ 0.020 compared with all other cutoffs) among the studied thresholds, with a sensitivity of 91.1 (95% CI = 89.7–92.4) and a specificity of 75.4 (95% CI = 74.1–76.7).

Table 1 Characteristics of treated hypertensive patients

Characteristics	$n = 6049$
Male sex, *n* (%)	2388 (40)
Age (years)	59.1 ± 14.4
Body mass index (kg/m^2)	28.9 ± 5.1
Office SBP (mmHg)	138.2 ± 21.1
Office DBP (mmHg)	82.9 ± 12.2
Home SBP (mmHg)	128.9 ± 16.3
Home DBP (mmHg)	77.2 ± 10.3
Valid home BP measures, *n*	23 ± 2
HT phenotypes, *n* (%)	
Controlled HT	2603 (43)
White-coat uncontrolled HT	1140 (19)
Masked uncontrolled HT	537 (9)
Sustained uncontrolled HT	1769 (29)
Office BP grades, *n* (%)	
Normal (<140/90 mmHg)	3140 (52)
Grade 1 HT (140–159/90–99 mmHg)	1811 (30)
Grade 2 HT (160–179/100–109 mmHg)	741 (12)
Grade 3 HT (≥180/110 mmHg)	357 (6)
Home BP grades, *n* (%)	
Normal (<135/85 mmHg)	3743 (62)
Grade 1 HT (135–154/85–94 mmHg)	1740 (29)
Grade 2 HT (155–174/95–104 mmHg)	435 (7)
Grade 3 HT (≥175/105 mmHg)	131 (2)

BP blood pressure, *SBP* systolic BP, *DBP* diastolic BP, *HT* hypertension

Masked effect

The distribution of treated hypertensive participants according to the 7 cutoffs for the detection of the masked effect (ΔSBP/ΔDBP = −15/−9, −8/−4, −6/−3, −5/−2 or −1/−1 mmHg, and ΔSBP = −8 or −6 mmHg) is shown in Supplementary Table 3. The sensitivity, specificity, PPV, NPV and AUC for the studied cutoffs for the detection of MUCH are shown in Table 4. The −1/−1 mmHg cutoff resulted in the highest AUC (0.822, 95% CI = 0.808–0.836; p at least ≤ 0.001 compared with the other studied cutoffs), with a sensitivity and specificity of 90.1 (95% CI = 87.3–92.5) and 74.2 (95% CI = 73.0–75.4), respectively.

We also tested the accuracy of the proposed cutoffs for the identification of all treated hypertensive individuals with significant increases in BP grades at home ($n = 701$), i.e., the sum of the participants with MUCH and those with SUCH who had hypertension grades higher at home than at the office (Table 5). The −1/−1 mmHg cutoff resulted in the highest AUC (0.826, 95% CI = 0.813–0.839; p at least ≤ 0.005 compared with the AUCs of the other cutoffs), with a sensitivity of 89.2 (95% CI = 86.6–91.4) and specificity of 76.0 (95% CI = 74.9–77.2).

Sensitivity analysis

We repeated the primary analysis stratified by sex. This sensitivity analysis showed that the 15/9 and −1/−1 mmHg

Table 2 Performance of studied cutoffs derived from the difference between office and home BP to detect white-coat uncontrolled hypertension* among treated hypertensive patients

ΔBP cutoffs, mmHg	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	AUC (95% CI)	*p*-value**
30/18	38.0 (35.2–40.9)	92.8 (92.1–93.5)	55.2 (51.6–58.7)	86.6 (85.6–87.5)	0.654 (0.640–0.669)	<0.001
20/15	66.3 (63.5–69.1)	84.0 (82.9–85.0)	49.0 (46.5–51.5)	91.5 (90.6–92.3)	0.751 (0.737–0.766)	<0.001
20/10	79.5 (77.0–81.8)	74.4 (73.1–75.6)	41.9 (39.8–44.0)	94.0 (93.2–94.7)	0.769 (0.756–0.783)	0.004
15/9	89.7 (87.8–91.4)	66.9 (65.6–68.3)	38.7 (36.8–40.5)	96.6 (95.9–97.1)	0.783 (0.772–0.794)	——
14/8	92.5 (90.9–94.0)	63.0 (61.6–64.4)	36.7 (35.0–38.5)	97.3 (96.7–97.9)	0.778 (0.768–0.788)	0.046
12 (SBP)	83.1 (80.8–85.2)	70.6 (69.3–71.8)	39.6 (37.6–41.6)	94.7 (93.9–95.4)	0.768 (0.756–0.781)	0.008
10 (SBP)	87.7 (85.7–89.6)	65.1 (63.8–66.5)	36.9 (35.1–38.7)	95.8 (95.1–96.5)	0.764 (0.753–0.776)	0.002

ΔBP difference between office and home BP, *AUC* area under ROC curve, *PPV* positive predictive value, *NPV* negative predictive value, *BP* blood pressure, *SBP* systolic BP; *DBP* diastolic BP; *CI* confidence interval

*Office SBP ≥ 140 or DBP ≥ 90 mmHg and home SBP < 135 and DBP < 85 mmHg

***p*-value for the difference between AUC of studied BP cutoffs vs. AUC of 15/9 mmHg cutoff

Table 3 Performance of studied BP cutoffs derived from the difference between office and home BP to detect the sum of patients with white-coat uncontrolled hypertension* and those with sustained uncontrolled hypertension who had hypertension grade higher at the office than at home among treated hypertensive patients

ΔBP cutoffs, mmHg	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	AUC (95% CI)	*p*-value**
30/18	39.9 (37.5–42.2)	97.9 (97.4–98.3)	88.3 (85.8–90.4)	80.1 (79.0–81.2)	0.689 (0.677–0.700)	<0.001
20/15	68.9 (66.7–71.1)	92.0 (91.1–92.8)	77.6 (75.5–79.7)	88.0 (87.0–88.9)	0.804 (0.793–0.816)	<0.001
20/10	81.8 (79.9–83.6)	82.8 (81.7–83.9)	65.8 (63.7–67.8)	91.9 (91.0–92.7)	0.823 (0.813–0.834)	0.020
15/9	91.1 (89.7–92.4)	75.4 (74.1–76.7)	59.9 (58.0–61.8)	95.5 (94.7–96.1)	0.833 (0.823–0.842)	–
14/8	93.6 (92.3–94.7)	71.1 (69.8–72.5)	56.7 (54.8–58.5)	96.5 (95.8–97.1)	0.823 (0.815–0.832)	<0.001
12 (SBP)	84.9 (83.2–86.6)	78.8 (77.5–80.0)	61.7 (59.8–63.7)	92.8 (92.0–93.7)	0.819 (0.808–0.829)	0.004
10 (SBP)	89.0 (87.4–90.4)	73.0 (71.6–74.3)	57.1 (55.2–58.9)	94.2 (93.4–95.0)	0.810 (0.800–0.820)	<0.001

ΔBP difference between office and home BP, *AUC* area under ROC curve, *PPV* positive predictive value, *NPV* negative predictive value, *BP* blood pressure, *SBP* systolic BP, *DBP* diastolic BP, *CI* confidence interval

*Office SBP ≥ 140 or DBP ≥ 90 mmHg and home SBP < 135 and DBP < 85 mmHg

***p*-value for the difference between AUC of studied BP cutoffs vs. AUC of 15/9 mmHg cut-off

Table 4 Performance of studied cutoffs derived from the difference between office and home BP to detect masked uncontrolled hypertension* among treated hypertensive patients

ΔBP cutoffs, mmHg	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	AUC (95% CI)	*p*-value**
−15/−9	32.6 (28.6–36.7)	95.7 (95.2–96.2)	42.6 (37.7–47.5)	93.6 (92.9–94.2)	0.642 (0.622–0.662)	<0.001
−8/−4	65.2 (61.0–69.2)	87.2 (86.3–88.1)	33.2 (30.3–36.1)	96.3 (95.7–96.8)	0.762 (0.741–0.783)	<0.001
−8 (SBP)	48.6 (44.3–52.9)	92.7 (91.9–93.3)	39.2 (35.5–43.0)	94.9 (94.2–95.4)	0.706 (0.685–0.728)	<0.001
−6/−3	74.1 (70.2–77.8)	84.0 (83.0–85.0)	31.1 (28.6–33.7)	97.1 (96.6–97.5)	0.791 (0.772–0.810)	<0.001
−6 (SBP)	57.5 (53.2–61.8)	90.6 (89.8–91.4)	37.4 (34.1–40.8)	95.6 (95.0–96.2)	0.741 (0.719–0.762)	<0.001
−5/−2	79.0 (75.3–82.3)	80.9 (79.8–81.9)	28.7 (26.4–31.1)	97.5 (97.0–98.0)	0.799 (0.781–0.817)	0.001
−1/−1	90.1 (87.3-92.5)	74.2 (73.0-75.4)	25.4 (23.5–27.4)	98.7 (98.3–99.0)	0.822 (0.808–0.836)	–

ΔBP difference between office and home BP, *AUC* area under ROC curve, *PPV* positive predictive value, *NPV* negative predictive value, *BP* blood pressure, *SBP* systolic BP, *DBP* diastolic BP, *CI* confidence interval

*Office SBP < 140 and DBP < 90 mmHg and home SBP ≥ 135 or DBP ≥ 85 mmHg

***p*-value for the difference between AUC of studied BP cutoffs vs. AUC of −1/−1 mmHg cutoff

Table 5 Performance of studied BP cutoffs derived from the difference between office and home BP to detect the sum of patients with masked uncontrolled hypertension* and those with sustained uncontrolled hypertension who had hypertension grade lower at the office than at home among treated hypertensive patients

ΔBP cutoffs, mmHg	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	AUC (95% CI)	*p*-value**
−15/−9	33.7 (30.2–37.3)	96.7 (96.2–97.2)	57.4 (52.5–62.3)	91.8 (91.0–92.5)	0.652 (0.634–0.670)	<0.001
−8/−4	65.8 (62.1–69.3)	88.9 (88.0–89.7)	43.7 (40.7–46.8)	95.2 (94.6–95.8)	0.773 (0.755–0.791)	<0.001
−8 (SBP)	49.2 (45.5–53.0)	94.0 (93.3–94.6)	51.8 (47.9–55.7)	93.4 (92.7–94.0)	0.716 (0.697–0.735)	<0.001
−6/−3	74.3 (70.9–77.5)	85.8 (84.9–86.8)	40.7 (38.0–43.5)	96.2 (95.6–96.7)	0.801 (0.784–0.818)	<0.001
−6 (SBP)	57.1 (53.3–60.8)	92.0 (91.3–92.7)	48.4 (44.9–51.8)	94.2 (93.6–94.9)	0.745 (0.727–0.764)	<0.001
−5/−2	79.2 (76.0–82.1)	82.7 (81.7–83.7)	37.6 (35.1–40.1)	96.8 (96.3–97.3)	0.810 (0.794–0.825)	0.005
−1/−1	89.2 (86.6–91.4)	76.0 (74.9–77.2)	32.8 (30.7–35.0)	98.2 (97.7–98.6)	0.826 (0.813–0.839)	–

ΔBP difference between office and home BP, *AUC* area under ROC curve, *PPV* positive predictive value, *NPV* negative predictive value, *BP* blood pressure, *SBP* systolic BP, *DBP* diastolic BP, *CI* confidence interval

*Masked effect was defined as office SBP < 140 and DBP < 90 mmHg and home SBP ≥ 135 or DBP ≥ 85 mmHg

***p*-value for the difference between AUC of studied BP cutoffs vs. AUC of −1/−1 mmHg cutoff

cutoffs resulted in the highest AUC values for the detection of WUCH and MUCH, respectively, in treated participants of both sexes (Supplementary Tables 4 and 5).

In 4091 treated participants, information regarding the use of antihypertensive drug classes was available. This subsample had similar clinical characteristics compared with the total population of treated hypertensive individuals (Supplementary Table 6), and the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, betablockers, calcium channel blockers, central alpha agonists and vasodilators was observed in 19%, 61%, 37%, 30%, 26%, 4%, and 1% of the participants, respectively. In this subsample, the 15/9 and −1/−1 mmHg cutoffs also resulted in the highest AUC values to identify WUCH and MUCH, respectively, as well as significant shifts in BP grades from office to home (Supplementary Tables 7 and 8).

We further evaluated the accuracy of the cutoffs for the identification of white-coat hypertension, masked hypertension and different office-than-home BP grades in 5521 individuals who performed home BP monitoring and were not taking BP-lowering medications (Supplementary Tables 9, 10, and 11). These additional analyses also showed that the 15/9 and −1/−1 mmHg cutoffs resulted in the highest AUC values for the identification of white-coat hypertension and masked hypertension, respectively, as well as differences in office and home BP grades.

Discussion

This study compared the performance of several ΔBP cutoffs for the detection of WUCH or MUCH, as well as higher or lower office-than-home BP grades in a large multicenter population of treated hypertensive patients and reported two major findings. First, the 15/9 mmHg cutoff resulted in the best performance with regard to the detection of WUCH, particularly in subjects with office grade 1 hypertension. This cutoff also had higher accuracy for the detection of all individuals who had a higher BP grade at the office than at home. Second, the −1/−1 mmHg cutoff resulted in the best performance for the identification of MUCH, as well as all individuals who had higher BP grades at home than in the office. These findings suggest that the 15/9 and −1/−1 mmHg cutoffs might be markers of significant white-coat and masked effects, respectively, among treated hypertensive individuals in clinical practice.

Hypertensive patients with a significant white-coat effect have been recommended to perform more routine out-of-office BP measures as an adjuvant strategy to monitor the therapeutic response [14]. However, there is no consensus value to define the presence of a significant white-coat effect because although several ΔBP cutoffs have been suggested, their clinical meaning is uncertain [13, 15–17, 19]. This lack of standardization in the definition of a significant white-coat effect may have potential deleterious impacts, either leading to unnecessary out-of-office monitoring, which can be costly and inconvenient for patients [24], or excluding from more routine out-of-office evaluation patients who would benefit from this approach. In our main analysis, we investigated the ability of several ΔBP cutoffs to detect WUCH among treated hypertensive patients. We chose the detection of WUCH as the primary endpoint because this phenotype is related to worse long-term prognosis and may result in the prescription of unnecessary treatment with potential adverse effects that may be markedly debilitating, particularly in elderly patients [7, 25]. We found that the 15/9 mmHg cutoff resulted in the best accuracy, as assessed by the AUC, for the identification of WUCH, particularly among participants with office grade 1 hypertension, which comprised the majority of patients with WUCH. This finding might be clinically relevant because it suggests that the 15/9 mmHg cutoff has the best performance for the detection of WUCH mainly among individuals who are at higher risk of having this phenotype. In contrast, no proposed cutoff showed good performance for the identification of WUCH among participants with office grade 2 and 3 hypertension, suggesting that the studied cutoffs might not be suitable for detecting WUCH in these subgroups of patients. It is also noteworthy that the 15/9 mmHg cutoff resulted in the highest accuracy for the detection of all individuals who had a lower BP grade at home than in the office, including participants with SUCH. Together, these results indicate that the 15/9 mmHg cutoff has a superior ability to identify treated hypertensive patients who are at greater risk of having a higher office-than-home BP grade. Given that office-induced increases in BP usually persist in subsequent measures [9, 10, 12], our data suggest that patients with uncontrolled BP at the office and a ΔBP ≥ 15/9 mmHg could be preferential targets for more routine home BP measures aiming to define appropriate therapy regimens.

The 20/10 mmHg cutoff has been the most commonly used value to define the presence of a significant white-coat effect according to several guidelines [13, 14, 25, 26]. This cutoff originally represented approximately 2.0 SD of a series of previously reported ambulatory BP readings [13]. However, in our analysis, the 20/10 mmHg cutoff resulted in an inferior AUC, as well as a lower sensitivity for the identification of WUCH compared with the 15/9 mmHg cutoff. These findings indicate that, compared with the 20/10 mmHg cutoff, the 15/9 mmHg cutoff may be a more representative marker of a significant white-coat effect. It should be acknowledged, however, that the 15/9 mmHg value reflects 1.0 SD of ΔSBP and ΔDBP, respectively, obtained from our sample. Because the ΔBP usually varies according to the studied population [17, 23], further studies

in alternative samples of treated hypertensive individuals are necessary to evaluate whether the 15/9 mmHg value per se or distinct values reflecting 1.0 SD of the ΔBP would result in the best accuracy for the detection of WUCH.

Few ΔBP cutoffs have been suggested to define the presence of the masked effect [17, 18, 23]. The −1/−1 mmHg cutoff, which considers all individuals who had lower SBP or DBP values at the office than at home, has been the most commonly used definition of the masked effect [18, 23, 24], even though its clinical relevance remains unknown. In our analysis, we compared the abilities of several ΔBP cutoffs to detect MUCH, a phenotype that is associated with an adverse prognosis [7, 8]. We found that the −1/−1 mmHg cutoff had the best accuracy and sensitivity for the detection of participants with MUCH. This cutoff also had the best accuracy for the identification of the combination of participants with MUCH and those with SUCH who had higher hypertension grades at home than at the office. Given that the masked effect has good reproducibility in subsequent measures [11], the present data suggest that the −1/−1 mmHg cutoff might be useful for the stratification of treated hypertensive patients with a higher risk of MUCH who would benefit from more regular out-of-office monitoring.

Some results of this report deserve additional comments. We observed that the cutoffs based solely on ΔSBP rather than on both ΔSBP and ΔDBP had inferior performance for the identification of either WUCH or MUCH. Therefore, the inclusion of both ΔSBP and ΔDBP appears to be necessary for the adequate definition of white-coat and masked effect thresholds. We also performed additional analyses evaluating the accuracy of the studied cutoffs for the detection of WUCH and MUCH, as well as higher or lower office-than-home BP grades in a large subsample of patients with available information on the use of antihypertensive drug classes. This analysis not only provided information on the pattern of BP-lowering medications used by our studied population but also suggested that the use of specific antihypertensive classes did not influence the association between the proposed cutoffs and the presence of WUCH or MUCH. Last, we tested the performance of the cutoffs in a large sample of individuals not using BP-lowering medications and observed that 15/9 and −1/−1 mmHg had the best accuracy for the detection of white-coat hypertension and higher office-than-home BP grades, as well as masked hypertension and lower office-than-home BP grades, respectively. These findings indicate that such cutoffs might also be useful for identifying individuals not using antihypertensive medications who would benefit from more routine home BP evaluations.

Some limitations in the present report must be considered. First, information on additional cardiovascular characteristics of the sample, such as smoking and diabetes status, as well as on alternative medications that might influence BP, including nasal vasoconstrictor agents, nonsteroidal anti-inflammatory drugs and oral contraceptives, was not available. Second, the lack of outcomes at follow-up does not allow us to confirm the prognostic value of the proposed cutoffs. Third, although both home BP and ambulatory BP monitoring are techniques used to obtain out-of-office measures, their results may not be interchangeable for estimating white-coat and masked effects [11, 27]. Therefore, further research should be performed in individuals undergoing ambulatory BP monitoring to validate the current findings. Conversely, the multicenter nature of the protocol and the large sample size are strengths of this study. Notably, to the best of our knowledge, this is the largest home BP monitoring study aiming to define thresholds for masked and white-coat effects.

In conclusion, our study showed that the 15/9 mmHg cutoff had the best performance for the detection of WUCH and higher office-than-home BP grades, while the −1/−1 mmHg cutoff had the best performance for the identification of MUCH and lower office-than-home BP grades in a large multicenter sample of hypertensive patients using BP-lowering medications. These cutoffs might be markers of significant white-coat and masked effects and could be useful for the identification of preferential targets for more routine home BP measures aiming to define appropriate therapy regimens.

Funding Dr. Nadruz was supported by grant 306154/2017-0 from CNPq, Brazil.

Compliance with ethical standards

Conflict of interest Dr. WN was supported by grant 306154/2017-0 from CNPq, Brazil. Drs. ADMF, MAM-G, WSB, AAB, RDM and ECDB are owners of the online TELEMRPA platform (TELEMRPA LTDA, Brazil). The remaining authors declare that they have no conflict of interest.

References

1. Nadruz W Jr, Claggett B, Henglin M, Shah AM, Skali H, Rosamond WD, et al. Racial disparities in risks of stroke. N Engl J Med. 2017;376:2089–90.
2. Nadruz W Jr, Claggett B, Henglin M, Shah AM, Skali H, Rosamond WD, et al. Widening racial differences in risks for coronary heart disease. Circulation. 2018;137:1195–7.
3. Lovibond K, Jowett S, Barton P, Caulfield M, Heneghan C, Hobbs FD, et al. Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: a modelling study. Lancet. 2011;378:1219–30.
4. Asayama K, Satoh M, Kikuya M. Diurnal blood pressure changes. Hypertens Res. 2018;41:669–78.

5. Munakata M. Clinical significance of stress-related increase in blood pressure: current evidence in office and out-of-office settings. Hypertens Res. 2018;41:553–69.
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;47:846–53.
7. 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;378:1509–20.
8. Fujiwara T, Yano Y, Hoshide S, Kanegae H, Kario K. Association of cardiovascular outcomes with masked hypertension defined by home blood pressure monitoring in a Japanese General Practice Population. JAMA Cardiol. 2018;3:583–90.
9. Mancia G, Bertinieri G, Grassi G, Parati G, Pomidossi G, Ferrari A, et al. Effects of blood-pressure measurement by the doctor on patient's blood pressure and heart rate. Lancet. 1983;2:695–8.
10. Muxfeldt ES, Fiszman R, de Souza F, Viegas B, Oliveira FC, Salles GF. Appropriate time interval to repeat ambulatory blood pressure monitoring in patients with white-coat resistant hypertension. Hypertension. 2012;59:384–9.
11. Viera AJ, Lin FC, Tuttle LA, Olsson E, Stankevitz K, Girdler SS, et al. Reproducibility of masked hypertension among adults 30 years or older. Blood Press Monit. 2014;19:208–15.
12. Mancia G, Facchetti R, Grassi G, Bombelli M. Adverse prognostic value of persistent office blood pressure elevation in white coat hypertension. Hypertension. 2015;66:437–44.
13. Myers MG, Haynes RB, Rabkin SW. Canadian hypertension society guidelines for ambulatory blood pressure monitoring. Am J Hypertens. 1999;12:1149–57.
14. NICE: National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. Clinical guideline [CG127]. Published date: August 2011. Last updated: November 2016. https://www.nice.org.uk/guidance/cg127.
15. Myers MG, Reeves RA. White coat phenomenon in patients receiving antihypertensive therapy. Am J Hypertens. 1991;4:844–9.
16. MacDonald MB, Laing GP, Wilson MP, Wilson TW. Prevalence and predictors of white-coat response in patients with treated hypertension. CMAJ. 1999;161:265–9.
17. Sheppard JP, Holder R, Nichols L, Bray E, Hobbs FD, Mant J, et al. Predicting out-of-office blood pressure level using repeated measurements in the clinic: an observational cohort study. J Hypertens. 2014;32:2171–8.
18. Adiyaman A, Aksoy I, Deinum J, Staessen JA, Thien T. Influence of the hospital environment and presence of the physician on the white-coat effect. J Hypertens. 2015;33:2245–9.
19. Schwartz CL, Clark C, Koshiaris C, Gill PS, Greenfield SM, Haque SM, et al. Interarm difference in systolic blood pressure in different ethnic groups and relationship to the "white coat effect": a cross-sectional study. Am J Hypertens. 2017;30:884–91.
20. Feitosa ADM, Mota-Gomes MA, Miranda RD, Barroso WS, Barbosa ECD, Pedrosa RP, et al. Impact of 2017 ACC/AHA hypertension guidelines on the prevalence of white-coat and masked hypertension: A home blood pressure monitoring study. J Clin Hypertens. 2018;20:1745–7.
21. Feitosa ADM, Mota-Gomes MA, Nadruz W. How should treated hypertensive patients with systolic blood pressure below 120 mmHg be managed? Eur Heart J. 2019. https://doi.org/10.1093/eurheartj/ehz123.
22. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens. 2018;36:2284–309.
23. Kabutoya T, Ishikawa J, Hoshide S, Eguchi K, Ishikawa S, Shimada K, et al. Determinants of negative white-coat effect in treated hypertensive patients: the Jichi Morning Hypertension Research (J-MORE) study. Am J Hypertens. 2009;22:35–40.
24. Sheppard JP, Stevens R, Gill P, Martin U, Godwin M, Hanley J, et al. Predicting out-of-office blood pressure in the clinic (PROOF-BP): derivation and validation of a tool to improve the accuracy of blood pressure measurement in clinical practice. Hypertension. 2016;67:941–50.
25. Franklin SS, Thijs L, Hansen TW, O'Brien E, Staessen JA. White-coat hypertension: new insights from recent studies. Hypertension. 2013;62:982–7.
26. MAPA GrupodeTrabalho, MRPA GrupodeTrabalho. Brazilian guidelines for ambulatory monitoring of arterial pressure and III Brazilian guidelines for home monitoring of blood pressure. J Bras Nefrol. 2011;33:365–88.
27. Stergiou GS, Salgami EV, Tzamouranis DG, Roussias LG. Masked hypertension assessed by ambulatory versus home blood pressure monitoring: is it the same phenomenon? Am J Hypertens. 2005;18:772–8.