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Impact of Clinic Blood Pressure Target on the Prevalence and Predictors of Masked Uncontrolled Hypertension and White-Coat Uncontrolled Hypertension

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ABSTRACT

Background: Identifying masked uncontrolled hypertension (MUCH) and white-coat uncontrolled hypertension (WUCH) without ambulatory blood pressure (ABP) monitoring is challenging. Recent literature advocates intensive blood pressure (BP) control, but standard guidelines still suggest a clinic BP threshold of ≥ 149/90 mmHg to diagnose hypertension. This study explored the impact of different clinic BP targets on the prevalence and predictors of MUCH and WUCH.

Methods: This multicenter prospective cohort study included 1,601 patients with hypertension from the Korean Ambulatory Blood Pressure registry, all with valid ABP records. Two clinic BP targets were evaluated: an intensive target (< 130/80 mmHg) and a conventional target (< 140/90 mmHg). Controlled hypertension was defined as a 24-hour mean ABP < 130/80 mmHg in patients treated with antihypertensive drugs who had a clinic BP below these targets.

Results: The prevalence of MUCH decreased significantly with the intensive target (15.5%) versus the conventional target (45.8%). In contrast, the prevalence of WUCH increased only marginally with the intensive targets. Most patients with MUCH (75.9%) had a clinic BP between 130/80 mmHg and 139/89 mmHg when MUCH was classified using the conventional target. For predicting MUCH, factors such as angiotensin-converting enzyme inhibitor use, body mass index, left ventricular mass index (LVMI), and use of ≥ 2 antihypertensive drugs

Clinic BP Target in MUCH and WUCH

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kim HJ, Lee Y, Shin JH. Data curation: Kim HJ, Lee Y, Kim JH, Hwang SH, Kim WS, Park S, Rhee SJ, Lee EM, Ihm SH, Pyun WB, Shin J. Formal analysis: Kim HJ, Lee Y. Investigation: Kim HJ, Lee Y. Methodology: Lee Y. Software: Lee Y. Validation: Ihm SH. Supervision: Pyun WB, Shin J. Writing - original draft: Kim HJ, Lee Y. Writing - review & editing: Kim HJ, Lee Y, Shin JH, Shin J. were significant under the intensive target, whereas clinic BP, LVMI, alcohol intake, stroke history, and use of ≥ 2 antihypertensive drugs were relevant under the conventional target. **Conclusion:** Adopting the intensive clinic BP target (< 130/80 mmHg) notably reduced the prevalence of MUCH, with a slight increase in WUCH, offering a more accurate assessment of BP control than the conventional target.

Keywords: Hypertension; Blood Pressure Monitoring, Ambulatory; Antihypertensive Agents; Blood Pressure

INTRODUCTION

Hypertension remains a key challenge in global healthcare^{1,2}; its effective management is important for reducing the risk of cardiovascular events. Recent clinical guidelines have increasingly emphasized the importance of intensively lowering blood pressure (BP), suggesting a paradigm shift from traditional targets.³⁻⁵ This new approach reduces the BP target for adequately controlled BP, particularly in high-risk patient groups.³ Such a shift has significant importance for the diagnosis and management of masked uncontrolled hypertension (MUCH) and white-coat uncontrolled hypertension (WUCH). MUCH is a condition wherein patients show controlled BP in a clinical setting but elevated BP levels on ambulatory blood pressure monitoring (ABPM).4,6,7 Conversely, WUCH is characterized by elevated BP readings in a clinical setting but shows controlled BP levels on ABPM.^{4,8} The current guidelines for diagnosing these hypertension phenotypes predominantly use the conventional clinic BP target of 140/90 mmHg.^{3,4} However, with the emerging focus on stricter BP control, there is a growing need to reevaluate these definitions and their implications. Regarding the conventional target, MUCH is known to be a therapeutic challenge in approximately 25% of treated patients as a neglected or masked entity unless ABPM or HBPM is performed.^{9,10} Moreover, there are concerns that more stringent BP targets might increase the risk of overtreatment and adverse effects, particularly in vulnerable populations.^{11,12}

Analyzing the prevalence and predictors of MUCH and WUCH based on the new intensive BP target is essential for several reasons. First, it allows us to better understand the actual burden of uncontrolled hypertension (UCH), which remains undetected by conventional clinical measurements, especially under strict BP control recommendations. Second, understanding how the predictors of MUCH and WUCH change when new BP targets are adopted can guide clinicians in optimizing treatment strategies and avoiding unnecessary interventions. Thus, this study aimed to investigate the impact of different clinic BP targets on the prevalence and predictors of MUCH and WUCH using data from the Korean Ambulatory Blood Pressure (Kor-ABP) registry.

METHODS

Study design and population

We conducted a cross-sectional study using data from the Kor-ABP Registry for Evaluation of the Prognostic Thresholds in Hypertension. This registry is a prospective, longitudinal, multicenter clinical cohort of patients undergoing ABPM established by the Korean Society of Hypertension. It comprised patients who underwent 24-hour ABPM for high BP assessment. The Kor-ABP registry collected data from 27 outpatient clinics at secondary and tertiary hospitals between August 2009 and December 2016. Detailed descriptions of the Kor-ABP registry are published in previous reports.⁶

In this study, we included patients with a valid ABPM who were on antihypertensive medication at the baseline evaluation of the registry. The valid ABPM was defined as the ABPM records with at least 20 BP recordings when awake and 7 BP recordings when asleep after excluding recordings either unmeasured or with extreme BP values (systolic BP [SBP] \geq 350 or 60 mmHg; diastolic BP [DBP] \geq 250 or < 30 mmHg).¹³ The management of hypertensive patients, including the administration of medication, was at the discretion of attending physicians, notably all of whom were cardiologists specializing in hypertension.

Data collection

We used a web-based electronic system to acquire the data. This system was linked to the Kor-ABP registry database and electronic case report forms were used for data collection. The collected data encompasses a range of demographic and clinical variables. These included sex, age, body mass index (BMI), waist circumference (WC), physical activity levels, smoking habits, and alcohol consumption. Additionally, we collected data on common cardiovascular risk factors such as a history of diabetes mellitus, dyslipidemia, stroke, myocardial infarction, heart failure, and cancer. Family history of hypertension, diabetes, and cardiovascular mortality was also recorded. This study included information on the use of antihypertensive medications, anti-platelet agents, and statins.

Regarding laboratory parameters, we extracted values for hemoglobin, triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, estimated glomerular filtration rate (eGFR), hemoglobin A1c, and fasting blood glucose levels. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.¹⁴ Cardiac function was assessed by extracting left ventricular ejection fraction and left ventricular mass index (LVMI) from M-mode echocardiography data. LVMI was calculated using the following formula:

 $LVMI = LVM/Height^{27} = [0.8 \times 1.04 \times \{(IVSd + LVIDd + LVPWd)^3 - LVIDs^3\} + 0.6]/Height^{27}$

where IVSd was the diastolic interventricular septum thickness, LVPWd was the diastolic left ventricular posterior wall thickness, LVIDd was the diastolic left ventricular internal dimension, and LVIDs was the systolic left ventricular internal dimension.

Measurement of BPs and definition of hypertension phenotypes

Controlled ABP was defined as a 24-hour mean SBP < 130 mmHg and a 24-hour mean DBP < 80 mmHg on ABPM. All participating institutions used the UA-767 monitor from A&D Co., Ltd., Tokyo, Japan, a device compliant with the European Hypertension Society protocol to measure clinic BP.¹³ The clinic BP was determined as the average of two separate readings obtained within a 1-minute interval following a 5-minute rest period prior to the first reading. The conventional clinic BP target was defined as SBP < 140 mmHg and/or DBP < 90 mmHg, whereas the intensive clinic BP target was defined as SBP < 130 mmHg and/or DBP < 80 mmHg.

In patients receiving antihypertensive medications, hypertension phenotypes were defined as established previously in international guidelines.^{3,15} UCH was defined as uncontrolled ABP without achieving the clinic BP target, MUCH was defined as uncontrolled ABP despite achieving the clinic BP target, WUCH was defined as controlled ABP without achieving

the clinic BP target, and controlled hypertension (CH) was defined as controlled ABP that achieved the clinic BP target. The number of hypertension phenotypes depends on the clinic BP target (conventional vs. intensive) used to classify the phenotypes.

Statistical analyses

The study population was divided into 4 groups based on hypertensive phenotypes: UCH, MUCH, WUCH, and CH. Two different clinic BP targets (conventional vs. intensive) were used to determine hypertension phenotypes. To investigate differences based on ABP levels, baseline characteristics were compared between the MUCH and CH groups and between the WUCH and UCH groups. As 9% of the data in the original dataset were missing, as mentioned in **Supplementary Fig. 1**, multiple imputations were performed using a bootstrap expectation-maximization algorithm. Five possible imputed datasets were created, and the average of the five imputed values was adopted as the missing value for the continuous variables. The most frequent of the five imputed values was adopted for the categorical variables. The distributions of several important imputed variables are shown in **Supplementary Fig. 1**.

Continuous variables including clinic SBP and DBP, age, BMI, and laboratory tests such as hemoglobin, LDL cholesterol, eGFR, and LVMI were compared using Student's *t*-test or the Mann-Whitney *U* test for variables with a skewed distribution. The categorical variables including sex, comorbidities, exercise frequencies and smoking were compared using the χ^2 test or Fisher's exact test for the variables with any number of cells counting 5 or less. Yates correction was not applied for categorical comparisons unless otherwise specified. The concordance between the controlled clinic BP and CH was assessed using Cohen's K.

Univariate logistic regression analyses were used to screen for associations between the clinical predictors and the presence of MUCH or WUCH. In the univariate logistic regression models, restrictive cubic spline fits (knot = 4 at 5, 35, 65, and 95%) were employed to assess clinic BP levels, and the trends in the risk of MUCH or WUCH changed. Multivariate logistic regression models were produced to evaluate the differences in the lists of significant predictors of MUCH and WUCH between conventional clinic BP and intensive clinic BP targets. Covariates in the multivariate models included clinic SBP, clinic DBP, heart rate, BMI, WC, exercise frequency (binary, ≥ 3 times/week), current smoking, current alcohol consumption, use of anti-platelet agents, the number of antihypertensive agent (binary, ≥ 2), the types of antihypertensive agents, LVMI and eGFR. The multivariate model was reduced using a backward variable selection process to minimize overfitting bias and identify significant predictors (cut-off criteria, P < 0.05). All statistical analyses were performed using statistical software R-4.2.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) and its packages including "descr," "psych," "rms," "tableone", "Amelia" and "pROC," in RStudio-2023.12.1 (Build 402; RStudio Team, BPC, Boston, MA, USA). A Pvalue < 0.05 was considered significant.

Ethics statement

This study adhered to the ethical principles outlined in the Declaration of Helsinki. The original study protocols were reviewed and approved by the ethics committees of all participating centers, including the Institutional Review Board (IRB) of Hanyang University Medical Center (reference number: 2009-R-12). Approval for the analysis of anonymized registry data in this study was obtained from an additional IRB of Hanyang University Guri Hospital (reference number: 2024-10-011). All participants provided written informed consent prior to inclusion in the study.

RESULTS

Baseline characteristics

Initially, 5,965 patients undergoing ABPM were enrolled in the registry. Among 5,404 patients who provided valid ABPM measurements, 1,601 were prescribed antihypertensive medications. We identified 472 patients with controlled ABP (24-hour mean SBP < 130 mmHg and mean DBP < 80 mmHg) and 1,129 patients with uncontrolled ABP (24-hour mean SBP \geq 130 mmHg and/or mean DBP \geq 80 mmHg) (Fig. 1).

The baseline characteristics of the 1,601 patients with valid ABPM data for antihypertensive drugs are shown in **Table 1**. Among them, 697 patients achieved the conventional clinic BP target (< 140/90 mmHg) and 348 patients achieved the intensive clinic BP target (< 130/80 mmHg).

Supplementary Table 1 shows the baseline characteristics of patients who achieved clinic BP targets based on ABP control. In the conventional clinic BP target cohort, the MUCH group had a significantly higher clinic SBP and DBP and comprised a higher proportion of men.

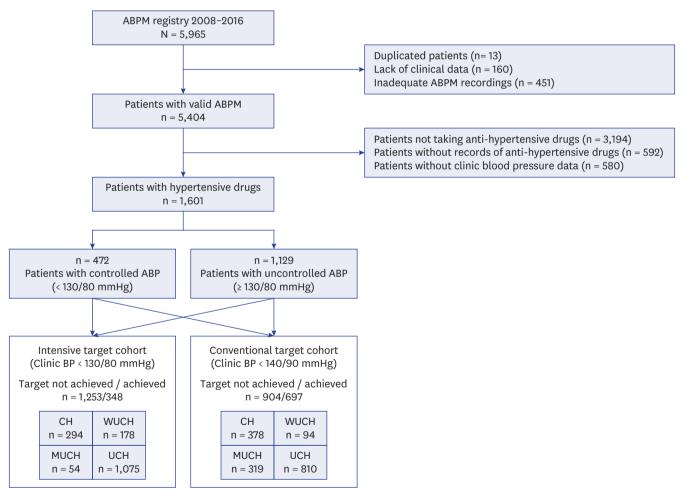


Fig. 1. Schematic description of the study population. This study included patients taking antihypertensive medications who had records of clinical BP and antihypertensive drugs and underwent valid ABPM. The study population (n = 1,601) was categorized into four hypertension phenotypes: CH, WUCH, MUCH, and UCH, using two different clinic BP targets: intensive (clinic BP < 130/80 mmHg) and conventional (clinic BP < 140/90 mmHg). BP = blood pressure, ABPM = ambulatory blood pressure monitoring, CH = controlled hypertension, WUCH = white-coat uncontrolled hypertension, MUCH = masked uncontrolled hypertension, UCH = uncontrolled hypertension, ABP = ambulatory blood pressure.



Table 1. Baseline characteristics of the population

Characteristics	Values (n = 1,601)
Office SBP, mmHg	140.0 (126.0-154.0)
Office DBP, mmHg	84.0 (76.0-93.0)
Heart rate, bpm	73.6 ± 12.0
Mean SBP, mmHg	135.9 ± 16.7
Mean DBP, mmHg	82.4 ± 10.6
Mean SBP during wake, mmHg	138.7 ± 16.8
Mean DBP during wake, mmHg	84.3 ± 10.9
Mean SBP during sleep, mmHg	127.0 ± 19.8
Mean DBP during sleep, mmHg	76.1 ± 11.6
Male sex	876 (54.7)
Age, yr	59.5 ± 13.1
BMI, kg/m²	25.0 ± 3.5
Waist	90.3 ± 9.7
Exercise, /week	
None	780 (48.7)
1	121 (7.6)
2	146 (9.1)
3	155 (9.7)
4	92 (5.7)
5	307 (19.2)
Exercise ≥ 3 /week	554 (34.6)
Smoking	
None	979 (61.1)
Ex-smoker	· · ·
	448 (28.0)
Current smoker Alcohol	174 (10.9)
None	349 (21.8)
Ex-drinker	785 (49.0)
Current drinker	467 (29.2)
Comorbidities	
DM	387 (24.2)
Dyslipidemia	409 (25.5)
Stroke	105 (6.6)
Myocardial infarction	154 (9.6)
Cancer	79 (4.9)
Family history of hypertension	731 (45.9)
Family history of DM	345 (21.5)
Family history of CV death	42 (2.6)
Medication	
Aspirin	735 (45.9)
Clopidogrel	142 (8.9)
New P2Y12 agent	5 (0.3)
Statin	672 (43.9)
ACEI	175 (10.9)
ARB	892 (55.7)
CCB	892 (33.7) 881 (55.0)
BB	664 (41.5)
Diuretics	318 (19.9)
Other antihypertensive	159 (9.9)
No. of antihypertensive agents	()
1	635 (39.7)
2	581 (36.3)
3	275 (17.2)
4	110 (6.9)
Antihypertensives ≥ 2	966 (60.3)
Antihypertensives ≥ 3	385 (24.0)
Echocardiography	
EF, %	64.8 ± 7.2
LVMI (BSA), g/m ²	105.3 ± 25.3
LVMI (Height ^{2.7}), g/m ^{2.7}	49.0 ± 12.6
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Characteristics	Values (n = 1,601)		
Laboratory tests			
Hb, g/dL	13.5 ± 1.9		
Triglyceride, mg/dL	123.0 (89.0-166.0)		
Total cholesterol, mg/dL	177.3 ± 44.4		
HDL, mg/dL	45.9 ± 12.5		
LDL, mg/dL	105.8 ± 35.3		
eGFR, mL/min/1.73 m ²	75.1 ± 26.0		
Fasting glucose, mg/dL	111.9 ± 34.2		
HbAlc,%	6.1 ± 1.0		

Table 1. (Continued) Baseline characteristics of the population

Values are presented as median (range), mean ± standard deviation, or number (%).

SBP = systolic blood pressure, DBP = diastolic blood pressure, BMI = body mass index, DM = diabetes mellitus, CV = cardiovascular, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, BB = beta-blocker, EF = ejection fraction, LVMI = left ventricular mass index, BSA = body surface area, Hb = hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c.

BMI, WC, and the number of current drinkers were higher in the MUCH group. Patients taking < 2 antihypertensive drugs were more frequent and the LVMI and total cholesterol levels were higher in the MUCH group. In the intensive clinic BP target cohort, no significant differences were observed in any variable, including clinic SBP and DBP, between the CH and MUCH groups, except that BMI and LVMI were significantly higher in the MUCH group than in the CH group.

Supplementary Table 2 shows the baseline characteristics of patients based on the control of ABP in patients not achieving clinic BP target. In the conventional clinic BP target cohort, 810 patients were classified with UCH and 94 patients were classified with WUCH. No significant differences were observed between the 2 groups, except that clinic SBP was only slightly lower, the use of angiotensin receptor blocker (ARB) was less frequent, and the use of betablocker was more frequent in the WUCH group. In the intensive target cohort, 1,075 patients were classified with UCH and 178 patients were classified with WUCH. No variables were different between the two groups, except for clinic SBP and DBP, WC, prevalence of hypertension, LVMI, and triglyceride levels, which were lower in the WUCH group than in the UCH group.

Table 2 outlines the ABP parameters in patients who achieved a conventional clinic BP target of < 140/90 mmHg and an intensive clinic BP target of < 130/80 mmHg. The table reveals significant differences between patients with CH and those with MUCH in mean 24-hour BP, daytime BP, and nighttime BP. There were also significant differences in all ABP parameters between UCH and WUCH in the conventional and intensive BP target groups.

Prevalence of hypertension phenotypes

Marked changes in the prevalence of hypertensive phenotypes were evident depending on the clinic BP target (**Fig. 2**). When the intensive clinic BP target was applied instead of the conventional clinic BP target, the prevalence of MUCH decreased from 20% to 3.4% (16.6% decrease); however, the prevalence of WUCH showed only a modest increase from 5.9% to 11.1% (5.2% increase). When applying the conventional target, 83.1% of patients with MUCH (265 of 319) had an elevated clinic BP level between 130/80 and 139/89 mmHg, based on the standard intensive BP target. Among patients achieving the clinic BP target, the prevalence of MUCH decreased by approximately 30%, which is 1/3 of the original proportion when the intensive target was applied. In contrast, among patients who did not achieve a clinic BP target, the prevalence of WUCH increased by approximately 4% when the intensive target was applied. Overall, the prevalence of MUCH markedly decreased, whereas that of WUCH

Table 2. Ambulator	ry blood pressure	parameters according	g to clinic BP target
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Characteristics	Conventional target (< 140/90 mmHg)					Intensive target (< 130/80 mmHg)						
	Clinic BP target achieved			Clinic BP target not achieved		Clinic BP target achieved			Clinic BP target not achieved			
	СН	MUCH	P value	UCH	WUCH	P value	СН	MUCH	P value	UCH	WUCH	P value
	(24-hr ABP	(24-hr ABP		(24-hr ABP	(24-hr ABP		(24-hr ABP	(24-hr ABP		(24-hr ABP	(24-hr ABP	
	< 130/80	≥ 130/80		≥ 130/80	< 130/80		< 130/80	≥ 130/80		≥ 130/80	< 130/80	
	mmHg;	mmHg;		mmHg;	mmHg;		mmHg;	mmHg;		mmHg;	mmHg;	
	n = 378)	n = 319)		n = 810)	n = 94)		n = 294)	n = 54)		n = 1,075)	n = 178)	
Heart rate, BPM	71.6 ± 11.5	73.0 ± 10.5	0.099	74.5 ± 12.2	76.1 ± 15.3	0.254	71.0 ± 11.4	74.2 ± 10.7	0.056	74.1 ± 11.8	75.0 ± 13.8	0.345
Mean 24-hr SBP, mmHg	117.7 ± 7.0	$\textbf{134.9} \pm \textbf{8.9}$	< 0.001	146.8 ± 13.8	119.5 ± 6.6	< 0.001	117.2 ± 7.1	136.3 ± 13.3	< 0.001	143.8 ± 13.6	$\textbf{119.4} \pm \textbf{6.4}$	< 0.001
Mean 24-hr DBP, mmHg	72.0 ± 5.1	$\textbf{82.2} \pm \textbf{7.1}$	< 0.001	$\textbf{88.3} \pm \textbf{9.6}$	73.4 ± 4.4	< 0.001	71.4 ± 4.9	$\textbf{81.4} \pm \textbf{6.9}$	< 0.001	$\textbf{86.8} \pm \textbf{9.4}$	73.6 ± 4.8	< 0.001
Mean SBP daytime, mmHg	120.5 ± 8.0	137.5 ± 9.3	< 0.001	149.5 ± 13.6	122.6 ± 7.1	< 0.001	120.1 ± 8.0	138.2 ± 13.2	2 < 0.001	146.5 ± 13.6	122.3 ± 7.3	< 0.001
Mean DBP daytime, mmHg	74.0 ± 5.8	84.1 ± 7.6	< 0.001	90.2 ± 10.0	75.3 ± 4.8	< 0.001	73.4 ± 5.6	82.7 ± 7.3	< 0.001	88.8 ± 9.8	75.6 ± 5.4	< 0.001
Mean SBP night, mmHg	109.5 ± 10.8	126.6 ± 13.4	< 0.001	137.5 ± 18.6	108.9 ± 10.1	< 0.001	109.3 ± 10.9	128.4 ± 17.1	< 0.001	134.7 ± 18.0	109.6 ± 10.1	< 0.001
Mean DBP night, mmHg	66.2 ± 7.1	76.3 ± 8.8	< 0.001	81.8 ± 10.8	66.5 ± 6.0	< 0.001	65.8 ± 7.1	75.8 ± 8.6	< 0.001	80.5 ± 0.7	67.1 ± 6.5	< 0.001

Values are presented as mean ± standard deviation.

BP = blood pressure, CH = controlled hypertension, ABP = ambulatory blood pressure, MUCH = masked uncontrolled hypertension, BPM = beats per minute, SBP = systolic blood pressure, DBP = diastolic blood pressure, UCH = uncontrolled hypertension, WUCH = white-coat uncontrolled hypertension.

minimally increased, when an intensive target was applied. The agreement between the controlled ABP and the achieved clinic BP target was higher when the intensive clinic BP target, rather than the conventional clinic BP target, was used to classify the hypertension phenotypes (**Fig. 3**, **Supplementary Fig. 2**).

Predictor of MUCH and WUCH according to clinic BP target

Univariate logistic regression analyses showed an association between the variables and hypertensive phenotypes in both the conventional and intensive clinic BP targets (**Fig. 4**). In patients achieving the intensive clinic BP target, the presence of MUCH was associated with BMI, dyslipidemia, and LVMIs, but not with clinic BPs. In contrast, the presence of MUCH was most strongly associated with higher clinic SBP and DBP, while additional associations were observed with male sex, BMI, central obesity, alcohol consumption, and LVMIs in patients who achieved the conventional target. In patients who did not achieve the intensive target, the absence of WUCH was associated with clinic SBP, DBP, and LVMIs.

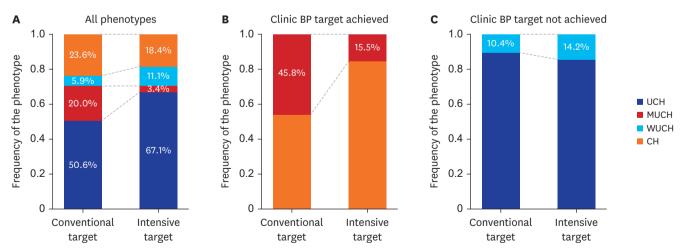


Fig. 2. Prevalence of hypertension phenotype based on 2 different clinic BP targets. (**A**) In all hypertension phenotypes, the prevalence of MUCH decreased markedly while the prevalence of WUCH increased modestly when the intensive clinic BP target, rather than the conventional one, was applied. (**B**) Among patients achieving the clinic BP target, the prevalence of MUCH decreased by > 30%, when the intensive target was applied. (**C**) Among patients not achieving the clinic BP target, the prevalence of WUCH increased by only < 4%, when the clinic BP target changed from the conventional to intentional target. BP = blood pressure, MUCH = masked uncontrolled hypertension, WUCH = white-coat uncontrolled hypertension, UCH = uncontrolled hypertension, CH = controlled hypertension.

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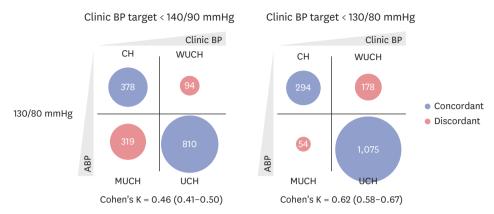


Fig. 3. Concordance between the achievement of clinic BP target and the controlled ABP in 2 different clinic BP targets. The size of the circles represents the number of patients in each category. The Cohen's Kappa (K) values indicate the level of agreement between the clinic BP target achievement and the controlled ABP is moderate in the conventional target cohort (K = 0.46 [0.41–0.50]), while substantial in the intensive target cohort (K = 0.62 [0.58–0.67]).

BP = blood pressure, ABP = ambulatory blood pressure, CH = controlled hypertension, WUCH = white-coat uncontrolled hypertension, MUCH = masked uncontrolled hypertension, UCH = uncontrolled hypertension.

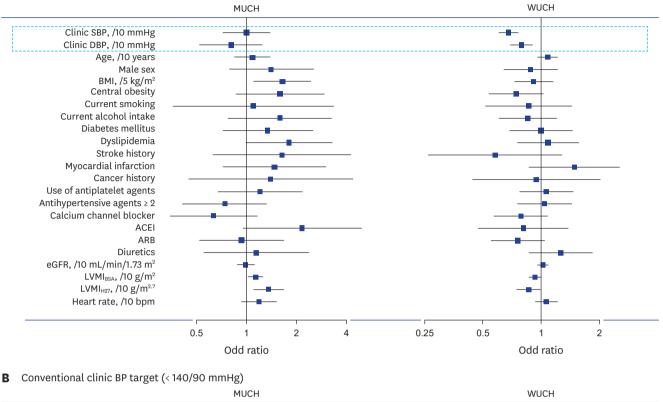
In patients not achieving the conventional target, the absence of WUCH was still associated with clinic SBP but with decreased association strength, and an additional association was observed with the use of ARBs.

We estimated how changes in the probability of MUCH or WUCH with clinic BP differed based on clinic BP targets using univariate logistic regression models with restrictive cubic spline fit (**Supplementary Fig. 3**). When the intensive clinic BP target was applied, neither clinic SBP nor DBP showed a significant relationship with the risk of MUCH. However, the risk of WUCH decreased with clinic SBP, and this decrease was stiffer in clinic SBP ranging between 120 and 140 mmHg. In contrast, when the conventional clinic BP target was applied, both clinic SBP and DBP had strong nonlinear relationships with the risk of MUCH, which increased with clinic BP beyond 120 mmHg and DBP of 70 mmHg. The risk of WUCH still decrease in the risk of WUCH observed when the intensive clinic BP target was applied.

Multivariate logistic regression analysis showed that the lists of independent predictors of MUCH and WUCH differed based on the clinic BP targets (**Table 3**). In patients achieving the clinic BP target, the use of angiotensin-converting enzyme inhibitors, BMI, LVMI, and < 2 antihypertensive drugs significantly predicted the presence of MUCH when the intensive target was applied, whereas, clinic SBP and DBP emerged as the strongest predictors of MUCH, and LVMI, current alcohol use, stroke history and < 2 antihypertensive drugs predicted the presence of MUCH additionally, when the conventional target was applied. In patients who did not achieve the clinic BP targets, beta-blocker use, non-canonical antihypertensive drug use, heart rate, age, lower WC, and lower clinic SBP significantly predicted the presence of WUCH when an intensive target was applied. The same set of variables, including beta-blocker use, heart rate, lower WC, and lower clinic SBP, remained associated with the risk of WUCH when the conventional target was applied instead of the intensive target. The nonuse of ARB was also associated with the risk of WUCH when a conventional clinic BP target was applied.



A Intensive clinic BP target (< 130/80 mmHg)



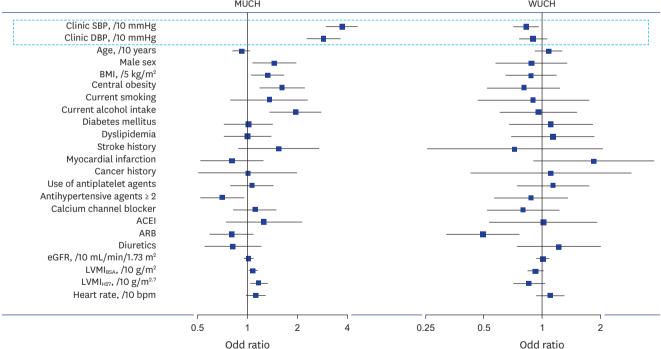


Fig. 4. Univariate logistic regression models for the predictors of MUCH and WUCH in 2 different clinic BP targets. (A) When the intensive clinic BP target was applied, BMI and LVMI were significant predictors of MUCH, while lower clinic SBP and DBP and lower LVMI were significant predictors of WUCH. (B) When the conventional clinic BP target was applied, higher clinic SBP and DBP, male sex, BMI, central obesity, current alcohol intake, antihypertensive drugs < 2 and LVMI were significant predictors of MUCH, while lower clinic SBP and underuse of ARB were significant predictors of WUCH.

MUCH = masked uncontrolled hypertension, WUCH = white-coat uncontrolled hypertension, BP = blood pressure, BMI = body mass index, LVMI = left ventricular mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, ARB = angiotensin receptor blocker, ACEI = angiotensin-converting enzyme inhibitor, eGFR = estimated glomerular filtration rate.

Cohorts	Clinic BP criteria	Summary	Predictors	HR	95% CI	P value
Target clinic BP achieved	< 130/80 mmHg	C-index: 0.677	ACEI use	2.41	1.01-5.45	0.048
MUCH vs. CH	Total N = 348	Negelkerke R ² = 0.084	BMI (per 5 kg/m²)	1.60	1.04-2.45	0.032
	MUCH = 54		LVMI _{H27} (per 10 g/m ^{2.7})	1.29	1.03-1.61	0.027
			Antihypertensive drugs ≥2	0.52	0.28-0.98	0.043
	< 140/90 mmHg	C-index: 0.830	Clinic SBP (per 10 mmHg)	3.16	2.49-4.01	< 0.001
	Total N = 697	Negelkerke R ² = 0.378	Clinic DBP (per 10 mmHg)	1.63	1.24-2.13	< 0.001
	MUCH = 319		LVMI _{H27} (per 10 g/m ^{2.7})	1.24	1.07-1.43	0.005
			Current alcohol use	1.63	1.06-2.50	0.025
			Past history of stroke	1.85	0.91-3.75	0.087
			Antihypertensive drugs ≥ 2	0.65	0.45-0.93	0.019
Target clinic BP not	< 130/80 mmHg	C-index: 0.719	Beta blocker use	2.17	1.55-3.05	< 0.001
achieved WUCH vs. UCH	Total N = 1,253	Negelkerke R ² = 0.128	Non-canonical antihypertensive	1.93	1.21-3.10	0.006
	WUCH = 178		Heart rate (per 10 bpm)	1.18	1.02-1.35	0.022
			Age (per 10 yr)	1.13	1.00-1.29	0.058
			Waist circumference (per 10 cm)	0.77	0.64-0.92	0.004
			Clinic SBP (per 10 mmHg)	0.66	0.59-0.74	< 0.001
	< 140/90 mmHg	C-index: 0.679	Beta blocker use	2.50	1.60-3.92	< 0.001
	Total N = 904	Nagelkerke R ² = 0.084	Heart rate (per 10 bpm)	1.16	0.98-1.37	0.096
	WUCH = 94		Clinic SBP (per 10 mmHg)	0.80	0.69-0.93	0.003
			Waist circumference (per 10 cm)	0.80	0.64-1.00	0.045
			ARB use	0.56	0.36-0.88	0.011

Table 3. Multivariate logistic regression models predicting MUCH and WUCH in 2 different clinic BP targets

MUCH = masked uncontrolled hypertension, WUCH = white-coat uncontrolled hypertension, BP = blood pressure, HR = hazard ratio, CI = confidence interval, CH = controlled hypertension, ACEI = angiotensin-converting enzyme inhibitor, BMI = body mass index, LVMI = left ventricular mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, UCH = uncontrolled hypertension, ARB = angiotensin receptor blocker.

DISCUSSION

We comprehensively analyzed the impact of the 2 different clinic BP targets, intensive and conventional, on the prevalence and predictors of MUCH and WUCH. We found remarkable changes in the hypertension phenotypes when the intensive clinic BP target was applied instead of the conventional target. The prevalence of MUCH decreased sharply from 20.0% to 3.4%, whereas that of WUCH increased only modestly from 5.9% to 11.1%. The concordance between the BP control status measured in the clinic BP and ABP was also higher when the intensive clinic BP target was implemented.

When using the conventional target, clinic BP was the most significant predictor of MUCH, suggesting that marginally elevated clinic BP values above the intensive target were associated with MUCH when assessed using conventional standards. This may be because clinic BPs in the range of 130/80–139/89 mmHg are often classified as controlled under the conventional target, potentially missing out-of-office hypertension, which contributes to MUCH in these patients. In contrast, with the intensive target, the predictors of MUCH shifted toward structural and metabolic indicators, such as BMI and LVMI. This suggests that, when clinic BP is strictly controlled, the underlying metabolic factors and cardiac structural changes may be more relevant indicators of MUCH than clinic BP alone. The association with LVMI highlights the importance of considering target organ damage, which reflects the cumulative BP burden, even when clinic measurements appear to be well controlled. For WUCH, beta-blocker use and lower clinic SBP remained significant predictors across both BP targets, although the predictors varied slightly, with the intensive target also identifying older age and higher heart rate. This profile suggests that individuals with WUCH may have specific characteristics, such as higher baseline sympathetic tone or BP variability, which could prompt clinicians to prescribe beta-blockers more frequently. In addition, the white-coat effect is likely driven by situational or anxiety-induced BP elevation rather than by the target BP criteria.

The global trend toward lowering the diagnostic criteria and target BP levels for hypertension is becoming increasingly evident,¹⁶ reflecting significant shifts in clinical practice guidelines. Notably, landmark trials such as SPRINT (Systolic Blood Pressure Intervention Trial) and STEP (Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients) have played pivotal roles in advocating for more aggressive BP reduction strategies to improve cardiovascular outcomes.^{17,18} Additionally, the European Society of Hypertension, the Korean Society of Hypertension, and the American College of Cardiology/American Heart Association have all supported lower BP targets in their recent guidelines, further supporting the shift toward stricter BP control.³⁻⁵ Despite these advancements, the diagnostic criteria for MUCH and WUCH remain at the conventional clinic BP target of 140/90 mmHg.¹⁰ Our findings emphasize the necessity of updating these criteria to align with the lower target BP levels now recommended for general hypertension management. By maintaining outdated diagnostic thresholds, we attempt to underestimate the prevalence and implications of these hypertension phenotypes, potentially compromising patient care. Adopting a more stringent BP target, such as < 130/80 mmHg, for diagnosing MUCH and WUCH could enhance the accuracy of hypertension control assessments and facilitate the more precise identification and management of high-risk individuals. Consequently, revising the diagnostic standards for MUCH and WUCH to reflect current BP targets is imperative to improve clinical outcomes in hypertensive populations.

Previous studies have primarily adhered to the conventional BP target of 140/90 mmHg when diagnosing MUCH and WUCH.^{6,19} Franklin et al.²⁰ and Stergiou et al.²¹ highlighted the clinical significance of these hypertension phenotypes using traditional BP targets, demonstrating that patients with MUCH are at a higher risk of cardiovascular events than those with well-CH based on clinic measurements alone.^{20,21} However, these studies did not explore the implications of adopting a more intensive BP target, such as < 130/80 mmHg, which recent guidelines now recommend. Our study builds on this foundation by examining the effect of stricter BP targets on the prevalence and predictors of MUCH and WUCH. The significant reduction in MUCH prevalence from 20.0% to 3.4% with a lower BP target underscores the potential benefits of intensive BP control. Conversely, the modest increase in WUCH from 5.9% to 11.1% suggests that, while stricter targets can improve the detection and management of masked hypertension, they also bring attention to the potential overdiagnosis of white-coat hypertension. These findings emphasize the need to revise current diagnostic thresholds for MUCH and WUCH to reflect lower BP targets, aligning them with updated hypertension guidelines.³⁻⁵ Recently, Ghazi et al.²² showed that targeting an office SBP of < 120 mmHg, compared with < 140 mmHg, was associated with a lower risk of cardiovascular disease and mortality, reinforcing the importance of intensive BP control. However, the prevalence of WUCH and MUCH in the lower target BP was similar to that in the standard target BP. Their findings, derived from the same SPRINT ABP ancillary study, suggested that out-of-office BP measurements remain crucial for accurately characterizing BP phenotypes, even with more stringent BP goals. This aligns with our conclusion that intensive BP targets may lead to better cardiovascular outcomes but also necessitate careful monitoring to effectively identify WUCH and MUCH. This reclassification could lead to more accurate risk stratification and targeted treatment strategies, ultimately enhancing patient outcomes.²³

From our analysis results, we propose a simplified illustration to promote the understanding of the relationship between mean ABP and clinic BP in the hypertension phenotype plain in **Fig. 5.** MUCH and WUCH exist because of the inevitable discrepancies between the mean ABP and clinic BP. At an extremely high or low clinic BP target, the prevalence of MUCH and

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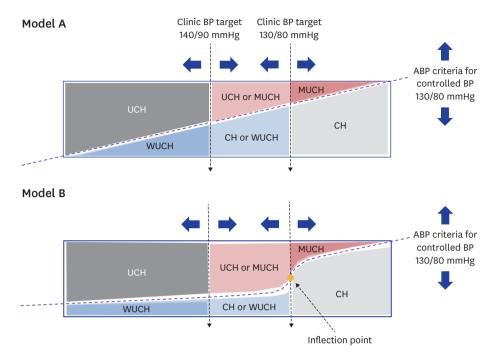


Fig. 5. Illustration for the relationship between the mean ABP and clinic BP in the determination of hypertension phenotypes. Hypertension phenotypes exist because of the discrepancies between clinic BP and ABP. These illustrations represent the relationship between clinic BP and ABP in the hypertension phenotype. The vertical division represents clinic BP target achievement, and the diagonal division represents the true control of BP. For extreme clinic BP targets, it is difficult for MUCH and WUCH to exist. Model A represents linear changes in the proportions of hypertension phenotypes where no optimal clinic BP target exists, whereas Model B represents nonlinear changes in the proportions of hypertensive phenotypes according to the clinic BP targets, where an optimal clinic BP target exists.

ABP = ambulatory blood pressure, BP = blood pressure, MUCH = masked uncontrolled hypertension, WUCH = white-coat uncontrolled hypertension, UCH = uncontrolled hypertension, CH = controlled hypertension.

WUCH must be negligible; however, within the conventional range of clinic BP targets, the prevalence of MUCH and WUCH should be reciprocal. Model A has a linear boundary on the hypertension phenotype plane, where the proportions of hypertension phenotypes change gradually with the clinic BP targets; thus, no optimal clinic BP target exists. In contrast, model B represents a nonlinear boundary on the plain with an inflection point at 130/80 mmHg, implying the existence of an optimal BP target to minimize the discrepancy between clinic BP and mean ABP. Our results demonstrated that the changes in the prevalence of MUCH and WUCH were grossly different, thus supporting the concepts in Model B. Given these results, we suggest that the optimal clinic BP target to maximize the concordance between clinic BP and mean ABP and minimize the presence of MUCH may be close to the intensive clinic BP target. This also suggests a potential shift in clinical practice, encouraging clinicians to regularly assess out-of-office BP, particularly in patients who meet intensive clinic BP targets but have risk factors for MUCH, such as high BMI or LVMI. Although ABPM remains the gold standard for detecting masked hypertension, wearable BP-monitoring devices are emerging as viable alternatives, offering continuous tracking with greater convenience.^{24,25} These devices may improve patient accessibility and enable more frequent monitoring during clinical follow-ups, potentially aiding in early detection and tailored hypertension management. Furthermore, combining intensive BP targets with individualized treatment plans, such as adjusting antihypertensive therapy based on specific cardiovascular risks, could support more accurate risk stratification and help clinicians decide when to intensify or de-escalate treatment, ultimately enhancing patient outcomes.

This study has several limitations. First, its cross-sectional design restricted the ability to speculate on causal relationships between clinic BP targets and the prevalence of MUCH and WUCH. This design limits our capacity to determine whether intensive BP targets directly reduce the risk of MUCH or if this is enabled by other contributing factors, such as lifestyle changes, medication adjustments, or evolving health conditions. Future longitudinal studies are needed to provide a more detailed interpretation of how sustained BP control affects the evolution of MUCH and WUCH. Second, the study population consisted only of Korean patients from outpatient clinics, which may limit the generalizability of the findings to other ethnic groups and healthcare environments. Differences in ethnic and cultural aspects, such as genetic factors influencing hypertension control and medication metabolism, can affect the prevalence of MUCH and WUCH. The prevalence of MUCH is notably higher among African-American populations than among Caucasians, often because of higher rates of comorbidities that affect BP regulation.^{26,27} East Asian populations, including Japanese cohorts, have shown a higher prevalence of MUCH than WUCH, possibly related to high sodium intake and lifestyle differences that elevate out-of-office BP. Additionally, countries with universal healthcare access, such as Japan and several European countries, often achieve better hypertension control due to early detection and consistent follow-up, potentially reducing the prevalence of masked hypertension. In contrast, inconsistent monitoring and varied access in the United States may have contributed to higher rates of both MUCH and WUCH. Third, clinic BP was measured only twice at a single time point, which may limit the accuracy and reproducibility of the BP assessment. This could affect the classification of hypertension phenotypes, as single-timepoint measurements are susceptible to situational factors and may not represent actual BP levels. Fourth, the reliance on 24-hour ABPM data may not fully capture the variations in BP throughout the day or under different conditions, potentially overlooking episodic hypertension or white-coat effects. The study did not account for potential confounding factors, such as stress, dietary habits, or medication adherence, which can significantly influence BP readings. Furthermore, categorizing hypertension phenotypes based on clinic BP targets may require a more balanced approach, considering the complex nature of hypertension management, which often requires individualized approaches. Fifth, as a typical multicenter prospective registry dataset, our study dataset harbored approximately 9% missing values spreading across 38 variables. To minimize information loss and maintain the population characteristics, we performed multiple imputations instead of excluding records with missing values. However, some variables, including left ventricular geometry parameters and HbA1c levels, had considerable missing values. The imputed values may have caused an information bias. Nevertheless, the fraction of missing values was small for the entire dataset, and the distributions of the imputed values closely resembled the distribution of the original variables, as shown in Supplementary Fig. 1. Sixth, the study data were collected more than a decade ago, and recent advances in hypertension management, such as emphasis on intensive BP control, may need to be fully represented. However, this historical perspective provides a valuable baseline for understanding the trends over time and examining the implications of shifting BP targets in clinical practice. Finally, the study's focus on clinic BP targets as the primary determinant of hypertension control might have neglected other important aspects of cardiovascular health management, such as lifestyle interventions, patient education, and management of comorbid conditions.

Despite these limitations, this study offers valuable perspectives and clinical implications for the management of hypertension. The shift toward lower clinic BP targets and the consequential reduction in MUCH prevalence highlights the potential benefits of intensive BP control. This suggests that healthcare providers should reconsider current BP targets to optimize patient outcomes. Additionally, identifying specific predictors of MUCH and WUCH under different BP targets provides insights into tailoring treatment strategies. Moreover, this study emphasizes the importance of ABPM in detecting hypertension phenotypes, which can lead to more accurate diagnoses and effective management strategies. However, these findings emphasize the need for individualized treatment approaches. Effective hypertension management should not depend only on clinical BP targets but should integrate patient-specific factors, such as age, comorbidities, and overall cardiovascular risk. This personalized approach is particularly relevant for high-risk populations, where intensive BP control may cause adverse effects such as hypotension. A balanced treatment plan that incorporates intensive BP targets and individualized assessments can reasonably support safe and effective care for various patient needs.

In conclusion, the intensive clinic BP target significantly contributed to reducing the prevalence of MUCH, with a slight increase in WUCH. This highlights the critical need for continuous re-evaluation and adaptation of hypertension management guidelines, particularly for evolving clinical evidence. Further research on optimal BP targets and their implementation in clinical practice is needed to classify hypertension phenotypes and tailored hypertension management strategies.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline characteristics of MUCH and CH in patients achieving clinic BP target

Supplementary Table 2

Baseline characteristics of WUCH and UCH in patients not achieving clinic BP target

Supplementary Fig. 1

Missing values in the dataset and the imputation results. (A) The dataset harbored approximately 9% of missing values ranged between 0% (clopidogrel use) and 47.2% (HbA1c). (B) After a multiple imputation using a bootstrap expectation-maximization algorithm, the distributions of the imputed values in the variables with missing values including the left ventricular geometry parameters resembled the original values of the variables.

Supplementary Fig. 2

Concordance between the achievement of clinic BP target and the controlled ABP in 2 different clinic BP targets. The size of the circles represents the number of patients in each category. The Cohen's Kappa (K) values indicate the level of agreement between the clinic BP target achievement and the controlled ABP is moderate in the conventional target cohort (K = 0.46 [0.41-0.50]), while higher in the intensive target cohort (K = 0.53 [0.47-0.58]).

Supplementary Fig. 3

Relationship between clinic BP and the risk of MUCH and WUCH estimated using restrictive cubic spline models. When the intensive clinic BP target (< 130/80 mmHg) was applied, both clinic SBP and DBP were not associated with the risk of MUCH, whereas the risk of WUCH decreased with clinic SBP, especially in the clinic SBP ranged between 120 and 140 mmHg. In contrast, when the conventional clinic BP target (< 140/90 mmHg) was applied, the risk of

MUCH increased with clinic SBP and DBP beyond the point of 120 and 70 mmHg, respectively, and the risk of WUCH decreased with clinic SBP, although the slope was more gradual.

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