

ORIGINAL RESEARCH

Prevalence of Isolated Nocturnal Hypertension and Development of Arterial Stiffness, Left Ventricular Hypertrophy, and Silent Cerebrovascular Lesions: The KoGES (Korean Genome and Epidemiology Study)

Seong Hwan Kim , MD, PhD*; Chol Shin, MD, PhD*; Sunwon Kim , MD, PhD; Jin-Seok Kim , MD, PhD; Sang Yup Lim, MD, PhD; Hyeong-Seok Seo , MD, PhD; Hong Euy Lim , MD, PhD; Ki-Chul Sung , MD, PhD; Goo-Yeong Cho, MD, PhD; Seung Ku Lee , PhD; Yong-Hyun Kim , MD, PhD

BACKGROUND: Apart from nondippers' impact on cardiovascular events, the prevalence of isolated nocturnal hypertension (INH) and its consequences on both the heart and brain were not clearly investigated in the general population.

METHODS AND RESULTS: The participants underwent ambulatory blood pressure monitoring evaluations for arterial stiffness, echocardiography, and brain magnetic resonance imaging. They were grouped into normotension, INH, and overt diurnal hypertension, based on ambulatory blood pressure monitoring and history of antihypertensive treatment. White matter hyperintensity, arterial stiffness, and echocardiographic parameters were compared. Of the 1734 participants, there were 475 (27.4%) subjects with normotension, 314 with INH (18.1%), and 945 with overt diurnal hypertension (54.5%). Prevalence of INH was not different between sex or age. Of INH, 71.3% ($n=224$) was caused by elevated diastolic blood pressure. After multivariable adjustment, INH showed higher pulse wave velocity ($P<0.001$) and central systolic blood pressure ($P<0.001$), left ventricular mass index ($P=0.026$), and worse left ventricular diastolic function (early diastolic mitral annular velocity) ($P<0.001$) than normotension. Mean white matter hyperintensity scores of INH were not different from normotension ($P=0.321$), but the odds for white matter hyperintensity presence were higher in INH than normotension (odds ratio, 1.504 [95% CI, 1.097–2.062]; $P=0.011$).

CONCLUSIONS: INH was common in the general population and associated with increased arterial stiffness, left ventricular hypertrophy, and diastolic dysfunction. White matter hyperintensity was more likely to be present in the INH group than in the normotension group. The use of ambulatory blood pressure monitoring should be encouraged to identify masked INH and prevent the occurrence of cardiovascular events.

Key Words: ambulatory blood pressure ■ nocturnal hypertension ■ target organ damage ■ white matter hyperintensity

As per the current guidelines, ambulatory blood pressure monitoring (ABPM) is recommended for the diagnosis of arterial hypertension because the white-coat effect often leads to misdiagnosis of hypertension and unnecessary medical expenses.^{1,2}

In general, blood pressure (BP) dips during nighttime because of circadian variation. The classification based on night-to-day systolic BP (SBP) ratio includes normal dipper, extreme dipper, reduced dipper, or reverse dipper.³ Diverse observational studies have

Correspondence to: Yong-Hyun Kim, MD, PhD, Division of Cardiology, Department of Internal Medicine, Korea University Ansan Hospital, 123, Jeokgeum-ro, Danwon-gu, Ansan-si, Gyeonggi-do 15355, Republic of Korea. Email: xkyhx@korea.ac.kr

*S. H. Kim and C. Shin contributed equally.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.025641>

For Sources of Funding and Disclosures, see page 9.

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CLINICAL PERSPECTIVE

What Is New?

- When using the latest diagnostic criteria of international guidelines, isolated nocturnal hypertension is common in the general population.
- Isolated nocturnal hypertension is associated with the presence of arterial stiffness, left ventricular hypertrophy, left ventricular diastolic dysfunction, and silent cerebrovascular lesions.

What Are the Clinical Implications?

- Many people with normal daytime blood pressure are at risk of cardio- and cerebrovascular events without being diagnosed with hypertension, and it is reasonable to assume that arterial stiffness induced by isolated nocturnal hypertension leads to silent cerebrovascular lesions.
- Ambulatory blood pressure monitoring is a simple and effective method of detecting isolated nocturnal hypertension that cannot be detected by measuring office blood pressure or monitoring home blood pressure.
- Active use of ambulatory blood pressure monitoring will help with the early diagnosis of isolated nocturnal hypertension and prevention of silent progression of cardiovascular complications.

Nonstandard Abbreviations and Acronyms

ABPM	ambulatory blood pressure monitor
baPWV	brachial-ankle pulse wave velocity
cIMT	carotid intima-media thickness
DBP	diastolic blood pressure
INH	isolated nocturnal hypertension
KoGES	Korean Genome and Epidemiology Study
LVMI	left ventricular mass index
NDR	night-to-day ratio
ODH	overt diurnal hypertension
SBP	systolic blood pressure
WMH	white matter hyperintensity

shown that nondippers (eg, reduced dippers or reverse dippers) are more susceptible to cardiovascular events than dippers.^{4,5}

Apart from night-to-day SBP ratios, international guidelines provide specific criteria for nocturnal hypertension, because there are some differences between the concept of nondipper and nocturnal hypertension. Patients with isolated nocturnal hypertension (INH) are known to be at a greater risk of cardiovascular

morbidity and mortality.^{6,7} However, with the limited use of ABPM, this unique subtype of hypertension is easily masked in clinical practice.

The mechanism by which nocturnal hypertension causes cardiovascular events is assumed to be no different from clinical hypertension. Observational studies have demonstrated links between nighttime hypertension and individual target organ damage such as proteinuria, retinopathy, left ventricular (LV) hypertrophy, and stiffening of conduit arteries.⁸

Silent cerebrovascular lesions, noted as asymptomatic white matter hyperintensity (WMH) on brain magnetic resonance imaging (MRI), is commonly seen in the elderly or even in Stage 1 hypertension and is believed to be associated with the future risk of stroke and dementia.^{9,10} Therefore, WMH could be considered as one of the target organ damage markers and used as an indicator of the effectiveness of early antihypertensive treatment before overt organ damage occurs.¹¹

In this study, we investigated the prevalence of INH in the Korean general population; studied the relationship between arterial stiffness, echocardiographic parameters, WMH, and INH; and attempted to explain their causal associations.

METHODS

Study Cohort

Study participants were enrolled from the KoGES (Korean Genome and Epidemiology Study), which is an ongoing prospective cohort study in South Korea. This cohort study was initiated in 2001 and has a biennial follow-up evaluation schedule. A detailed description of the cohort study has been described elsewhere.¹² We used the data set of the sixth and seventh visits of the cohort participants for this cross-sectional analysis because the research protocols for both ABPM and brain MRI examinations were conducted over 4 years. The data from ABPM and MRI used in the study were obtained during the same visit. The data that support the findings of this study are available from the corresponding author upon reasonable request. Among a total of 1958 participants who completed both ABPM and brain MRI, 1905 had fully assessable ABPM and MRI data. Thereafter, we excluded study participants if they had atrial fibrillation (n=18), previous history of symptomatic cerebrovascular accidents (n=73), and missing data on covariates (n=80). The current analysis included a total of 1734 neurologically asymptomatic participants. The Human Subjects Review Committee at the Korea University Ansan Hospital approved the protocol of the study. All study participants provided written informed consent for the study.

Office BP Measurement and Risk Factor Assessment

Mercury sphygmomanometers were used for the measurement of BP by following a standardized protocol. The participants were seated for >5 minutes, and BP measurements were repeated 3 times with a 30-second interval for office BP measurements. Averaged values of BP were used for analysis. Office hypertension was defined as clinic SBP ≥ 140 mmHg, diastolic BP (DBP) ≥ 90 mmHg, or taking antihypertensive medication. Blood samples were obtained after at least 8 hours of fasting for the measurement of serum lipid levels, fasting blood glucose, and serum creatinine. The presence of type 2 diabetes was defined as fasting blood glucose ≥ 126 mg/dL or use of oral hypoglycemic agents or insulin injection.

ABPM Measurement

All ABPM data were obtained using the Mobil-O-Graph NG (I.E.M. GmbH, Stolberg, Germany).¹³ BP was recorded every 30 minutes during the day (6:00 AM–11:00 PM) and every hour during the night (11:00 PM–6:00 AM). Adequate measurements of BP were defined when >70% of expected measurements were obtained with at least 20 and 7 valid readings during daytime and nighttime, respectively. According to the European Society of Cardiology and European Society of Hypertension guidelines, an abnormally elevated BP was considered when averaged diurnal BP was $\geq 135/85$ mmHg, averaged nocturnal BP was $\geq 120/70$ mmHg, or averaged 24-hour mean BP was $\geq 130/80$ mmHg.²

The study participants were classified into 3 categories as follows: (1) normotension: diurnal BP <135/85 mmHg, nocturnal BP <120/70 mmHg, and no history of antihypertensive medication; (2) INH: diurnal BP <135/85 mmHg, nocturnal BP $\geq 120/70$ mmHg, and no history of antihypertensive medication; and (3) overt diurnal hypertension (ODH): diurnal BP $\geq 135/85$ mmHg or history of antihypertensive medication. In addition, they were grouped according to the dipping pattern of nocturnal BP. Based on night-to-day ratio (NDR) of SBP, normal dipper ($0.8 < \text{NDR} \leq 0.9$), extreme dipper ($\text{NDR} \leq 0.8$), reduced dipper ($0.9 < \text{NDR} \leq 1.0$), and reverse dipper ($\text{NDR} > 1.0$) were determined.^{3,5}

Evaluation of Arterial Stiffness and Echocardiography

All physiological parameters were acquired after resting for >5 minutes in a quiet place to avoid external stimuli. Brachial–ankle pulse wave velocity (baPWV) and central BP were measured to evaluate arterial stiffness. Carotid intima-media thickness (cIMT) and ankle–brachial index were measured to assess the degree of atherosclerosis in peripheral arteries. Briefly,

baPWV was calculated from the pulse transit time and the distance between the 2 sampling points (upper arms and ankles). Ankle–brachial index was measured simultaneously with baPWV using an automatic volume plethysmographic device (VP-1000; Omron, Japan). The average values of the left and right baPWVs were used for analysis. Experienced researchers obtained tonometric parameters, such as central SBP, using same device. The cIMT values were measured using B-mode ultrasonography (SonoSite TITAN; SonoSite, Bothell, WA), and the average values of the left and right cIMT were used for analysis.

Conventional 2-dimensional echocardiography was performed at rest, using a 4-MHz transducer (GE Vingmed, Horton, Norway). In brief, the Devereux formula was used for LV mass, which was indexed by body surface area, and the modified biplane Simpson's method was used for LV ejection fraction. Early diastolic mitral annular velocity (Em) was measured at the septal mitral annulus from apical 4-chamber images. A single investigator, who was blinded to each patients' clinical information, collected all echocardiographic variables during the examination. The methods for echocardiography conducted in this study are detailed in a previous report.¹⁴

Silent Cerebrovascular Lesion

The methods of scanning and interpretation of brain MRI have been described elsewhere.¹⁵ Briefly, T2-weighted fluid-attenuated inversion recovery images were used for the evaluation of cerebral WMH. When hyperintensities on fluid-attenuated inversion recovery images were 5 mm or larger, it was defined as the presence of WMH. In each hemisphere, WMH was rated as 0 (no lesion), 1 (focal lesions ≤ 10 mm), 2 (early confluent lesions), and 3 (confluent lesions involving the entire lesion) in 5 different lesions (frontal, parieto-occipital, temporal, basal ganglia, or infratentorial regions) as described previously.¹⁶ All scans were performed using a GE Signa HDxt 1.5T MRI scanner (GE Medical Systems, Waukesha, WI) with an 8-channel head coil. One neuroradiologist interpreted all MRI information and determined the WMH rating without any clinical information of the participants (Cronbach α reliability, 0.96).¹⁷

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD, and categorical variables are presented as number and percentage. Demographic, ABPM, and brain MRI variables were compared using 1-way ANOVA, and other categorical variables were compared using the χ^2 test, wherever appropriate. An independent *t* test was used for pairwise comparisons between groups. We compared the estimated means

of baPWV, central SBP, cIMT, LV mass index (LVMI), Em, and WMH scores between ABPM categories using ANCOVA. Adjusted covariables included age, sex, body mass index, antidiabetic treatment, smoking, triglycerides, and high-density lipoprotein cholesterol based on the clinical relevance and the results from univariate analyses. Bonferroni correction was used for post hoc multiple comparisons. Thereafter, multivariable binary logistic regression analyses were used to assess the associations of the presence of WMH with ABPM groups, baPWV, central SBP, and

LVMI and Em, adjusted for age, sex, body mass index, antidiabetic treatment, smoking, triglycerides, and high-density lipoprotein cholesterol. Because the normal range of baPWV, central SBP, LVMI, and Em for Koreans has not yet been clearly determined, they were analyzed in tertiles, and the bottom third became a reference value. Odds ratios (ORs) and their 95% CIs were also reported. All analyses were conducted using SPSS version 18.0 (IBM, Armonk, NY). A 2-sided *P* value <0.05 was considered as statistically significant.

Table 1. Characteristics of 1734 Study Subjects According to Different Ambulatory Blood Pressure Status

	Normotension, n=475	INH, n=314	ODH, n=945	<i>P</i> value
Age, y	58.5±6.4	59.8±6.9*	60.6±7.2*	<0.001
Men, n (%)	127 (26.7)	144 (45.9)*	526 (55.7)*†	<0.001
Body mass index, kg/m ²	23.5±2.6	24.2±3.0*	25.3±3.0*†	<0.001
Type 2 diabetes, n (%)	27 (5.7)	23 (7.3)	145 (15.3)*†	<0.001
Smoker, n (%)	179 (37.7)	109 (34.7)	367 (38.8)	0.426
SBP, mmHg				
Office	106.3±10.9	113.8±12.1*	122.3±13.9*†	<0.001
24 h	110.9±6.9	117.8±7.1*	126.5±11.9*†	<0.001
Diurnal	113.3±7.3	118.7±7.3*	128.6±12.2*†	<0.001
Nocturnal	101.3±7.7	114.4±8.9*	117.5±13.9*†	<0.001
DBP, mmHg				
Office	68.9±7.6	74.0±7.9*	78.3±9.6*†	<0.001
24 h	69.6±6.0	77.6±3.9*	83.8±9.5*†	<0.001
Diurnal	71.4±6.5	78.3±4.3*	85.6±9.8*†	<0.001
Nocturnal	62.1±5.3	74.7±4.6*	76.0±10.2*†	<0.001
SBP-NDR	0.90±0.06	0.96±0.06*	0.92±0.08*†	<0.001
Total cholesterol, mg/dL	203±35	203±33	192±36*†	<0.001
Triglyceride, mg/dL	122±73	135±82*	149±102*†	<0.001
HDL cholesterol, mg/dL	51.6±13.2	49.3±12.7*	46.6±11.5*†	<0.001
Fasting glucose, mg/dL	91.1±14.6	94.6±18.5*	100.5±23.4*†	<0.001
baPWV, cm/s	1342±191	1437±220*	1532±251*†	<0.001
cIMT, mm	0.73±0.08	0.75±0.08*	0.76±0.08*	<0.001
Central SBP, mmHg	122.1±12.9	129.6±14.2*	138.4±16.4*†	<0.001
ABI	1.15±0.07	1.16±0.09	1.16±0.10	0.711
Left ventricular ejection fraction, %	64.6±5.0	64.1±4.9	64.5±5.3	0.380
LVMI, g/m ²	84.4±15.0	90.4±14.9*	98.1±17.3*†	<0.001
Em, cm/s	7.8±1.7	7.2±1.5*	6.6±1.4*†	<0.001
E/Em	8.8±2.3	9.0±2.2	9.8±2.5*†	<0.001
Presence of WMH, n (%)	138 (29.1)	122 (38.9)*	417 (44.1)*	<0.001
None	337 (70.9)	192 (61.1)	528 (55.9)	
Mild	106 (22.3)	98 (31.2)	268 (28.4)	
Moderate to severe	32 (6.7)	24 (7.6)	149 (15.8)	
Score of WMH	0.7±1.4	1.0±1.8*	1.4±2.2*†	<0.001

Data are shown as mean±SD or number (%). ABI indicates ankle-brachial index; baPWV, brachial-ankle pulse wave velocity; cIMT, carotid intima-media thickness; DBP, diastolic blood pressure; Em, early diastolic mitral annular velocity; HDL, high-density lipoprotein; INH, isolated nocturnal hypertension; LVMI, left ventricular mass index; NDR, night-to-day ratio; ODH, overt diurnal hypertension; SBP, systolic blood pressure; and WMH, white matter hyperintensity. *P* for the overall differences among the 3 groups.

**P*<0.05 vs normotension.

†*P*<0.05 vs INH, independent *t* test was used.

RESULTS

Among the 1734 participants in this study, 797 (46.0%) were men, and their mean age was 59.9 ± 7.0 years. There were 527 (30.4%) patients who were taking antihypertensive drugs, 195 (11.2%) patients with type 2 diabetes, and 655 (37.8%) were past or current smokers. WMH was present in 677 (39.0%) individuals, and their mean WMH score was 2.89 ± 2.22 .

The clinical characteristics of the 3 ABPM groups are shown in Table 1. There were 475 (27.4%) people in the normotension group, 314 (18.1%) in the INH group, and 945 (54.5%) in the ODH group. Compared with normotensive participants, subjects with INH were older and heavier with higher serum concentrations of triglycerides and lower high-density lipoprotein cholesterol. Pairwise comparisons using independent *t* tests are displayed in Tables S1 through S3. Both in men

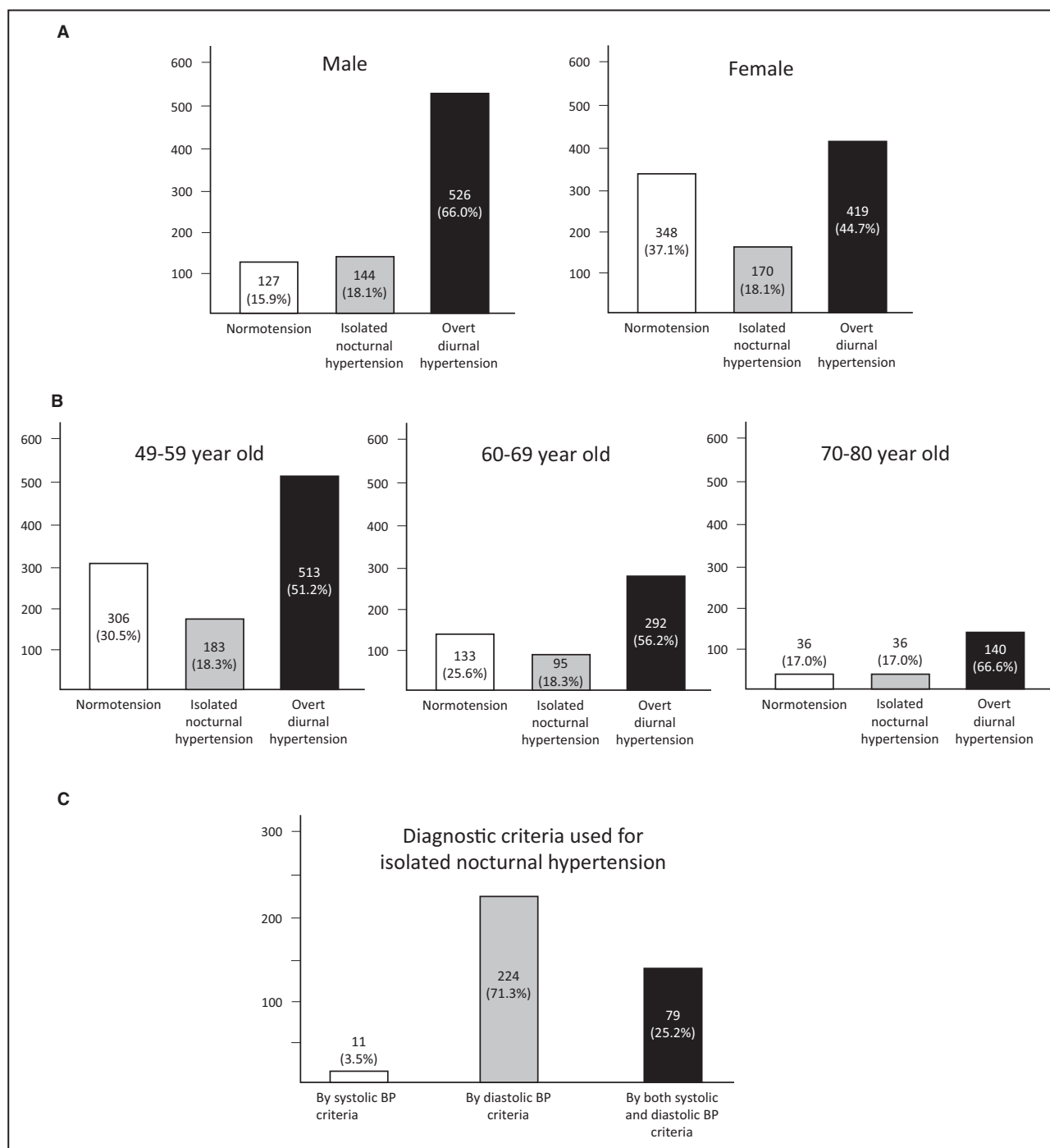


Figure 1. Differences in prevalence of isolated nocturnal hypertension by sex (A), age (B), and systolic/diastolic pressure (C). BP indicates blood pressure.

and women, the prevalence of INH was equally 18.1% (Figure 1A). By age group, the prevalence of INH was 18.3% in people in their 50s (49–59 years old), 18.3% in people in their 60s (60–69 years old), and 17.0% in people in their 70s (70–80 years old) (Figure 1B). Most INHs were because of increased DBP. Of 314 people with INH, 71.3% (n=224) had isolated DBP elevation, whereas 3.5% (n=11) had isolated SBP elevation and 25.2% (n=79) had both SBP and DBP elevation (Figure 1C). Subjects with ODH showed significant differences in all clinical variables compared with other groups except for their smoking status.

Indicators of arterial or myocardial stiffness were deteriorating in INH rather than normotension and ODH rather than INH (Table 1 and Table S1 through S3). INH as well as ODH had increased baPWV, cIMT, central SBP, LVMI, and decreased Em. However, ankle-brachial index and LV ejection fraction did not show significant differences between the ABPM categories ($P=0.711$ and $P=0.380$, respectively) (Table 1). The mean values of SBP-NDR were 0.90 ± 0.06 in normotension, 0.96 ± 0.06 in INH, and 0.92 ± 0.08 in ODH, which indicated that there was a considerable number of nondippers in the normotension (46%) and ODH (55%) groups as well as in the INH (86%) group (Figure 2). WMH development was most frequent in the ODH group, followed by the INH and normotension groups, and the WMH scores also showed the same trend (Table 1).

In multivariable adjusted analysis, ODH showed significant increases in baPWV, central BP, cIMT, LVMI, Em, and WHM scores, compared with normotension. INH also had increased baPWV (1441.7 cm/s versus 1369.5 cm/s, $P<0.001$), central BP (130 mmHg versus 122 mmHg, $P<0.001$), cIMT (0.753 mm versus 0.740 mm, $P=0.050$), LVMI (91 g/m² versus 88 g/m², $P=0.026$), and decreased Em (7.17 cm/s versus 7.56 cm/s, $P<0.001$) compared with normotension, but there was no difference in WMH scores between normotension and INH (0.767 versus 0.986, $P=0.321$) (Table 2).

Table 3 shows the probability of WMH presence, according to ABPM categories, level of arterial stiffness, or level of abnormal LV structures/functions after multivariable adjustment. Among the 3 ABPM categories, both INH (OR, 1.504 [95% CI, 1.097–2.062]; $P=0.011$) and ODH (OR, 1.840 [95% CI, 1.416–2.390]; $P<0.001$) were significantly associated with increased development of WMH compared with the normotension group. The highest tertiles of baPWV (OR, 1.800 [95% CI, 1.343–2.414]; $P<0.001$) and central SBP (OR, 1.342 [95% CI, 1.040–1.732]; $P=0.024$) were also associated with increased development of WMH. However, neither increased LVMI nor decreased Em were associated with development of WMH.

When we excluded 527 patients who took anti-hypertensive medication, the office and ambulatory blood pressure in the ODH group increased further.

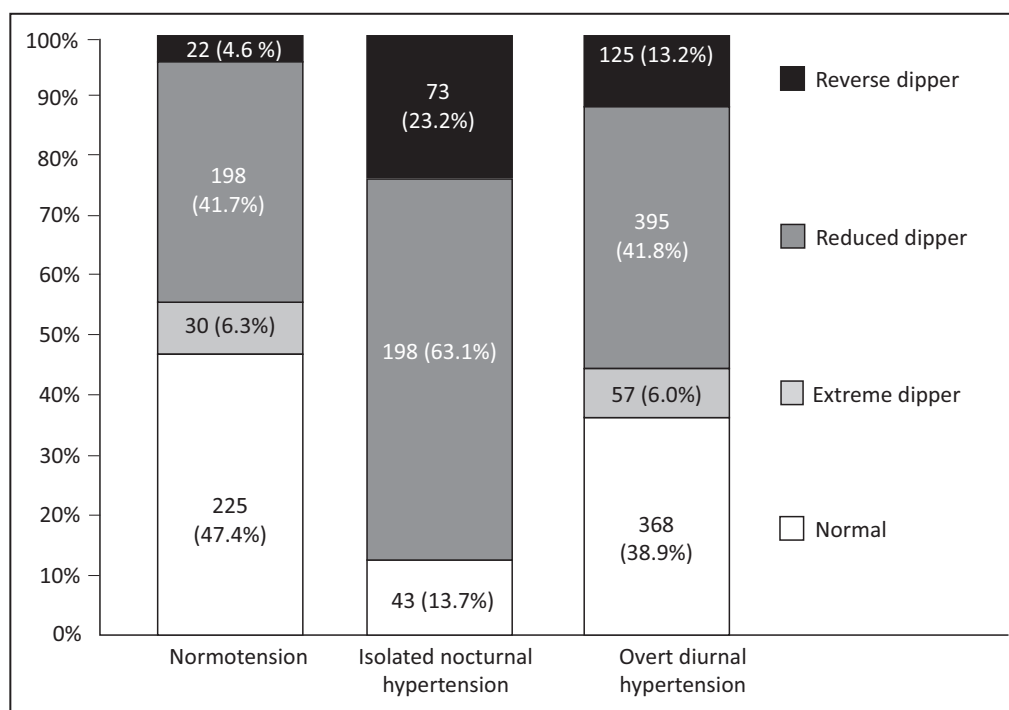


Figure 2. Distribution of dipping pattern in normotension, isolated nocturnal hypertension, and overt diurnal hypertension.

Table 2. Estimated Means of baPWV, Central SBP, cIMT, LVMI, Em, and WMH According to Ambulatory Blood Pressure Category After Multivariable Adjustment

	Estimated mean value (95% CI)*	P value, vs normotension	P value, vs INH
baPWV, cm/s			
Normotension	1369.5 (1350.3–1388.7)		
INH	1441.7 (1419.1–1464.2)	<0.001	
ODH	1516.8 (1503.2–1530.4)	<0.001	<0.001
Central SBP, mmHg			
Normotension	121.9 (120.5–123.3)		
INH	129.6 (127.9–131.2)	<0.001	
ODH	138.5 (137.5–139.5)	<0.001	<0.001
cIMT, mm			
Normotension	0.740 (0.733–0.747)		
INH	0.753 (0.745–0.760)	0.050	
ODH	0.754 (0.749–0.759)	0.004	1.000
LVMI, g/m ²			
Normotension	88.138 (86.707–89.568)		
INH	91.069 (89.388–91.750)	0.026	
ODH	96.020 (95.017–97.022)	<0.001	<0.001
Em, cm/s			
Normotension	7.562 (7.439–7.684)		
INH	7.167 (7.023–7.311)	<0.001	
ODH	6.788 (6.702–6.874)	<0.001	<0.001
WMH scores			
Normotension	0.767 (0.593–0.941)		
INH	0.986 (0.782–1.190)	0.321	
ODH	1.359 (1.237–1.480)	<0.001	0.007

baPWV indicates brachial–ankle pulse wave velocity; cIMT, carotid intima-media thickness; Em, early diastolic mitral annular velocity; INH, isolated nocturnal hypertension; LVMI, left ventricular mass index; ODH, overt diurnal hypertension; SBP, systolic blood pressure; and WMH, white matter hyperintensity.

*Adjusted for age, sex, body mass index, antidiabetic treatment, smoking, serum triglycerides, and high-density lipoprotein cholesterol levels.

The baPWV, central SBP, cIMT, LVMI, and Em of the ODH group showed significant deterioration compared with the normotension group (Table S4 through S6).

We investigated multiplicative interaction between dependent variables (WMH according to ABPM, baPWV, central SBP, cIMT, LVMI, and Em levels) with age or sex, but there was no interaction.

DISCUSSION

The main finding of this study is that INH is common in the general population and significantly associated with arterial stiffness, abnormal LV changes, and early cerebral damage, which is comparable with clinical daytime hypertension.

With the use of ABPM in clinical practice, the major focus has been on a blunted drop of nocturnal SBP, which is related to disrupted circadian rhythm. However, there is a difference between the concepts of INH and nondippers. Nondipping is relatively high nocturnal SBP compared with daytime SBP, whereas INH is elevated nocturnal SBP or DBP (but normal SBP

or DBP during daytime). Since INH was first described by Li et al in 2007,⁶ it has attracted attention because of its association with various types of target organ damage and cardiovascular events.^{18–20}

Although the prevalence of INH is not well documented, it seems higher than generally known. In Argentina, the prevalence of INH increases to 12.9% among normotensive subjects who have never been diagnosed with hypertension. Notably, the prevalence of INH was higher in untreated normotensives than in patients with hypertension on antihypertensive treatment (17.2% versus 7.4%, $P<0.001$).²¹ Among patients with hypertension in Australia, uncontrolled nocturnal BP was associated with elevated central SBP and pulse wave velocity, where isolated elevation of nocturnal BP was as high as 14.4% despite antihypertensive treatment.²² The prevalence of INH in the Chinese general population is 13.2%, and INH in China is related to increased central augmentation index and baPWV.²³ Black individuals in the United States seemed to have a prevalence of INH as high as 19.1%, and INH was associated with LV hypertrophy.¹⁹ In our

Table 3. Presence of White Matter Hyperintensity According to Ambulatory Blood Pressure, baPWV, Central SBP, cIMT, LVMI, and Em

	OR (95% CI)	P value
ABPM category		
Normotension	(Reference)	
INH	1.504 (1.097–2.062)	0.011
ODH	1.840 (1.416–2.390)	<0.001
baPWV		
Lowest	(Reference)	
Middle	1.278 (0.972–1.681)	0.079
Highest	1.800 (1.343–2.414)	<0.001
Central SBP		
Lowest	(Reference)	
Middle	1.001 (0.777–1.288)	0.996
Highest	1.342 (1.040–1.732)	0.024
cIMT		
Lowest	(Reference)	
Middle	0.935 (0.719–1.216)	0.615
Highest	1.012 (0.770–1.332)	0.929
LVMI		
Lowest	(Reference)	
Middle	1.195 (0.923–1.547)	0.175
Highest	1.262 (0.956–1.665)	0.101
Em		
Highest	(Reference)	
Middle	0.955 (0.731–1.247)	0.735
Lowest	1.186 (0.891–1.577)	0.242

Each model was adjusted for age, sex, body mass index, antidiabetic treatment, smoking, serum triglycerides, and high-density lipoprotein cholesterol levels. ABPM indicates ambulatory blood pressure monitoring; baPWV, brachial–ankle pulse wave velocity; cIMT, carotid intima-media thickness; Em, early diastolic mitral annular velocity; INH, isolated nocturnal hypertension; LVMI, left ventricular mass index; ODH, overt diurnal hypertension; OR, odds ratio; and SBP, systolic blood pressure.

population-based study in Korea, the prevalence of INH was 18.1%. Assuming from the above studies and our findings, a considerable number of general populations are exposed to cardiovascular risk without being properly evaluated for nocturnal BP.

In our study, using multivariable-adjusted models, individuals with INH as well as ODH were likely to have increased arterial stiffness, LV hypertrophy, and more WMH.

Although WMH has been considered a normal aging-related degenerative process, recent studies have provided evidence that WMH is a marker of increased risk of stroke, dementia, depression, and death.²⁴ Moreover, the presence of hypertension is the strongest predictor of WMH progression over time.^{9,25,26} Intensive antihypertensive treatment reduced the rate of increase in WMH volume in patients with hypertension or type 2 diabetes.^{11,27} Thus, the

reduction of increased BP is of paramount importance to slow the progression of WMH. Our study findings are in line with these studies and indicate that the presence of INH results in silent cerebral lesions, probably via arterial stiffness.

The presence of INH appears to cause LV hypertrophy and LV diastolic abnormality as well. However, WMH incidence did not increase further in the group with LVH or in the group with LV diastolic dysfunction. Therefore, it is more reasonable to interpret the development of WMH as a result of arterial stiffness rather than LV changes.

To the best of our knowledge, no prior studies have comprehensively evaluated the effect of INH on arterial stiffness, LV changes, and WMH, which are established markers to target organ damage. Nondipping BP is associated with WMH, regardless of the presence of clinical hypertension.^{28,29} Many studies have reported the prognostic importance of nondipping BP on cardiovascular outcomes such as coronary artery disease and heart failure.^{5,30} However, because of discrepancies in classifications criteria, many INH subjects are normal dippers, just as many nondippers are healthy normotensive individuals (Figure 2). Given that most individuals with INH have normal office BP,⁸ we should try not only to predict the prognosis of patients with hypertension who are already being treated but also to find hidden INH. Therefore, it would be reasonable to use ABPM for both untreated normotensive and treated hypertensive subjects.

It is notable that most INH in our study was caused by elevated DBP (≥ 70 mmHg). In an epidemiologic study with 1.7 million Japanese subjects, isolated diastolic hypertension was associated with cardiovascular events independent of age and sex,³¹ which is in line with our study results.

Study Limitations

Despite the relatively large sample size of this study, there were certain limitations. First, because of the limitations of the cross-sectional design, temporal relationships between target organ damage could not be established. Second, the prevalence of INH in our study is higher than previously reported, which was because of the high prevalence of nocturnal diastolic hypertension. Previous reports did not specify the proportion of diastolic hypertension in INH, and there were significant ethnic differences in the prevalence of INH.³² Further research is required on the prevalence and detailed composition of INH. Although the ABPM device in our study was well validated,³³ it may have systemically overestimated DBP. However, our finding that elevated nocturnal DBP is associated with target organ damage remains meaningful. Third, the diagnostic reproducibility for INH with a single ABPM was

not high.³⁴ Therefore, there might be a misclassification of BP categories.

CONCLUSIONS

In this community-based cohort study with 24-hour ABPM, we found that individuals with increased nocturnal BP and normal daytime BP were at increased risk of developing arterial stiffness and hypertension-related heart and brain damage. Considering that INH is not uncommon, more active use of ABPM in clinical practice might be helpful in identifying individuals at risk of subclinical vascular-cardio-cerebral damage or preventing disease progression.

ARTICLE INFORMATION

Received February 3, 2022; accepted August 9, 2022.

Affiliations

Division of Cardiology, Department of Internal Medicine (S.H.K., S.K., J.-S.K., S.Y.L., Y.-H.K.); and Institute of Human Genomic Study, Department of Radiology (C.S., H.S., S.K.L.), Korea University Ansan Hospital, Ansan, Republic of Korea; Division of Cardiology, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea (H.E.L.); Division of Cardiology, Department of Internal Medicine, Kangbuk Samsung Medical Center, Seoul, Republic of Korea (K.-C.S.); and Division of Cardiology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea (G.-Y.C.).

Acknowledgments

The authors thank all participants for their participation and all research staff of the Institute of Human Genomic Study at Korea University Ansan Hospital for their contribution to data collection.

Sources of Funding

This study was supported by grants from the Korean Centers for Disease Control and Prevention (2011-E71004-00, 2012-E71005-00, 2013-E71005-00, and 2014-E71003-00).

Disclosures

None.

Supplemental Material

Tables S1–S6

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics of Study Subjects According to Different Ambulatory Blood Pressure Status. Between NT and INH. Independent t-test was used.

	NT (n = 475)	INH (n = 314)	<i>P</i>
Age (year)	58.5 ± 6.4	59.8 ± 6.9	0.008
Male (n, %)	127 (26.7)	144 (45.9)	<0.001
Body mass index (kg/m ²)	23.5 ± 2.6	24.2 ± 3.0	0.001
Type 2 diabetes (n, %)	27 (5.7)	23 (7.3)	0.218
Smoker (n, %)	179 (37.7)	109 (34.7)	0.220
SBP (mmHg)			
Office	106.3 ± 10.9	113.8 ± 12.1	<0.001
24-hour	110.9 ± 6.9	117.8 ± 7.1	<0.001
Diurnal	113.3 ± 7.3	118.7 ± 7.3	<0.001
Nocturnal	101.3 ± 7.7	114.4 ± 8.9	<0.001
DBP (mmHg)			
Office	68.9 ± 7.6	74.0 ± 7.9	<0.001
24-hour	69.6 ± 6.0	77.6 ± 3.9	<0.001

Diurnal	71.4 ± 6.5	78.3 ± 4.3	<0.001
Nocturnal	62.1 ± 5.3	74.7 ± 4.6	<0.001
SBP-NDR	0.90 ± 0.06	0.96 ± 0.06	<0.001
Total cholesterol (mg/dL)	203 ± 35	203 ± 33	0.827
Triglyceride (mg/dL)	122 ± 73	135 ± 82	0.017
HDL cholesterol (mg/dL)	51.6 ± 13.2	49.3 ± 12.7	0.015
Fasting glucose (mg/dL)	91.1 ± 14.6	94.6 ± 18.5	0.003
baPWV (cm/sec)	1342 ± 191	1437 ± 220	<0.001
cIMT (mm)	0.73 ± 0.08	0.75 ± 0.08	<0.001
Central SBP (mmHg)	122.1 ± 12.9	129.6 ± 14.2	<0.001
ABI	1.15 ± 0.07	1.16 ± 0.09	0.505
Left ventricular ejection fraction (%)	64.6 ± 5.0	64.1 ± 4.9	0.185
LVMI (g/m ²)	84.4 ± 15.0	90.4 ± 14.9	<0.001
Em (cm/sec)	7.8 ± 1.7	7.2 ± 1.5	<0.001
E/Em	8.8 ± 2.3	9.0 ± 2.2	0.351

Presence of WMH (n, %)	138 (29.1)	122 (38.9)	0.003
None	337 (70.9)	192 (61.1)	
Mild	106 (22.3)	98 (31.2)	0.013
Moderate to severe	32 (6.7)	24 (7.6)	
Score of WMH	0.7 ± 1.4	1.0 ± 1.8	0.017

Table S2. Characteristics of Study Subjects According to Different Ambulatory Blood Pressure Status. Between NT and ODH. Independent t-test was used.

	NT (n = 475)	ODH (n = 945)	<i>P</i>
Age (year)	58.5 ± 6.4	60.6 ± 7.2	<0.001
Male (n, %)	127 (26.7)	526 (55.7)	<0.001
Body mass index (kg/m ²)	23.5 ± 2.6	25.3 ± 3.0	<0.001
Type 2 diabetes (n, %)	27 (5.7)	145 (15.3)	<0.001
Smoker (n, %)	179 (37.7)	367 (38.8)	0.359
SBP (mmHg)			
Office	106.3 ± 10.9	122.3 ± 13.9	<0.001
24-hour	110.9 ± 6.9	126.5 ± 11.9	<0.001
Diurnal	113.3 ± 7.3	128.6 ± 12.2	<0.001
Nocturnal	101.3 ± 7.7	117.5 ± 13.9	<0.001
DBP (mmHg)			
Office	68.9 ± 7.6	78.3 ± 9.6	<0.001
24-hour	69.6 ± 6.0	83.8 ± 9.5	<0.001

Diurnal	71.4 ± 6.5	85.6 ± 9.8	<0.001
Nocturnal	62.1 ± 5.3	76.0 ± 10.2	<0.001
SBP-NDR	0.90 ± 0.06	0.92 ± 0.08	<0.001
Total cholesterol (mg/dL)	203 ± 35	192 ± 36	<0.001
Triglyceride (mg/dL)	122 ± 73	149 ± 102	<0.001
HDL cholesterol (mg/dL)	51.6 ± 13.2	46.6 ± 11.5	<0.001
Fasting glucose (mg/dL)	91.1 ± 14.6	100.5 ± 23.4	<0.001
baPWV (cm/sec)	1342 ± 191	1532 ± 251	<0.001
cIMT (mm)	0.73 ± 0.08	0.76 ± 0.08	<0.001
Central SBP (mmHg)	122.1 ± 12.9	138.4 ± 16.4	<0.001
ABI	1.15 ± 0.07	1.16 ± 0.10	0.420
Left ventricular ejection fraction (%)	64.6 ± 5.0	64.5 ± 5.3	0.838
LVMI (g/m ²)	84.4 ± 15.0	98.1 ± 17.3	<0.001
Em (cm/sec)	7.8 ± 1.7	6.6 ± 1.4	<0.001
E/Em	8.8 ± 2.3	9.8 ± 2.5	<0.001

Presence of WMH (n, %)	138 (29.1)	417 (44.1)	<0.001
None	337 (70.9)	528 (55.9)	
Mild	106 (22.3)	268 (28.4)	<0.001
Moderate to severe	32 (6.7)	149 (15.8)	
Score of WMH	0.7 ± 1.4	1.4 ± 2.2	<0.001

Table S3. Characteristics of Study Subjects According to Different Ambulatory Blood Pressure Status. Between INH and ODH. Independent t-test was used.

	INH (n = 314)	ODH (n = 945)	<i>P</i>
Age (year)	59.8 ± 6.9	60.6 ± 7.2	0.096
Male (n, %)	144 (45.9)	526 (55.7)	0.002
Body mass index (kg/m ²)	24.2 ± 3.0	25.3 ± 3.0	<0.001
Type 2 diabetes (n, %)	23 (7.3)	145 (15.3)	<0.001
Smoker (n, %)	109 (34.7)	367 (38.8)	0.108
SBP (mmHg)			
Office	113.8 ± 12.1	122.3 ± 13.9	<0.001
24-hour	117.8 ± 7.1	126.5 ± 11.9	<0.001
Diurnal	118.7 ± 7.3	128.6 ± 12.2	<0.001
Nocturnal	114.4 ± 8.9	117.5 ± 13.9	<0.001
DBP (mmHg)			
Office	74.0 ± 7.9	78.3 ± 9.6	<0.001
24-hour	77.6 ± 3.9	83.8 ± 9.5	<0.001

Diurnal	78.3 ± 4.3	85.6 ± 9.8	<0.001
Nocturnal	74.7 ± 4.6	76.0 ± 10.2	0.001
SBP-NDR	0.96 ± 0.06	0.92 ± 0.08	<0.001
Total cholesterol (mg/dL)	203 ± 33	192 ± 36	<0.001
Triglyceride (mg/dL)	135 ± 82	149 ± 102	0.027
HDL cholesterol (mg/dL)	49.3 ± 12.7	46.6 ± 11.5	0.001
Fasting glucose (mg/dL)	94.6 ± 18.5	100.5 ± 23.4	<0.001
baPWV (cm/sec)	1437 ± 220	1532 ± 251	<0.001
cIMT (mm)	0.75 ± 0.08	0.76 ± 0.08	0.069
Central SBP (mmHg)	129.6 ± 14.2	138.4 ± 16.4	<0.001
ABI	1.16 ± 0.09	1.16 ± 0.10	0.944
Left ventricular ejection fraction (%)	64.1 ± 4.9	64.5 ± 5.3	0.212
LVMI (g/m ²)	90.4 ± 14.9	98.1 ± 17.3	<0.001
Em (cm/sec)	7.2 ± 1.5	6.6 ± 1.4	<0.001
E/Em	9.0 ± 2.2	9.8 ± 2.5	<0.001

Presence of WMH (n, %)	122 (38.9)	417 (44.1)	0.058
None	192 (61.1)	528 (55.9)	
Mild	98 (31.2)	268 (28.4)	0.001
Moderate to severe	24 (7.6)	149 (15.8)	
Score of WMH	1.0 ± 1.8	1.4 ± 2.2	0.001

Table S4. Characteristics of 1,207 Study Subjects According to Different Ambulatory Blood Pressure Status. Subjects taking anti-hypertensive drugs were excluded.

	NT (n = 475)	INH (n = 314)	ODH (n = 418)	<i>P</i>
Age (year)	58.5 ± 6.4	59.8 ± 6.9	58.3 ± 5.9	0.002
Male (n, %)	127 (26.7)	144 (45.9)	275 (65.8)	<0.001
Body mass index (kg/m ²)	23.5 ± 2.6	24.2 ± 3.0	24.9 ± 2.8	<0.001
Type 2 diabetes (n, %)	27 (5.7)	23 (7.3)	26 (6.2)	0.648
Smoker (n, %)	179 (37.7)	109 (34.7)	194 (46.4)	0.003
SBP (mmHg)				
Office	106.3 ± 10.9	113.8 ± 12.1	123.3 ± 13.5	<0.001
24-hour	110.9 ± 6.9	117.8 ± 7.1	130.9 ± 10.9	<0.001
Diurnal	113.3 ± 7.3	118.7 ± 7.3	133.5 ± 11.0	<0.001
Nocturnal	101.3 ± 7.7	114.4 ± 8.9	120.4 ± 14.0	<0.001
DBP (mmHg)				
Office	68.9 ± 7.6	74.0 ± 7.9	81.4 ± 9.0	<0.001

24-hour	69.6 ± 6.0	77.6 ± 3.9	88.9 ± 7.0	<0.001
Diurnal	71.4 ± 6.5	78.3 ± 4.3	91.1 ± 7.1	<0.001
Nocturnal	62.1 ± 5.3	74.7 ± 4.6	79.5 ± 9.8	<0.001
SBP-NDR	0.90 ± 0.06	0.96 ± 0.06	0.90 ± 0.08	<0.001
Total cholesterol (mg/dL)	203 ± 35	203 ± 33	203 ± 33	0.972
Triglyceride (mg/dL)	122 ± 73	135 ± 82	156 ± 92	<0.001
HDL cholesterol (mg/dL)	51.6 ± 13.2	49.3 ± 12.7	47.3 ± 11.5	<0.001
Fasting glucose (mg/dL)	91.1 ± 14.6	94.6 ± 18.5	97.0 ± 18.6	<0.001
baPWV (cm/sec)	1342 ± 191	1437 ± 220	1500 ± 226	<0.001
cIMT (mm)	0.73 ± 0.08	0.75 ± 0.08	0.76 ± 0.07	<0.001
Central SBP (mmHg)	122.1 ± 12.9	129.6 ± 14.2	139.7 ± 15.8	<0.001
ABI	1.15 ± 0.07	1.16 ± 0.09	1.15 ± 0.13	0.711
Left ventricular ejection fraction (%)	64.6 ± 5.0	64.1 ± 4.9	63.7 ± 5.2	0.044
LVMI (g/m ²)	84.4 ± 15.0	90.4 ± 14.9	97.9 ± 17.2	<0.001
Em (cm/sec)	7.8 ± 1.7	7.2 ± 1.5	6.9 ± 1.4	<0.001

E/Em	8.8 ± 2.3	9.0 ± 2.2	9.1 ± 2.2	0.173
Presence of WMH (n, %)	138 (29.1)	122 (38.9)	147 (35.2)	0.013
None	337 (70.9)	192 (61.1)	271 (64.8)	
Mild	106 (22.3)	98 (31.2)	104 (24.9)	0.014
Moderate to severe	32 (6.7)	24 (7.6)	43 (10.3)	
Score of WMH	0.7 ± 1.4	1.0 ± 1.8	1.0 ± 1.9	0.015

Data are shown as mean ± SD or number (%). NT, normotension; INH, isolated nocturnal hypertension; ODH, overt diurnal hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; hsCRP, high-sensitive C-reactive protein; NDR, night-to-day ratio; baPWV, brachial-ankle pulse wave velocity; cIMT, carotid intima-media thickness; ABI, ankle-brachial index; LVMI, left ventricular mass index; WMH, white matter hyperintensity. *P* for the overall differences among the three groups.

Table S5. Estimated Means of Brachial-Ankle Pulse Wave Velocity, Central Systolic Blood Pressure, Carotid Intima-Media Thickness, Left Ventricular Mass Index, Early Diastolic Mitral Annular Velocity and White Matter Hyperintensity According to Ambulatory Blood Pressure Category after multivariable adjustment. Subjects taking anti-hypertensive drugs were excluded.

	Estimated mean value (95%CI)*	<i>P</i> , vs <i>NT</i>	<i>P</i> , vs <i>INH</i>
baPWV (cm/sec)			
NT	1349.9 (1332.2-1367.5)		
INH	1421.9 (1400.9-1442.8)	<0.001	
ODH	1503.7 (1484.3-1523.1)	<0.001	<0.001
Central SBP (mmHg)			
NT	121.8 (120.5-123.1)		
INH	129.3 (127.7-130.8)	<0.001	
ODH	140.3 (138.8-141.7)	<0.001	<0.001
cIMT (mm)			
NT	0.734 (0.727-0.740)		
INH	0.745 (0.737-0.752)	0.088	

	ODH	0.762 (0.754-0.769)	<0.000	0.005
LVMI (g/m ²)				
	NT	87.050 (85.674-88.425)		
	INH	90.012 (88.381-91.643)	0.020	
	ODH	95.185 (93.697-96.672)	<0.001	<0.001
Em (cm/sec)				
	NT	7.736 (7.614-7.858)		
	INH	7.345 (7.200-7.490)	<0.001	
	ODH	6.852 (6.720-6.985)	<0.001	<0.001
WMH scores				
	NT	0.663 (0.512-0.814)		
	INH	0.915 (0.736-1.093)	0.105	
	ODH	1.102 (0.940-1.264)	<0.001	0.381

*Adjusted for age, sex, body mass index, anti-diabetic treatment, smoking, serum triglyceride, and HDL-cholesterol levels. CI, confidence interval; NT, normotension; INH, isolated nocturnal hypertension; ODH, overt diurnal hypertension; baPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; cIMT, carotid intima-media thickness; LVMI, left ventricular mass index; WMH, white matter hyperintensity.

Table S6. Odd Ratios and 95% Confidence Intervals for the Presence of White Matter Hyperintensity According to Ambulatory Blood Pressure, baPWV, central SBP, cIMT, LVMI and Early Diastolic Mitral Annular Velocity (Em). Subjects taking anti-hypertensive drugs were excluded.

	OR (95% CI)	<i>P</i>
ABPM category		
NT	(Reference)	
INH	1.548 (1.128–2.124)	0.007
ODH	1.615 (1.178–2.215)	0.003
baPWV		
Lowest	(Reference)	
Middle	1.328 (0.969–1.820)	0.077
Highest	1.896 (1.335–2.692)	<0.001
Central SBP		
Lowest	(Reference)	
Middle	0.996 (0.738–1.346)	0.981

Highest	1.510 (1.099-2.073)	0.011
cIMT		
Lowest	(Reference)	
Middle	0.869 (0.632–1.196)	0.389
Highest	1.070 (0.760-1.507)	0.700
LVMI		
Lowest	(Reference)	
Middle	1.259 (0.928-1.706)	0.139
Highest	1.045 (0.741-1.474)	0.801
Em		
Highest	(Reference)	
Middle	0.815 (0.594-1.119)	0.206
Lowest	1.267 (0.899-1.785)	0.176

Each model was adjusted for age, sex, body mass index, anti-diabetic treatment, smoking, serum triglyceride, and HDL-cholesterol levels. ABPM, ambulatory blood pressure monitoring; PWV, pulse wave velocity; CI, confidence interval; OR, odds ratio; NT, normotension; INH, isolated nocturnal hypertension; ODH, overt diurnal hypertension; PWV, brachial-ankle pulse wave velocity; BP, blood pressure; cIMT, carotid intima-media thickness; LVMI, left ventricular mass index; WMH, white matter hyperintensity.