Ambulatory Blood Pressure Levels in the Prediction of Progression of Cerebral Small Vessel Disease

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OBJECTIVES: We aimed to study the value of ambulatory blood pressure monitoring (ABPM) in predicting the global progression of cerebral small vessel disease (cSVD).

DESIGN: Longitudinal cohort study.

SETTING: Data from the population-based Investigating Silent Strokes in Hypertensives study.

PARTICIPANTS: Individuals with hypertension who were 50 to 70 years of age and stroke free at baseline. In baseline and follow-up visits, patients underwent magnetic resonance imaging and ABPM.

MEASUREMENTS: Ambulatory systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels were studied as continuous variables and dichotomized according to good or poor control on the basis of 125/75 (24 hours), 130/80 (day), and 110/65 (night) mm Hg cutoff values. Whole cSVD progression was qualitatively scored with 1 point when an incident lesion (incident lacunar infarcts, deep cerebral microbleeds, white matter hyperintensities, and basal ganglia enlarged perivascular spaces) was detected. The score ranged from 0 to 4.

RESULTS: We followed up 233 participants with a median age of 65 years within 4 years. A total of 61 (26.2%) and 23 (9.9%) subjects showed cSVD progression in one and two or more markers, respectively. Baseline ambulatory SBP and DBP and nighttime pulse pressure (PP) values were positively correlated with the number of incident cSVD lesions. Interestingly, patients without incident lesions showed greater differences between office and ambulatory BP, thus suggesting an increased white coat effect. Poor DBP control, nighttime PP, and DBP white coat effect were independently associated with cSVD progression. The inclusion of these metrics in a clinical model resulted in a significant increase in the prediction of incident lesions (integrated discrimination improvement = 9.09%; *P* value <.001).

CONCLUSION: ABPM may help assess cSVD risk of progression, especially by the identification of poor BP control, masked hypertension, and increased nighttime PP. **J Am Geriatr Soc 68:2232-2239, 2020.**

Keywords: longitudinal study; hypertension; blood pressure monitoring; cerebral small vessel disease; cerebrovascular diseases

Cerebral small vessel disease (cSVD) refers to all pathologic processes affecting the small vessels of the brain.[1,2] Lacunar infarcts, deep cerebral microbleeds (CMBs), white matter hyperintensities (WMH), and basal ganglia enlarged perivascular spaces (BG-EPVS) are considered the principal magnetic resonance imaging (MRI) markers of age-related cSVD. These lesions may accumulate on brain parenchyma over time, and, although the course might be subclinical, they are associated with mild cognitive impairment,[3] stroke, and increased mortality.[4]

Hypertension is a principal risk factor for age-related cSVD that via sustained elevated blood pressure (BP) levels produces arteriolosclerosis in small vessels and alterations in cerebrovascular function.[5] Other mechanisms such as arterial stiffness may also be involved in the pathogenesis of small vessel disease.[6] However, in-office BP measurements are subject to different sources of bias.[7] Thus ambulatory blood pressure monitoring (ABPM) provides a more reliable

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measure of BP with greater reproducibility than in-office measurements.[8,9]

Several studies have described associations between ABPM levels and individual MRI markers of cSVD[8,10-12] and total cSVD burden.[13,14] However, most results have come from cross-sectional studies.[11-16] Given that cSVD progression is prevalent in older adults with hypertension,[3] longitudinal studies assessing the relationship between ABPM levels and cSVD progression may be of interest.

We first aimed to construct a cSVD progression score. We then studied the relationship between serial ABPM measurements and this cSVD progression score, considering both baseline ambulatory recordings and changes in BP levels between visits. Finally, we determined the usefulness of ABPM control, as defined by 2018 clinical guidelines,[17] together with other ABPM metrics (such as pulse pressure [PP] and white coat effect), in addition to clinical features in the prediction of cSVD progression.

METHODS

Participants

This investigation was performed as part of the Investigating Silent Strokes in Hypertensives study (ISSYS), an observational, longitudinal, and population-based study aiming to assess silent cerebrovascular lesions and determine their consequences in patients with hypertension.[18] The inclusion criteria included (1) age between 50 and 70 years at the baseline visit, (2) primary hypertension diagnosed at least 1 year earlier, and (3) no previous history of stroke or dementia. Between 2010 and 2012, we randomly recruited 976 patients from 14 primary healthcare centers in Barcelona. Patients underwent procedures including clinical data assessment, a brain MRI, office and ABPMs, and blood and urine sampling. The follow-up visit was conducted between 2014 and 2016 in a sample of 361 individuals at high risk of cSVD progression, defined by the presence of extensive WMH or silent brain infarcts.[3]

In this study we selected 233 patients who underwent baseline and follow-up MRIs and had at least ABPM recordings at the baseline visit (Figure 1).

This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the local ethics committee. All patients provided signed informed consent before inclusion at both visits.

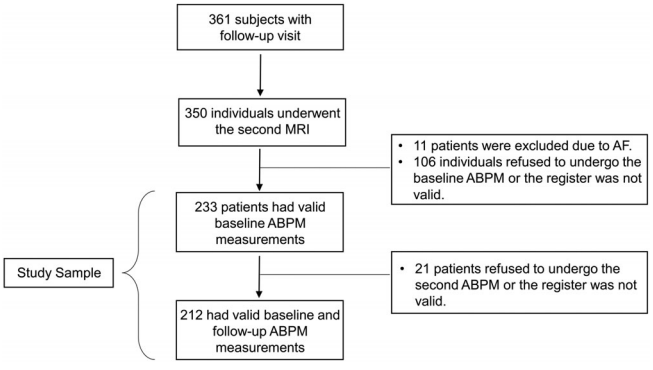

Figure 1. Flowchart of the sample. ABPM, ambulatory blood pressure monitoring; AF, atrial fibrillation.

Magnetic Resonance Imaging Characteristics

Patients underwent a brain MRI on the same 1.5-T magnet at the baseline and follow-up visits (Signa HD × 1.5; General Electric, Waukesha, WI). Our MRI protocol included T1- and T2-weighted, fluid-attenuated inversion recovery, and gradient-recalled echo sequences.[18]

Cerebral Small Vessel Disease Score at Baseline

At the baseline visit, we rated several MRI markers of cSVD according to the Standards for Reporting Vascular Changes on Neuroimaging criteria.[19] The baseline total cSVD burden was estimated with a previously described scale.[14,20,21] This score evaluates the presence of lacunar infarcts, deep CMB, extensive deep or periventricular WMH, and moderate to severe BG-EPVS.

Cerebral Small Vessel Disease Progression Score

Changes in markers of cSVD were evaluated separately by two researchers blinded to the clinical data and the time of MRI acquisition. For discordant cases, consensus was reached through consultation with a third reader.

Similarly to the baseline cSVD burden score, 1 point was awarded when progression in each of the following lesions was present: (1) incident lacunar infarcts, (2) incident deep CMB, (3) marked progression of WMH as defined by a score above 2.5 in the Rotterdam Progression Scale,[22,23] and (4) change in BG-EPVS, determined as the difference between both MRIs in at least one category according to a previously published scale.[24] We considered the slide and the side presenting the highest number of BG-EPVS and better visualization of basal ganglia.[24] Patients with the highest BG-EPVS score at baseline (>40 EPVS) were excluded from the rating for this marker (two cases).

The κ coefficient for interrater agreement for BG-EPVS was .79 at baseline and .73 at follow-up. Moreover, we achieved correct interrater and intrarater reliability in the assessment of all markers.

Ambulatory and Office Blood Pressure Assessment

At the baseline (n = 233) and follow-up (n = 212) visits (Figure 1), on working days, patients underwent 24 hours ABPM with an automatic device (Spacelabs Healthcare, Issaquah, WA).[25] We used cuffs for obese patients when required. Participants were encouraged to follow their usual activities and to keep a record of their waking and sleeping periods. Readings were obtained every 20 minutes during the day (06:00-22:59) and every 30 minutes during the night (23:00-05:59). We excluded cases with less than 70% valid measures, and those with fewer than two and one valid measurement per hour during the daytime and nighttime periods, respectively.

Mean 24-hour day and night systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained at both visits. ABPM PP was calculated as the difference between systolic and diastolic ABPM in each period (24 hours, day and night). ABPM control was defined at both visits according to the cutoffs of the American hypertension clinical guidelines.[17] Hence poor SBP/DBP control at 24 hours during the

day and night periods was considered to be indicated by values greater than or equal to 125/75 (24 hours), 130/80 (day), and 110/65 (night). We used both continuous and dichotomized ABPM measurements in our analyses.

Office BP was measured at both visits with an oscillometric device (OMRON M6 Comfort), as the mean of the last two of three measurements after 5 minutes of rest. We additionally calculated the difference between office and daytime ambulatory SBP and DBP to obtain an estimate of the white coat effect.

Covariables

We collected information on demographic and vascular risk factors at the baseline and follow-up visits. Regarding the BP-lowering treatment, we gathered information on the numbers of changes and drug classes (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, thiazide-type diuretics, calcium channel blockers, and β-adrenergic blockers) during the follow-up period. Blood pressure lowering drug (BPLD) compliance was measured with the Morisky-Green scale that evaluates medication-taking behavior in patients receiving antihypertensive treatment on a scale of 0 to 4. Poor BPLD at any visit was defined by a score of 1 or higher at the baseline and/or the follow-up Morisky-Green scale.

Statistical Analysis

All analyses were conducted with R software v.3.4.3 (R Foundation for Statistical Computing). The cSVD progression score was categorized into no progression (0 markers), minor progression (1 marker), and marked progression (≥2 markers). Changes in BP metrics were calculated by subtraction of the follow-up mean BP from the respective baseline mean BP. Regarding ABPM control, we considered patients with poor ambulatory BP at baseline or in both visits.

In univariate analyses we observed which variables were associated with the cSVD progression score by using analysis of variance, Kruskal-Wallis, and chi-square tests, as appropriate. Differences between the ABPM levels at the baseline and follow-up visits were measured via a paired-samples *t* test.

To study the relationship between the previously described ABPM parameters and the risk of total cSVD progression burden, we used ordinal logistic regression models. In these models, the three-category progression score was introduced as the outcome. ABPM levels (continuous variables) and ABPM controls (binary variables) were introduced in separate models as determinants of interest. These models were adjusted for age, sex, number of changes and classes of BPLD, time between MRIs, poor BPLD compliance at any visit, and baseline total cSVD burden.

To determine the clinical utility of ABPM in the prediction of cSVD progression, we subsequently categorized the cSVD progression score into a two-category variable: no progression (score of 0) and presence of progression (score ≥1). Forward stepwise binary logistic regression models were constructed introducing the same covariables as in the previous analysis. Predictors of interest were 24-hour SBP and DBP control at baseline and at both visits, PP, and the white coat effect. We subsequently calculated the improvement due to the addition of these ABPM parameters in a clinical model by using the integrated discrimination improvement (IDI) index that assesses the improvement in sensitivity compared with the decrease in specificity after the addition of a new variable. Positive values indicate better discrimination of the new model.

We additionally studied the effects of ABPM parameters in the progression of WMH. Therefore, we constructed multiple linear regression models by using the total Rotterdam Progression Scale score as the outcome and adjusting for the same variables as in the previous models.

RESULTS

Sample

The median age of the sample was 65 years (61-68); 43.8% were female, and patients were followed up for 4 years (3.8-4.5 years). The median time of hypertension diagnosis was 8 years (6-12 years). Regarding cSVD, 61 (26.2%) individuals showed minor progression (one MRI marker); 23 (9.9%) showed a marked progression (≥2 markers). Regarding individual lesions, 55 (24.8%) participants showed a marked progression of WMH, 41 (18.3%) showed a change in BG-EPVS, and 9 (3.9%) and 7 (3.0%) had incident lacunar infarcts and deep CMB, respectively. Among patients with two or more MRI markers of cSVD progression, the most frequent combination of lesions was WMH and BG-EPVS, as shown in Figure 2.

The mean 24-hour and nighttime systolic BP increased significantly during the follow-up, whereas all diastolic metrics showed a decrease over time (all repeated measures test *P* values <.05). Thus there was an increase in ambulatory PP within visits. However, these differences, although significant, were slight, and the means of each metric at each visit showed relative stability (Supplementary Figure S1).

In univariate analysis, demographic and vascular risk factor information was not associated with the cSVD progression score (Table 1). Interestingly, we observed that as the white coat effect increased, the number of incident lesions decreased (Table 1 and Supplementary Figure S2).

Blood Pressure and Cerebral Small Vessel Disease Progression Score

Table 2 displays results regarding office BP and ambulatory BP variables (continuous variables) and the risk of cSVD progression. Higher baseline ambulatory SBP and DBP in any period were associated with an increased risk of new cSVD lesions after adjustment for potential confounders. Regarding ambulatory PP, the nighttime PP was associated with higher odds of incident lesions. Furthermore, we observed a greater white coat effect in subjects without cSVD progression. By contrast, changes in ABPM or in-office BP were not related to this risk.

Regarding ambulatory BP control (dichotomized variables), as shown in Table 3, poor ambulatory baseline SBP and DBP control in any period was independently associated with cSVD progression. Similarly, poor control at both visits according to ABPM was associated with the cSVD progression score considering all metrics, with the exception of daytime DBP.

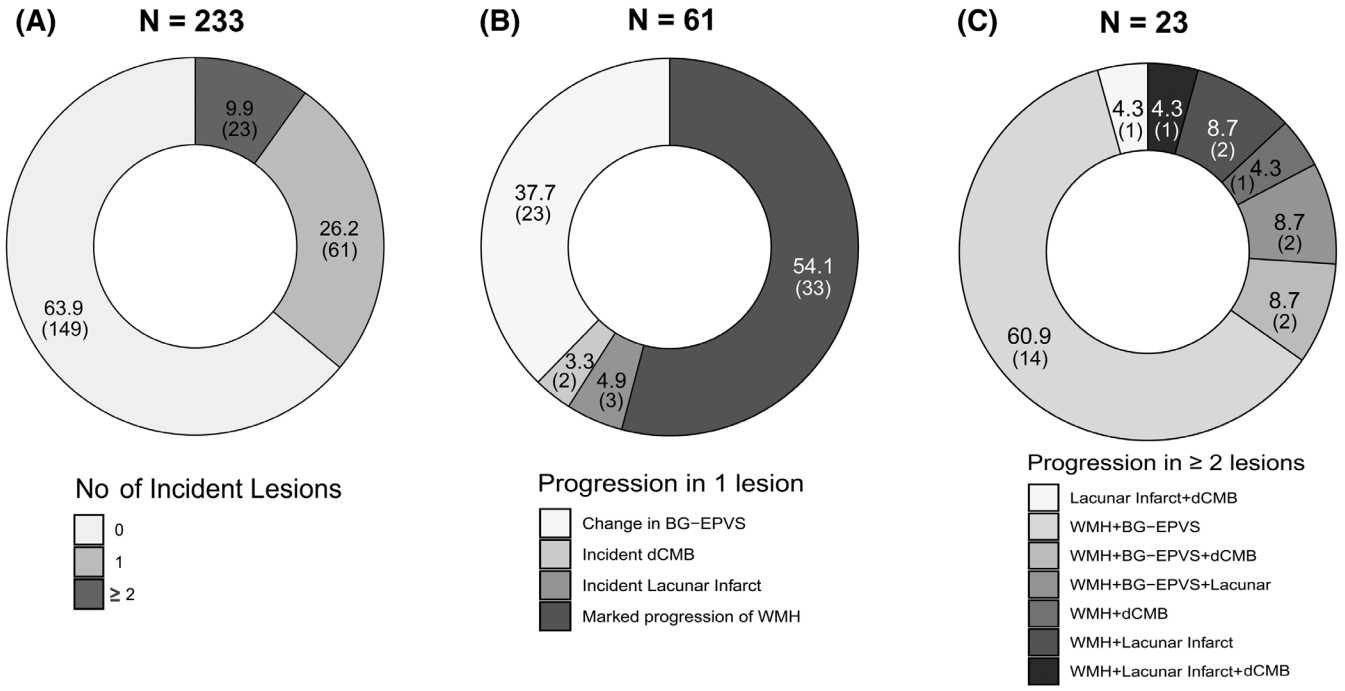

Figure 2. Cerebral small vessel disease (cSVD) progression score in the sample. (A) Percentage and number of patients with incidental lesions according to the cSVD progression score. (B) Type of cSVD lesions in patients showing progression in one magnetic resonance imaging (MRI) marker of cSVD. (C) Number and percentage of lesion combinations in patients showing changes in two or more MRI markers of cSVD. BG-EPVS, basal ganglia enlarged perivascular spaces; dCMB, deep cerebral microbleeds; WMH, white matter hyperintensities.

Table 1 Principal Characteristics of the Cohort According to cSVD Progression Score (n = 233)

	None (n = 149)	Minor[a] (n = 61)	Marked[a] (n = 23)	*P* value
Demographics				
Baseline age, y	65 (60-69)	65 (61-67)	64 (62-67)	.970
Sex, male	82 (55.0)	34 (55.7)	15 (65.2)	.650
Time between MRIs, y	4.0 (3.8-4.6)	4.0 (3.8-4.4)	4.0 (3.9-4.5)	.333
Baseline vascular risk factors				
Previous ischemic cardiopathy	17 (11.4)	9 (14.8)	3 (13.0)	.800
Poor BPLD compliance	68 (45.6)	30 (49.2)	14 (60.9)	.390
Diabetes mellitus	40 (26.9)	22 (36.1)	3 (13.0)	.100
Active smoker	18 (12.1)	8 (13.1)	3 (13.0)	.970
Hypertension duration, y	8 (5-11)	9 (6-16)	11 (6-12)	.236
Total cholesterol, mg/dL	214.0 (40.5)	215.0 (42.0)	226.7 (44.5)	.386
HDL-cholesterol, mg/dL	47.2 (39.4-57.3)	47.2 (40.8-52.7)	46 (37.8-50.7)	.506
Waist, cm	101.3 (10.5)	100.5 (12.1)	103.6 (9.0)	.514
Blood pressure lowering drugs				
No. of changes	1 (0-2)	1 (0-2)	1 (0-2)	.210
No. of classes	2 (2-3)	3 (2-3)	2.5 (2-3)	.114
Baseline BP metrics				
Office SBP, mm Hg	143.4 (16.6)	145.0 (19.3)	138.4 (14.1)	.282
Office DBP, mm Hg	78.0 (9.6)	77.8 (10.2)	79.0 (7.6)	.884
24-h SBP, mm Hg	124.5 (11.5)	131.1 (14.3)	132.3 (13.9)	<.001
24-h DBP, mm Hg	75.0 (7.3)	78.1 (7.3)	80.3 (5.3)	<.001
24-h PP, mm Hg	49.3 (42.1-54.3)	49.8 (44.8-60.5)	52.9 (42.3-58.2)	.112
White coat effect SBP[b]	13.0 (14.2)	8.1 (14.6)	1.4 (8.7)	<.001
White coat effect DBP[b]	−1.4 (8.0)	−4.9 (8.4)	−5.9 (5.8)	.002

Note: Values represent mean (SD), median (Q1-Q3), or n° (%).

Abbreviations: BP, blood pressure; BPLD, blood pressure lowering drug; cSVD, cerebral small vessel disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; MRI, magnetic resonance imaging; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation.

[a]Minor and marked progressions are defined as an increase in one or two or more MRI markers of cSVD.

[b]SBP and DBP white coat effects have been calculated as office SBP minus ambulatory daytime SBP and office DBP minus ambulatory daytime DBP, respectively.

Table 2 Association of Baseline and ΔBP Metrics with the Risk of Progression of cSVD

	OR (CI) by 10 mm Hg	*P* value
Baseline BP measurements		
Office BP		
SBP	.91 (.78-1.07)	.299
DBP	.98 (.73-1.32)	.907
ABPM SBP		
24 h	1.36 (1.10-1.69)	.008
Daytime	1.30 (1.05-1.61)	.020
Nighttime	1.36 (1.12-1.66)	.002
ABPM DBP		
24 h	1.95 (1.27-3.01)	.002
Daytime	1.94 (1.28-2.92)	.002
Nighttime	1.68 (1.16-2.44)	.006
ABPM PP		
24 h	1.17 (.91-1.51)	.238
Daytime	1.08 (.84-1.40)	.526
Nighttime	1.30 (1.01-1.67)	.039
White coat effect		
White coat effect SBP[a]	.71 (.57-.87)	.001
White coat effect DBP[a]	.58 (.40-.84)	.003
Change in BP measurements		
Office BP		
ΔSBP	1.09 (.94-1.28)	.225
ΔDBP	1.16 (.85-1.59)	.345
ABPM SBP		
Δ24 h	1.05 (.88-1.25)	.549
ΔDaytime	1.05 (.90-1.23)	.564
ΔNighttime	1.02 (.87-1.19)	.787
ABPM DBP		
Δ24 h	1.06 (.73-1.54)	.761
ΔDaytime	.99 (.71-1.38)	.940
ΔNighttime	1.09 (.80-1.50)	.574
ABPM PP		
Δ24 h	1.11 (.84-1.45)	.471
ΔDaytime	1.14 (.88-1.47)	.333
ΔNighttime	1.05 (.82-1.36)	.712

Note: Ordinal logistic regression models were constructed by entering the cSVD progression score (none, minor, or marked progression) as the outcome, and each BP metric as a determinant of interest in separate models. These models were adjusted for baseline age, sex, time between MRIs, number of changes, and classes of BPLD, BPLD compliance, and baseline cSVD burden score.

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; BPLD, blood pressure lowering drug; CI, confidence interval; cSVD, cerebral small vessel disease; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure.

[a]SBP and DBP white coat effects were calculated as office SBP minus ambulatory daytime SBP and office DBP minus ambulatory daytime DBP, respectively.

We additionally studied the relationship between ABPM levels and the individual progression of WMH (Supplementary Table S1). The results were similar to those of the cSVD progression score. However, considering baseline ABPM levels, we observed that ambulatory nighttime SBP, but not daytime SBP, was associated with an increase in WMH.

Table 3 Relationship between ABPM Control and the Risk of cSVD Progression

	Poor control at baseline		Poor control at both visits	
	OR (CI)	*P* value	OR (CI)	*P* value
SBP				
24 h	2.18 (1.20-3.98)	.011	2.21 (1.20-4.07)	.011
Daytime	1.83 (1.01-3.31)	.045	1.97 (1.07-3.62)	.030
Nighttime	2.48 (1.22-5.04)	.012	2.30 (1.21-4.34)	.010
DBP				
24 h	3.12 (1.64-5.94)	.001	2.07 (1.08-3.94)	.027
Daytime	2.15 (1.17-3.96)	.014	1.35 (.67-2.73)	.398
Nighttime	2.42 (1.21-4.84)	.012	2.11 (1.14-3.89)	.017

Note: Ordinal logistic regression models were constructed by entering the cSVD progression score (none, minor, or marked progression) as the outcome and each ABPM control as a predictor of interest. These models were adjusted for baseline age, sex, time between MRIs, number of blood pressure lowering drugs (BPLD) changes and classes, baseline cSVD burden score, and BPLD compliance. Values represent ORs for the presence of a poor control in each metric and 95% CI.

Abbreviations: ABPM, ambulatory blood pressure monitoring; CI, confidence interval; cSVD, cerebral small vessel disease; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure.

Clinical Utility

To provide clinical insight, we dichotomized the cSVD progression score into no progression (score of 0) and presence of progression (score ≥1). Among the clinical variables introduced in the model, only baseline cSVD burden remained significant after stepwise logistic regression analysis, thus indicating that the baseline cSVD burden was the unique predictor of progression in this model. We subsequently added 24-hour SBP and DBP control, either at baseline or considering both visits, nighttime PP, and SBP and DBP white coat effects. Among these variables, poor baseline 24-hour DBP control (odds ratio [OR] = 2.55; 95% confidence interval [CI] = 1.36-4.78; *P* value = .004), nighttime PP (OR = 1.03 per mm Hg increase; 95% CI = 1.00-1.06; *P* value = .023), and the DBP white coat effect (OR = .95; 95% CI = .91-.99; *P* value = .009) remained in the final model as independently associated variables with cSVD progression (Supplementary Table S2).

The predictive value of models containing or not containing ABPM information was compared with the IDI. The inclusion of ABPM information was found to result in a significant improvement of discrimination as shown in Supplementary Figure S3 (IDI = 9.09%; 95% CI = 5.17-13.00; $P < .001$).

DISCUSSION

In this study we constructed a cSVD progression score and found that 61 (26.2%) and 23 (9.9%) individuals showed progression in one marker and two or more markers, respectively. Our main finding was that ABPM may be a useful source of information in cSVD prediction. Specifically, poor baseline 24-hour DBP control, nighttime PP, and the DBP white coat effect were the variables that best predicted cSVD progression. The inclusion of these parame-

ters in a clinical model resulted in an 9.09% improvement in discrimination that corresponds to a significant but small increase in the prediction of cSVD progression. In further studies, this effect could be improved to be clinically meaningful by combining ABPM information with other clinically relevant variables, such as blood biomarkers.[26] Ambulatory SBP in all periods was also associated with incident lesions.

The progression of cSVD is prevalent in patients with hypertension and involved in cognitive decline as well as an increased risk of stroke, among other consequences.[1,3] However, the use of serial MRIs may not be a feasible method to detect this progression in routine clinical practice, owing to its high cost. ABPM may provide a useful source of information to identify which patients have higher odds of progression. Interestingly, patients with less progression showed larger differences between office and ambulatory BP measurements, thus suggesting a white coat effect. Hence office BP assessment may not be a reliable method to stratify the risk of cSVD progression. Similarly, the SPRINT trial found discrepancies between office and ambulatory BP, even using an automated office BP measurement in the absence of a doctor.[27,28] Furthermore, there is also a risk of the existence of masked uncontrolled hypertension, associated with higher cardiovascular risk.[29] Of note, in our study, for each ambulatory DBP mm Hg unit above the office DBP, the risk of incident lesions increased by approximately 5%, independently of BP levels and PP. Altogether these results indicate that ABPM, or possibly home BP monitoring, should be obtained more routinely.[28]

We considered the new definitions of ABPM control according to recent clinical guidelines.[17] Interestingly, in the INFINITY and SPRINT trials, an intensive lowering of ambulatory BP over a follow-up period resulted in decreased WMH progression.[30,31] However, it is important to consider that other groups have described a J-shaped association of BP levels with the risk of stroke,[32] cognitive decline, and progression of WMH volume.[33] Therefore, a threshold may exist below which reducing BP may not be beneficial.

We observed that nighttime PP was positively correlated with the number of incident cSVD lesions. Specifically, the risk of cSVD progression increased by 30% for each 10 mm Hg increase in nighttime PP. Moreover, this effect was independent of BP levels and other confounding variables. These results were in line with previously reported findings relating higher PP to the burden of WMH.[12] Because PP is considered a surrogate marker of arterial stiffness, which has been consistently associated with microvascular disease,[34] ambulatory PP should be assessed in the prediction of cSVD. However, few research articles have investigated the temporal dynamics of arterial stiffness changes and cSVD progression. Therefore, further studies are needed to confirm our results.[35,36]

In our study, 24-hour DBP showed a stronger association with incident lesions than 24-hour SBP. A previous study found that 24-hour DBP is associated with total cSVD burden independently of 24-hour SBP.[14] Otherwise, most epidemiological studies have placed greater importance on SBP in the prediction of cardiovascular risk and mortality, especially in older individuals.[37,38] Nevertheless, in our study, 24-hour SBP was also associated with incident lesions, and both ambulatory SBP and DBP indicated risk similarly. However, the relationship between cSVD and BP may depend on the neuroanatomical localization and the type of lesion.[39] For instance, we observed that nighttime rather than daytime ambulatory SBP was associated with the individual progression of WMH. These results are in line with those from previous studies.[40,41]

By contrast, changes in ambulatory metrics were not related to incident lesions, possibly because ABPM levels in each visit showed relative stability, and both recordings may be explaining the same information. However, serial measurements may help discriminate which patients are at risk of cSVD progression and which patients have improved BP levels.

This study has several strengths and limitations. The limitations included that changes in BG-EPVS were measured according to the increase in Potter's scale because there is no progression scale available for this MRI marker. This method may not have captured slight changes. Also importantly, these results came from patients with hypertension, and cSVD was described to be prevalent in nonhypertensive individuals with other vascular risk factors.[42,43] Therefore, further studies in the general population should be conducted to confirm these results. Finally, owing to MRI technical limitations, we were unable to assess brain atrophy. Given the relationship between brain volume and cSVD, future research may include measures of cortical and subcortical atrophy in cSVD burden scores.[44,45]

Strengths of our study included that we provide novel longitudinal data regarding ABPM, cSVD, and their interplay over time. Furthermore, we constructed a novel cSVD progression score that may be used in future investigations to estimate total cSVD progression.

In conclusion, ABPM may provide more clinically useful information than office measurements for the prediction of cSVD progression. Among ambulatory measurements, baseline 24-hour DBP control, nighttime PP, and masked uncontrolled hypertension were the variables that best predicted the progression of cSVD. These results indicate that ambulatory BP, or equivalent measurements, should be obtained more routinely. Future studies should combine ABPM information with other clinical variables to refine the risk prediction of cSVD progression.

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Author Contributions: *Designed the study*: Delgado, Riba-Llena, and Jiménez-Balado. *Visited the patients*: Delgado, Riba-Llena, and Jiménez-Balado. *Read the MRIs*: Delgado, Riba-Llena, and Jiménez-Balado. *Conducted the statistical analysis*: Jiménez-Balado. *Interpreted the results*: Delgado, Jiménez-Balado, Riba-Llena, Maisterra, Pizarro, and Palasí. *Wrote the manuscript*: Jiménez-Balado and Delgado. *Performed critical revision of the manuscript for important intellectual content*: Pujadas, Maisterra, Vinyoles, and Mundet.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Figure S1: Changes in ambulatory blood pressure monitoring (ABPM) levels from baseline to follow-up visit. Thin lines represent changes in ABPM levels from baseline to the follow-up visit for systolic blood pressure (SBP) (blue) and diastolic blood pressure (DBP) (red) in each patient. Solid black lines indicate the mean SBP and DBP at each visit. Solid black whiskers show the standard error of the mean for each metric at each visit. *$P < .05$.

Supplementary Figure S2: Distribution of white coat effect estimation by cerebral small vessel disease (cSVD) progression. Lines represent the density functions in patients showing no cSVD progression (green), one incident lesion (orange), and two or more incident lesions (red).

Supplementary Figure S3: Improvement in baseline ambulatory blood pressure monitoring (ABPM) information in the prediction of cerebral small vessel disease (cSVD). Graphical representation of the integrated discrimination improvement (IDI) index. Bars show the mean risk (%) for each predictive model (gray: magnetic resonance imaging [MRI] model; dark gray: MRI model plus ABPM information) of patients with and without cSVD progression, as defined by a change in at least one marker of cSVD. ID) index = 9.09%, 95% confidence interval = 5.17-13.00; $P < .001$. Increase in sensitivity = 5.93%. Increase in specificity = 3.15%.

Supplementary Table S1: Association of baseline and ΔBP metrics with the risk of progression of white matter hyperintensities

Supplementary Table S2: Logistic regression models combining clinical and ambulatory blood pressure measurements information