# Cognitive Impact of Cerebral Small Vessel Disease Changes in Patients With Hypertension

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***Abstract***—Hypertension is one of the principal risk factors for cerebral small vessel disease progression and cognitive impairment. We aimed to investigate how changes in cerebral small vessel disease lesions relate to cognitive decline and incident mild cognitive impairment in hypertensive patients. Data were obtained from the ISSYS cohort (Investigating Silent Strokes in Hypertensives: a Magnetic Resonance Imaging Study)—a longitudinal population-based study on hypertensive patients aged 50 to 70 years without dementia and stroke at baseline. Patients underwent a brain magnetic resonance imaging, a cognitive screening test, and cognitive diagnosis (normal aging or mild cognitive impairment) at baseline and follow-up. We evaluated incident lacunar infarcts and cerebral microbleeds. Changes in the periventricular and deep white matter hyperintensities (WMH) were qualitatively defined as none, minor, or marked. We followed up 345 patients (median age, 65 [61–68]; 55.4% men) for 3.95 (3.83–4.34) years. Incident mild cognitive impairment was diagnosed in 9.1% of the sample. Considering the progression of cerebral small vessel disease, the prevalence of incident infarcts was 6.1% and that of incident cerebral microbleeds was 5.5%; progression of periventricular WMH was 22% and that of deep WMH was 48%. Patients with marked progression of periventricular WMH showed a significant decrease in global cognition compared with patients without progression (adjusted mean [SE], −0.519 [0.176] versus 0.057 [0.044], respectively; *P* value=0.004) and a higher risk of incident mild cognitive impairment (OR, 6.184; 95% CI, 1.506–25.370; *P* value=0.011). Therefore, our results indicate that hypertensive patients with progression of periventricular WMH have higher odds of cognitive impairment, even in the early stages of cognitive decline. **(*Hypertension*. 2019;73:342-349. DOI: 10.1161/HYPERTENSIONAHA.118.12090.)** ● **Online Data Supplement**

**Key Words:** cerebral small vessel diseases ■ cognitive dysfunction ■ hypertension ■ longitudinal cohort study ■ magnetic resonance imaging ■ white matter hyperintensities



The term cerebral small vessel disease (cSVD) refers to a group of pathological processes that affect the small arteries, arterioles, venules, and capillaries of the brain.[1] CSVD is assessed via magnetic resonance imaging (MRI), and the hallmark imaging markers include white matter hyperintensities (WMH), lacunar infarcts, and cerebral microbleeds (CMB),[2] among other markers. Although the course of the disease may be silent, cSVD lesions can accumulate over time on brain parenchyma, thereby increasing the risk of cognitive impairment.[2,3]

Different longitudinal studies have examined how cognition is affected by the progression of these markers. Research groups have reported that the progression of WMH parallels cognitive decline, particularly WMH located at the periventricular area.[3–5] By contrast, the consequences of incident infarcts and CMB in cognitive function have been less studied.[5]

Another focus of interest is whether these markers are associated with change in the cognitive diagnosis. Most studies have focused on the predictive role of baseline lesions in the conversion to dementia or mild cognitive impairment (MCI),[6,7] whereas few authors have assessed the progression of cSVD markers and incident MCI, obtaining opposite results.[8,9] Moreover, no investigation has addressed this question in a cohort of hypertensive patients, and considering that hypertension is one of the principal risk factors for cognitive impairment and the progression of cSVD, this is an important gap in the literature.[10]

In this study, we first aimed to determine the prevalence of changes in periventricular WMH (PVH), deep WMH (DWMH), incident infarcts, and CMB in a longitudinal study of hypertensive individuals with no previous dementia or stroke at the baseline visit. We subsequently aimed to

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determine whether this progression is involved in the decline in cognitive function, as well as in the change in cognitive status.

## Methods

Anonymized data will be shared following the request of qualified investigators for research purposes.

### Sample

This study was conducted in a sample of the ISSYS cohort (Investigating Silent Strokes in Hypertensives: a Magnetic Resonance Imaging Study). The ISSYS study is an ongoing epidemiological, observational, and longitudinal study that aims to determine the prevalence of silent cerebrovascular lesions in a cohort of hypertensive participants and investigate their associated factors and consequences. At baseline (2010–2012), we randomly recruited 976 patients with hypertension from 14 primary care centers in the north area of Barcelona. The inclusion criteria were an age between 50 and 70 years and no previous history of dementia or clinical stroke. Patients underwent a clinical data collection, a vascular risk assessment, a brain MRI, a cognitive evaluation, and blood sampling.[11]

Between 2014 and 2016, a follow-up visit was planned for the full cohort, although because of budget limitations, only half of the cohort was invited to participate in the follow-up. Individuals were selected based on the presence of at least one of the following baseline lesions of interest: extensive WMH or silent brain infarcts. We proposed a follow-up visit to them with the same characteristics as at the baseline, and 350 patients participated (acceptance rate, 72.4%). We excluded 5 patients with incidental dementia; thus, 345 subjects were included in the final study sample. Figure 1 represents the study flowchart.

This study was approved by the Ethics Committee at Vall d'Hebron Hospital, and patients provided their written informed consent before study participation.

### Neuroimaging Characteristics

At baseline and follow-up, MRI acquisition was performed on the same 1.5-Tesla magnetic resonator (Signa HD×1.5; General Electrics, Waukeska, WI). We obtained axial T1- and T2-weighted, fluid-attenuated inversion recovery, and gradient-recalled echo sequences. The slice thickness was 5 mm with a 1.5-mm gap, and there were 20 slices covering the whole brain in axial images.[11]

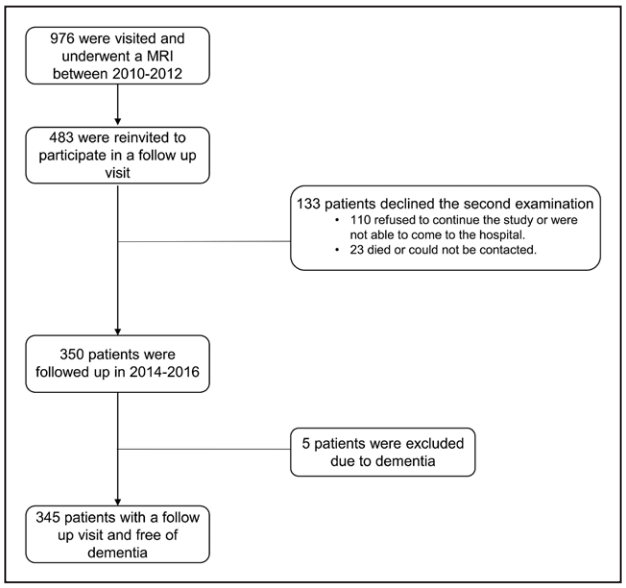


**Figure 1.** Flowchart of the sample. MRI indicates magnetic resonance imaging.

### Rating of cSVD Markers at Baseline

Several cSVD markers were rated at the baseline visit according to the standards for reporting vascular changes on neuroimaging criteria.[12]

Silent brain infarcts were defined as lesions of ≥3 mm in diameter at their widest dimension, with cerebrospinal fluid signal characteristics in all pulse sequences and a hyperintense rim surrounding the lesion in fluid-attenuated inversion recovery images.

WMH of presumed vascular origin appeared as hyperintense signal lesions in T2-weighted and fluid-attenuated inversion recovery sequences. We graded them according to Fazekas scale[13] at deep and periventricular locations. We categorized WMH as 0 to 1 score (mild) and 2 to 3 score (extensive).

CMBs were rated in gradient-recalled echo sequence according to the Brain Observer Microbleed Scale.[14]

### Evaluation of Longitudinal Changes in cSVD Markers

Changes in cSVD markers over time were evaluated by duplicated readers and considering both MRI images (baseline and follow-up) at the moment of the rating. The readers were blinded to the clinical data and the time of MRI acquisition. Discordant cases were agreed on between readers or by consensus with a senior researcher.

We rated the incident infarcts and CMB considering the same criteria as at baseline. The progression of WMH was evaluated by means of the Rotterdam Progression scale.[15] Briefly, this scale evaluates the change in WMH in a side-by-side manner in which recession, absence, or presence (score of −1, 0, or 1, respectively) of change (increase of size of a previous lesion or appearance of new lesions) was rated in 3 periventricular regions (frontal horns, lateral bands, and occipital horns of lateral ventricles) and 4 subcortical regions (frontal, parietal, temporal, and occipital lobes) at each hemisphere. The scores range from −6 to 6 for PVH and −8 to 8 for DWMH. WMH changes were assessed by duplicated, and the interrater and intrarater reliability were good for PVH and DWMH (9.1% and 14.9% of the cases had to be agreed for PVH and DWMH, respectively).

### Cognitive Decline

Subjects were cognitively evaluated at baseline and follow-up via the Dementia Rating Scale–second version (DRS-2), which is a screening tool that provides a general measure of cognitive functions.[16] The DRS-2 is composed of 5 subscales: attention (0–37 points), initiation/perseveration (0–37 points), construction (0–6 points), conceptualization (0–39 points), and memory (0–25 points). The total score ranges from 0 to 144 points.

Raw DRS-2 scores were standardized into *Z* scores (individual mean minus sample mean and divided by sample SD) at each time to normalize the results. The conceptualization and initiation/perseveration *Z* scores were averaged at each time to obtain an executive function score.

### Cognitive Diagnosis

At baseline, participants suspected to be cognitively impaired according to the DRS-2 score adjusted by age and education were invited to undergo a complete cognitive reevaluation. This reevaluation consists of a cognitive, functional, and behavioral complaints anamnesis and a neurological and neuropsychological evaluation to establish the cognitive diagnosis.[17,18] MCI was defined based on previously described criteria.[19] Briefly, we diagnosed MCI if there was evidence of cognitive impairment through our neuropsychological battery and individuals or proxies may report a history of subjective cognitive complaints (which lasted from months to years). The patients over the cutoff of normality for the DRS-2 or those who did not fulfill MCI criteria were considered normal aging (NA) patients.

The same procedure was repeated at the time of follow-up when cognitive impairment was suspected, as well as in the patients who had experienced a significant decline in the DRS-2 during the follow-up (defined as 1 SD below the mean decline).

Based on the cognitive status at baseline and follow-up, the change in diagnosis over time was subsequently categorized as stable

NA (NA at baseline and follow-up), reversion to normal (MCI at baseline and NA at follow-up), stable MCI (MCI at baseline and follow-up), and incident MCI (NA at baseline and MCI at follow-up).

## Covariables

The demographic variables and vascular risk factors were recorded at the baseline and follow-up visits following the same protocol.[11] We defined education as years of formal education. Systolic and diastolic office blood pressures (SBP and DBP, respectively) were calculated as the mean of the 2 last of 3 measurements after 5 minutes of rest at baseline and follow-up. Average SBP and DBP during the follow-up were calculated as the mean of the office blood pressure (BP) measures at both periods. Considering hypertension treatment, we collected the number of treatment changes and classes received during the follow-up. Cholesterol and HDL (high-density lipoprotein) cholesterol were measured by an automated clinical chemistry analyzer (Olympus AU 2007). Diabetes mellitus was defined as fasting glucose levels >7 mmol/L or the use of oral antidiabetic drugs or insulin. Smoking habit was categorized as active or inactive. Abdominal obesity was defined as a waist circumference ≥88 cm for women and 102 cm for men.

## Statistical Analyses

All analyses were conducted using R software (R version 3.4.3, November 30, 2017; R Foundation for Statistical Computing).

Differences between the baseline and follow-up variables were measured by means of paired-samples Wilcoxon signed-rank test or paired-samples *t* tests depending on their distribution.

We categorized the progression of WMH in both locations as none progression (score, <1), minor progression (score, 1–2.5), and marked progression (score, >2.5) according to a previously published categorization.[20] To determine whether there was a differential effect on cognition depending on the anatomic region of the WMH change, we also investigated the relationship between the WMH change at each anatomic area previously described and the cognitive change over time. Changes in the regional WMH were categorized as follows for all regions of interest: no change; change at 1 hemisphere; or change at both hemispheres.

To assess the relationship between decline in cognitive function and changes in cSVD markers, the DRS-2 *Z* scores at follow-up were considered as outcomes and each marker of cSVD progression as predictors (severity of WMH changes, incidental infarcts, and CMBs) in ANCOVA or linear autoregressive models as appropriate.[21] Furthermore, all models were adjusted by the respective baseline DRS-2 *Z* scores, respective baseline cSVD marker, age, sex, education, time between visits, and baseline DBP.

Multinomial logistic regression models were subsequently constructed considering the change in cognitive diagnosis as the outcome, and stable NA was used as the reference category. cSVD markers over time were entered as predictors, and we adjusted by baseline age, sex, education, time between visits, DBP, abdominal obesity, and respective baseline cSVD marker.

# Results

Table 1 shows the principal characteristics of the cohort at the baseline and follow-up visits. The mean time between visits was 3.95 (3.83–4.34) years.

Compared with the individuals who participated in the follow-up, the individuals who refused to participate were less educated (median [interquartile range (IQR)], 8 [6–12] versus 8 [6–10], respectively; *P* value=0.029) and had a lower baseline total score in the DRS-2 (median [IQR], 132 [126–137] versus 128 [122.5–135], respectively; *P* value=0.001). We did not identify significant differences in other risk factors or baseline cSVD lesions.

Regarding BP control, the average SBP and DBP of the sample during the follow-up was 144.5 (135–155.1) and 76.5 (71–82.1), respectively. Hypertension treatment at baseline was identified in 324 (94.2%) participants. Considering BP-lowering drugs during follow-up, the median number of treatment changes and pharmacological classes received was 1 (0–2) and 2 (2–3), respectively.

Regarding the progression of cSVD lesions, 21 (6.1%) patients showed new infarcts; 19 (5.5%) patients had incident

**Table 1. Principal Characteristics of the Sample at Baseline and Follow-Up (n=345)**

| Variables | Baseline | Follow-Up | *P* Value |
|---|---|---|---|
| Demographics | | | |
| Age, y | 65 (61–68) | 68 (64–72) | <0.001 |
| Sex, men | 191 (55.4) | … | … |
| Education, y | 8 (6–12) | … | … |
| Vascular risk factors | | | |
| Mean SBP, mm Hg | 143 (131–154) | 146.5 (136–157.6) | <0.001 |
| Mean DBP, mm Hg | 78.2 (71–84.5) | 75 (69–81.1) | <0.001 |
| Cholesterol, mg/dL | 214.5 (42.1) | 205.9 (43.4) | <0.001 |
| HDL, mg/dL | 47.2 (39.8–55) | 51 (44–60) | <0.001 |
| Diabetes mellitus | 91 (26.4) | 106 (30.7) | <0.001 |
| Active smoker | 44 (12.8) | 38 (11.2) | 0.18 |
| Abdominal obesity | 238 (70.0) | 238 (72.6) | 0.11 |
| Baseline cSVD markers | | | |
| Silent brain infarcts | 78 (22.6) | … | … |
| Cerebral microbleeds | 38 (11.0) | … | … |
| Extensive PVH | 63 (18.3) | … | … |
| Extensive DWMH | 35 (10.1) | … | … |
| Progression of cSVD markers | | | |
| Incident infarcts | … | 21 (6.1) | … |
| Incident cerebral microbleeds | … | 19 (5.5) | … |
| Minor change in PVH | … | 59 (17.3) | … |
| Marked change in PVH | … | 16 (4.7) | … |
| Minor change in DWMH | … | 96 (28.1) | … |
| Marked change in DWMH | … | 68 (19.9) | … |
| DRS-2 | | | |
| Total score | 132 (126–137) | 133 (126–138) | 0.263 |
| Attention score | 35 (34–36) | 35 (34–36) | 0.039 |
| Executive function | 34 (32–36) | 34.5 (32–36.5) | 0.481 |
| Memory score | 23 (22–24) | 24 (22–25) | 0.079 |

Data are displayed as the mean (±SD), median (IQR), or number of cases (%) as appropriate. Missing data: we could not assess incident CMB in 1 patient and WMH change in 3 patients. The baseline total and executive function scores were missed in 3 and 1 patients, respectively. The follow-up total, attention, executive function, and memory scores were lost in 16, 7, 15, and 6 patients, respectively. CMB indicates cerebral microbleeds; cSVD, cerebral small vessel disease; DBP, diastolic blood pressure; DRS-2, Dementia Rating Scale–second version; DWMH, deep white matter hyperintensities; HDL, high-density lipoprotein; IQR, interquartile range; PVH, periventricular white matter hyperintensities; SBP, systolic blood pressure; and WMH, white matter hyperintensities.

CMB; and 75 (22%) and 164 (48%) patients had changes (minor or marked) in PVH and DWMH, respectively. The baseline BP measures and the average BP during the follow-up were not associated with changes in cSVD lesions. Regarding hypertension treatment, we observed that patients with incident infarcts had a higher number of pharmacological changes during the follow-up than those without incident infarcts (median [IQR], 2 [0.25–3] versus 1 [0–2], respectively; *P* value=0.027).

Considering cognition, the baseline and average follow-up DBP were positively correlated with the total, attention, and executive function DRS-2 *Z* scores at follow-up. The baseline and average SBP were not associated with cognition at follow-up. Similarly, the number of pharmacological changes or pharmacological classes received during follow-up did not relate to the cognitive outcomes. Moreover, diabetes mellitus was not significantly related to a faster decline in cognitive function.

## Change in Cognition and Progression of cSVD

Table 2 displays the results regarding the changes in cognitive function and progression of WMH. A significant decrease was observed in the subjects with a marked progression of PVH compared with those with no changes in the total DRS-2 *Z* score (adjusted mean [SE], −0.519 [0.176] versus 0.057 [0.044], respectively; corrected *P* value=0.004) and executive function *Z* score (adjusted mean [SE], −0.506 [0.158] versus 0.058 [0.039], respectively; corrected *P* value=0.002). By contrast, the progression of DWMH was not associated with cognitive changes on follow-up.

Incident CMBs were related to a decline in the attention *Z* score (β=−0.473; 95% CI, −0.945 to −0.001; *P* value=0.049); however, significant differences were not identified with other cognitive functions. Incidental infarcts were not associated with cognitive changes in our sample (data not shown).

We decided to further investigate the relationship between cognitive decline and WMH changes depending on their localization. Figure 2 and Figure S1 in the online-only Data Supplement show the change in cognition for each DRS-2 *Z* score and each WMH region of interest. As shown, bilateral PVH progression at any location was related to a significant decrease in executive function. By contrast, bilateral occipital DWMH was associated with a significant worsening in the attention *Z* score.

## Change in cSVD Markers and Cognitive Status

Of the 345 patients, 25 patients had no valid cognitive data or refused to participate in the cognitive visit at the baseline or follow-up, and 3 patients were excluded for medical conditions and alcohol abuse. Therefore, analyses were conducted on the remaining 317 patients. Considering the change in the cognitive status, 238 (75.1%) patients remained NA at both times; 21 (6.6%) patients showed reversion to NA; 29 (9.1%) patients had stable MCI; and 29 (9.1%) patients had incident MCI. Therefore, 50 patients (29 subjects with stable MCI and 21 patients with reversion to NA) had MCI at baseline, which represents 15.7% of the sample.

Stable MCI subjects had fewer years of education than the patients with stable NA (median [IQR], 8 [4.5–8] versus 8 [8–12], respectively; *P* value=0.012). The patients with incident MCI showed a higher prevalence of baseline abdominal obesity than the subjects with stable NA and reversion to NA (89.7% versus 67.1% and 57.1%, respectively; *P* value=0.032). The baseline SBP and DBP were not different between the groups. Moreover, the stable NA patients showed a higher average follow-up DBP compared with stable MCI patients (median [IQR], 77.75 [72–82.75] versus 72.5 [67.25–77.5], respectively; *P* value=0.006). Regarding hypertension treatment, the number of changes and pharmacological classes received during the follow-up were not different across the groups. Moreover, diabetes mellitus and other vascular risk factors were not associated with a change in cognitive status.

Table 3 shows the results considering the relationship between the changes in cSVD markers and cognitive status. A marked progression of PVH was related to higher odds of developing incident MCI (OR, 6.184; 95% CI, 1.506–25.370; *P*

**Table 2. Relationship Between Changes in Cognitive Function and Progression of WMH**

| cSVD Marker | Total | | | Attention | | | Memory | | | Executive Function | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean (SE) | β | *P* Value | Mean (SE) | β | *P* Value | Mean (SE) | β | *P* Value | Mean (SE) | β | *P* Value |
| PVH | | | | | | | | | | | | |
| None | 0.057 (0.044) | REF | … | −0.037 (0.057) | REF | … | 0.038 (0.055) | REF | … | 0.058 (0.039) | REF | … |
| Minor | −0.118 (0.096) | −0.175 | … | 0.165 (0.124) | 0.202 | … | −0.128 (0.119) | −0.166 | … | −0.126 (0.086) | −0.183 | … |
| Marked | −0.519 (0.176) | −0.576 | 0.003* | −0.219 (0.234) | −0.182 | 0.218 | −0.308 (0.226) | −0.346 | 0.187 | −0.506 (0.158) | −0.564 | 0.001* |
| DWMH | | | | | | | | | | | | |
| None | 0.074 (0.055) | REF | … | 0.011 (0.071) | REF | … | 0.006 (0.069) | REF | … | 0.054 (0.049) | REF | … |
| Minor | −0.105 (0.076) | −0.179 | … | −0.027 (0.097) | −0.039 | … | −0.085 (0.093) | −0.091 | … | −0.054 (0.068) | −0.107 | … |
| Marked | −0.059 (0.103) | −0.133 | 0.131 | −0.051 (0.130) | −0.063 | 0.897 | 0.072 (0.124) | 0.065 | 0.574 | −0.075 (0.092) | −0.128 | 0.299 |

ANCOVA models were constructed taking the follow-up DRS-2 *Z* scores as outcomes and the severity of WMH as predictors and adjusting for baseline age, sex, education, time between visits, baseline DBP, periventricular or deep baseline WMH, and the respective baseline cognitive subscale *Z* score. Post hoc pairwise comparisons were performed using Sidak tests. Values in the table represent the adjusted means and SEs at each level of progression; the global *P* value is shown. Lower scores indicate a worse performance. cSVD indicates cerebral small vessel disease; DBP, diastolic blood pressure; DRS-2, Dementia Rating Scale–second version; DWMH, deep white matter hyperintensities; PVH, periventricular white matter hyperintensities; REF, reference category; and WMH, white matter hyperintensities.

*Post hoc: marked vs none *P* value, <0.05.

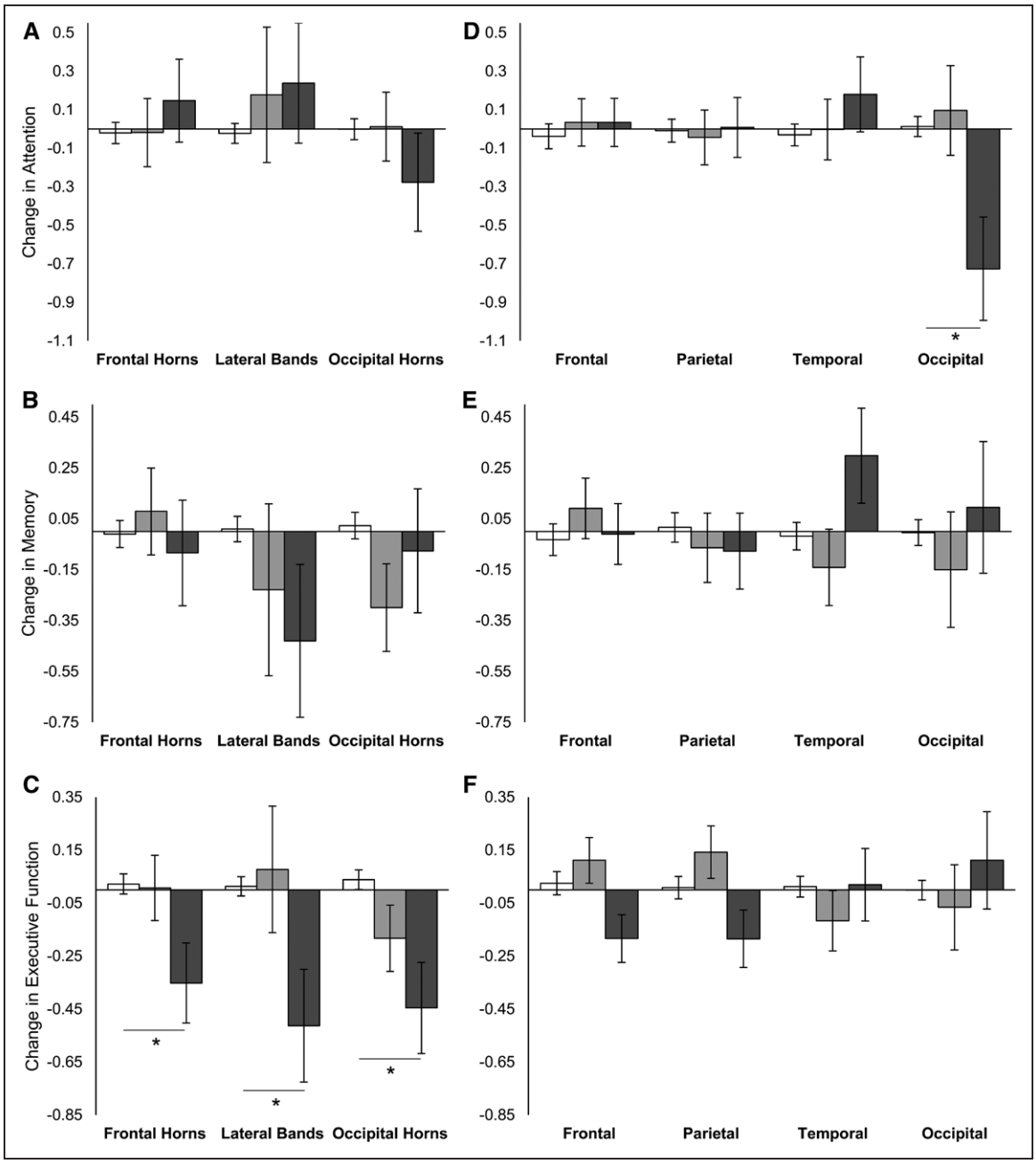


**Figure 2.** Boxplots representing the relation between changes in Dementia Rating Scale–second version *Z* scores and changes in white matter hyperintensities. Changes in attention, memory, and executive function *Z* scores by periventricular white matter hyperintensity grades in **A**, **B**, and **C**, respectively; changes in attention, memory, and executive function *Z* scores by deep white matter hyperintensity grades in **D**, **E**, and **F**, respectively. Colors represent no progression (white), unilateral progression (gray), and bilateral progression (dark gray). Values represent adjusted means and SEs of the mean in ANCOVA models (adjusted for baseline age, sex, education, time between visits, diastolic blood pressure, respective baseline WMH, and respective baseline cognitive *Z* score). Lower scores indicate worse performance. **P*<0.05.



value=0.011) compared with subjects without progression. By contrast, the changes in DWMH, incident infarcts, and CMB were not related to incident MCI.

Otherwise, the studied markers of cSVD progression were not associated with a reversion to NA or stable MCI diagnoses compared with the subjects with stable NA.

## Discussion

In the present study, we followed up a sample of 345 patients with hypertension for 4 years. Our results showed a relationship between the progression of PVH and cognitive decline in global and executive function, as well as CMB and decline in attention. Moreover, we observed an association between PVH change and the risk of incident MCI.

Incident rates of any progression (minor or marked) of PVH and DWMH were 22% and 48%, respectively. Different studies have used Rotterdam Progression scale to assess changes in WMH. The Rotterdam Scan Study found a similar rate of change considering PVH (27%) and an inferior prevalence of the progression of DWMH (32%) during 3

**Table 3. Progression of cSVD MRI Markers and Changes in Cognitive Diagnosis**

| | Reversion to NA | | Stable MCI | | Incident MCI | |
|---|---|---|---|---|---|---|
| cSVD Marker | OR (CI) | *P* Value | OR (CI) | *P* Value | OR (CI) | *P* Value |
| PVH | | | | | | |
| None | REF | … | REF | … | REF | … |
| Minor | 0.238 (0.030–1.863) | 0.172 | 0.642 (0.175–2.362) | 0.505 | 2.155 (0.788–5.900) | 0.135 |
| Marked | 0.802 (0.086–7.513) | 0.847 | 0.945 (0.102–8.747) | 0.960 | 6.184 (1.506–25.370) | 0.011 |
| DWMH | | | | | | |
| None | REF | … | REF | … | REF | … |
| Minor | 0.641 (0.195–2.107) | 0.464 | 0.995 (0.390–2.542) | 0.992 | 1.015 (0.408–2.528) | 0.974 |
| Marked | 0.905 (0.225–3.632) | 0.887 | 0.231 (0.038–1.414) | 0.113 | 0.893 (0.261–3.055) | 0.857 |
| Other incident lesions | | | | | | |
| Incident infarcts | 1.768 (0.349–8.970) | 0.491 | 0.445 (0.052–3.849) | 0.462 | 2.718 (0.739–9.997) | 0.132 |
| Incident CMB | 2.079 (0.203–21.233) | 0.537 | 3.117 (0.606–16.035) | 0.174 | 4.477 (0.967–20.732) | 0.055 |

The multinomial logistic regression model was constructed considering stable NA as the reference category. Changes in cSVD markers were entered in the model as predictors and adjusted for baseline age, sex, education, time between visits, baseline DBP, baseline abdominal obesity, and respective baseline MRI marker. Values in the table represent ORs with 95% CIs and *P* values.

CMB indicates cerebral microbleeds; cSVD, cerebral small vessel disease; DBP, diastolic blood pressure; DWMH, deep white matter hyperintensities; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NA, normal aging; OR, odds ratio; PVH, periventricular white matter hyperintensities; and REF, reference category for the change in cSVD marker.

years of follow-up compared with our cohort.[20] This higher prevalence of DWMH may be explained by the different follow-up periods (4 years in our cohort versus 3.4 years in the Rotterdam study) and the characteristics of our sample, which is composed only of participants with hypertension. Furthermore, we identified lower incidences of infarcts and CMB than other studies.[5,20,22]

We observed an incident rate of conversion from NA to MCI of 9.1%. Other community-based studies have reported a rate of new-onset MCI of 13.5% during 6 years of follow-up, which is relatively similar to our results.[9] Moreover, in our sample, 21 (6.6%) subjects reverted to normal, and they represent 42% of the patients with MCI at baseline. Similar rates of reversion to NA have previously been reported in population-based studies.[23,24] Only a marked progression of PVH was associated with incident MCI in our sample. By contrast, a previous study observed that the baseline load of WMH was associated with incident MCI, whereas WMH change was not associated with it, although in this previous study, PVH and DWMH were not assessed separately.[9] In line with our results, another study observed that both changes in the PVH and total WMH were associated with persistent cognitive impairment (defined as 2 consecutive semiannual clinical Dementia Rating Scale scores ≥0.5) in a small sample of community-dwelling participants.[8] Similarly, we observed that a change in PVH parallels the decline in global and executive function. Previous studies have reported similar results on an association of PVH progression with a decline in cognition, particularly executive function, and information processing speed.[4,5,20]

Different hypotheses may explain why in most studies PVH are associated with cognitive decline, whereas DWMH tend not to be associated with it. First, DWMH may disrupt cortico-cortical connections, whereas PVH may affect long cortico-subcortical association fibers.[25] According to this point of view, the WMH location, rather than load, would be an important variable to determine the impaired networks involved in cognition.[26] In line with this hypothesis, occipital DWMH are related to attention function decline. Our results may be explained by the involvement of the fronto-occipital fasciculus within the occipital area. Second, PVH and DWMH may affect different neuromodulator systems. In particular, periventricular white matter may be adjacent to ascending cholinergic bundles, which may have a role in vascular cognitive impairment.[27] Third, DWMH and PVH may have a different pathophysiology; in particular, PVH is associated with venous collagenosis, which may induce ischemia and disturb the interstitial fluid circulation, thereby accelerating amyloid deposition.[28,29] By contrast, DWMH may be more related to hypoperfusion because deep areas are particularly vulnerable to low BP.[30] However, it is important to highlight that WMH pathophysiology is not fully understood, and further studies are required to confirm these hypotheses.[31] Nevertheless, other authors using 3-dimensional mapping techniques have postulated that DWMH, when viewed axially, are adjacent to PVH.[32] Therefore, visual bias may be skewing to distinguish between DWMH and PVH, thus complicating to disentangle the specific mechanisms by which PVH affect cognition.

CMBs were associated with an attention function decline. However, because we found a reduced number of incident CMB in the sample and previous literature showed conflicting results,[33] these results should be confirmed in future studies. Moreover, incident infarcts were not associated with cognitive decline, and this result contrasts with other studies that reported an association with cognitive decline.[20,34] However, these populations were older at baseline (range, 71–73.1) and had a higher rate of incident infarcts.

This study has strengths and limitations. As limitations, we could only reevaluate half of the sample, which thus limits the generalization of our results. Moreover, patients were selected according to the severity of baseline cSVD, which may

overestimate the progression of cSVD MRI markers. However, we found similar rates of cSVD progression in the sample compared with other population studies without this bias.[20,22] Another limitation may be that we qualitatively measured the progression of cSVD. However, although volumetric approaches may be more precise, Rotterdam Progression scale showed good correlation with WMH volumes in previous studies.[15] Furthermore, we did not assess markers of neurodegeneration, such as Tau or amyloid-β, which may be related to hypertension and cSVD lesions. As strengths, the cognitive status was established through a complete longitudinal, neuropsychological, neurological, and functional examination and clinical diagnostic criteria.

## Perspectives

In this sample of patients with hypertension, we observed associations of marked PVH progression with cognitive decline and incident MCI. Because MCI is one of the most important risk factors in the development of dementia,[35] future research should investigate the mechanisms by which PVH trigger cognitive impairment and the clinical use of its assessment.

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## Disclosures

None.

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## Novelty and Significance

### What Is New?

- A marked progression in periventricular white matter hyperintensities was associated with incident mild cognitive impairment in this sample of patients with hypertension.

### What Is Relevant?

- A marked progression in periventricular white matter hyperintensities was related to a significant decline in executive and global cognitive function.
- We identified a relationship between incident cerebral microbleeds and attention decline.

### Summary

The progression of white matter hyperintensities during 4 years of follow-up was prevalent in this sample of well-controlled patients with hypertension. We observed that periventricular white matter hyperintensities were related to incident mild cognitive impairment and global cognitive decline. Because patients with hypertension are at high risk for cerebral small vessel disease progression, the identification of specific lesions that have higher odds of impairing cognition may have useful implications in clinical practice.