Prevalence and Associated Factors of Silent Brain Infarcts in a Mediterranean Cohort of Hypertensives

Pilar Delgado, Iolanda Riba-Llena, José L. Tovar, Carmen I. Jarca, Xavier Mundet,
Antonio López-Rueda, Francesc Orfila, Judit Llussà, Josep M. Manresa, José Álvarez-Sabín,
Cristina Nafría, José L. Fernández, Olga Maisterra, Joan Montaner, on behalf of ISSYS Investigators*

Abstract—Silent brain infarcts (SBIs) are detected by neuroimaging in approximately 20% of elderly patients in population-based studies. Limited evidence is available for hypertensives at low cardiovascular risk countries. Investigating Silent Strokes in Hypertensives: a Magnetic Resonance Imaging Study (ISSYS) is aimed to assess the prevalence and risk factors of SBIs in a hypertensive Mediterranean population. This is a cohort study in randomly selected hypertensives, aged 50 to 70 years old, and free of clinical stroke and dementia. On baseline, all participants underwent a brain magnetic resonance imaging to assess prevalence and location of silent infarcts, and data on vascular risk factors, comorbidities, and the presence of subclinical cardiorenal damage (left ventricular hypertrophy and microalbuminuria) were collected. Multivariate analyses were performed to determine SBIs associated factors. A total of 976 patients (49.4% men, mean age 64 years) were enrolled, and 163 SBIs were detected in 99 participants (prevalence 10.1%; 95% CI, 8.4%–12.2%), most of them (64.4%) located in the basal ganglia and subcortical white matter. After adjustment, besides age and sex, microalbuminuria and increasing total cardiovascular risk (assessed by the Framingham-calibrated for Spanish population risk function) were independently associated with SBIs. Male sex increased the odds of having SBIs in 2.5 as compared with females. Our results highlight the importance of considering both global risk assessment and sex differences in hypertension and may be useful to design future preventive interventions of stroke and dementia. (*Hypertension*. 2014;64:658-663.) ● Online Data Supplement

Key Words: hypertension ■ stroke

Although a large amount of data are available on the prevalence of silent brain infarcts (SBIs) in the general population and of their role as independent predictors for future stroke and dementia, still further studies are needed to determine their frequency in various populations, particularly those at high risk. This information may be potentially useful to design further studies for prevention of stroke and dementia.[1] Besides age, hypertension is the risk factor most consistently associated with SBIs. Remarkably, in most of these studies, the diagnosis of hypertension was based on self report from participants or on single measurements of blood pressure (BP). Also, some studies have been conducted specifically in selected groups of essential hypertensives and described a wide SBIs prevalence ranging from 20% to 86%. Several factors may be related to this large variation in prevalence. Among all studies, nearly half of them included few participants, and from those with larger sample size (Table 1),[2–17] it should be noted that patients with hypertension were mainly selected among those who

attended specialized units (cardiology, internal medicine, kidney departments, etc) at hospitals and were probably more representative of newly diagnosed or more severe or resistant forms of hypertension than average.

Moreover, the vast majority of studies have been conducted in Asian cohorts, which indeed differ from western countries about their distribution of vascular risk factors and stroke incidence.[18] A few studies have been conducted in European countries, such as those from 1 group in The Netherlands which described prevalences of SBIs ranging from 22% to 29%.[4,5,19] Because some of them included ambulatory BP monitoring, only patients in whom treatment could be removed before monitoring were enrolled.

Even less information is available for lower cardiovascular and stroke risk populations, such as those living at Mediterranean areas.[20] To our knowledge, 1 group from Italy[16] reported a prevalence of asymptomatic brain damage in 54.9% hypertensive individuals. However, they included not only lacunes and territorial

Table 1. Other Published Studies Describing Silent Brain Infarcts in Hypertensive Cohorts

Authors	Country	Sample Size	Patient Selection	Sex, % Male	Age	Office BP	SBI %	Previous Antihypertensive Treatment
Kwon et al[2]	Korea	550	Voluntary health check	68.2	59.3 (25–83)	Control, 136/91 SBI, 141/90	11.1	Previous treatment in 79% of the controls and 85% SBI patients
Kato et al[3]	Japan	100	Selected from outpatient office (cardiovascular and renal medicine)	66	62 (42–81)	NA	24	Treatment for ≥1 mo prior inclusion
Henskens et al[4,5]	The Netherlands	192	Referral to internal medicine department	49	51.6 (20–83)	170/104	29 (23–36)	Nontreated patients
Kario et al[6–15]	Japan	519	Patients coming from 2 hospitals, 3 clinics, and 1 outpatient clinic	40	72 (≥50)	164/90	50	58% of those with sustained HTN (removed for ABPM)
Selvetella et al[16]	Italy	195	Patients who visited the department of angio-cardio-neurology	44.1	SBD, 67±1 No SBD, 54±1	Control, 140/86 SBI, 147/85	54.9	90% were treated with anti-hypertensive drugs
Ma et al[17]	China	188	Retrospective analyses from hospital records	42.5	64 (45–75)	NA	59	All treated (monotherapy)

Only studies with a minimum sample size of 100 participants are shown. Studies are sorted by increasing silent brain infarcts (SBIs) prevalence. Office BP is expressed in mm Hg. Age is expressed as mean±SD or mean (range) as it was provided by the authors. ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; HTN, hypertension; NA, not available; and SBD, silent brain damage.

lesions but also other punctate lesions (>5 mm) that might not be infarcts in all cases. Also in Spain, Sierra et al[21] performed a study in middle-aged hypertensives, in which they found that white matter lesions (also manifestations of subclinical brain damage) were a common finding (40.9%). However, lesions appearing as lacunar infarcts were not assessed in their study.

The differentiation of SBIs from other similar lesions, such as enlarged perivascular spaces, has been done poorly in the past,[22] and more efforts are needed to overcome the lack of consistency and advance in this field.[23]

With all that in mind, we aimed to determine the prevalence of SBIs in a large cohort of randomly selected hypertensives in a Mediterranean population and to study their associated risk factors.

Methods

Subjects Selection

Investigating Silent Strokes in Hypertensives: a Magnetic Resonance Imaging Study (ISSYS) is an observational, cross-sectional, and longitudinal study aimed to determine the prevalence of SBIs and their relationship with future stroke and dementia in a large cohort of Mediterranean hypertensives.[24]

Briefly, this study has been carried out in patients aged 50 to 70 years and diagnosed of essential hypertension who are routinely attended by general practitioners in our health area.

Participants were randomly selected after stratification by age and sex among 27 000 potentially eligible subjects living in the district of the north metropolitan area of Barcelona. They were invited by phone to participate and a visit was then scheduled where fulfillment of inclusion and exclusion criteria was assessed by trained investigators. Inclusion criteria consisted of (1) patients with essential hypertension diagnosed ≥1 year earlier; (2) age comprised between 50 and 70 years, and (3) patients who gave their informed consent to participate. Patients were excluded when (1) they had history of previous clinical stroke or dementia, (2) brain magnetic resonance imaging (MRI) was contraindicated, (3) there was a suspicion of white coat hypertension syndrome, or (4) patients were affected by a terminal illness preventing any future follow-up examination, based on the investigator criteria.

To rule out the presence of a previous stroke, medical records were reviewed and the patient was interviewed following an adaptation of the Stroke Symptom Questionnaire.[25] Also, when dementia was suspected, following *Diagnostic and Statistical Manual of Mental Disorders, fourth edition*, revised (*DSM-IV-R*) criteria, the patient was not included in the study and a proper evaluation in the presence of a caregiver was recommended.[26]

Enrollment visits were conducted between November 2010 and May 2012. Among 1037 participants who were initially enrolled in this study, 94.1% (n=976) completed all baseline procedures, including a brain MRI scan. The remaining participants were excluded as a result of claustrophobia (n=17), presence of a cranial metallic artifact (n=8), consent withdrawal (n=33), and lost to follow-up before MRI was performed (n=3). Excluded patients were more often men, overweighted, and diabetic than those who were finally included.

Clinical Data Collection and Physical Examination

The study protocol was approved by the Ethics Committee of Vall d'Hebron Hospital and IDIAP Jordi Gol (University Research Institute in Primary Care).

Assessment of all covariates was done by interviewing participants and reviewing medical records. Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or use of antihypertensive medication. We obtained data on demographical characteristics and personal medical history, including duration of hypertension and presence of other vascular risk factors, such as smoking habit, alcohol abuse, dyslipidemia, and diabetes mellitus. The presence of a previous cardiovascular, kidney, or systemic disease was also assessed. For those participants without previous vascular disease, global vascular risk was estimated applying the Framingham-calibrated Registre Gironí del Cor (REGICOR) function, and participants were divided into the following categories depending on their 10-year estimated risk of having a coronary event: low risk (<5%), moderate risk (5%–9.9%), high risk (10%–14.9%), and very high risk (≥15%).[20]

Data concerning office and home BP, BP control (optimal/ poor), and antihypertensive treatment were collected, and treatment compliance was assessed with the Moriski questionnaire.[27]

Also weight, height, and waist circumference were measured, and abdominal obesity was recorded.[28] Office BP was measured with an oscillometric device (Omron M6 Comfort), and the mean of the last 2 of 3 determinations after 5-minute rest was recorded.

A detailed description of all covariates is presented in the online-only Data Supplement (Expanded Materials and Methods).

Several other well-known hypertensive target organ damage (TOD) markers, such as the presence of left ventricular hypertrophy or renal dysfunction (microalbuminuria and decreased estimated glomerular filtration rate [GFR]), were analyzed. Specifically, a standard 12-lead ECG was performed to assess for signs of left ventricular hypertrophy (single measurement of R wave in aVL [augmented vector left])[29] and heart rhythm disorders. Regarding kidney function, a single-spot urine sample was collected and sent to central laboratory for albumin-to-creatinine ratio determination. Microalbuminuria was determined as >21 mg/g in men and >30 in women.[28] Moreover, GFR was estimated with the Modified Diet in Renal Disease-Isotope Dilution Mass Spectrometry formula.[30] Impaired renal function was considered whenever values were below 60 mL/min per 1.73 m².

Neuroimaging Protocol

A brain MRI was performed within the next month after study entry. Data acquisition details have been published elsewhere.[24] SBIs were defined as in previous studies as lesions of ≥3 mm of diameter in their widest dimension, with cerebrospinal-like fluid signal characteristics in all pulse sequences, and the presence of an hyperintense rim surrounding the lesion in fluid attenuation inversion recovery sequence was also required.[22] All MRIs were assessed by 2 neuroradiologists and an experienced stroke neurologist, and disagreements were solved by consensus. Intrarater agreement was calculated for each reader in a training set before undertaking the present reading, ranging from 0.60 to 0.75. The main source of disagreements came from the differentiation of SBIs from enlarged perivascular spaces; therefore, lesions located in areas with high prevalence of enlarged perivascular spaces, such as the lower part of basal ganglia, were not considered as infarcts.

Statistical Methods

Sample size calculation representative for our population concerning prevalence of SBIs was estimated using data from population-based studies published before, which reported specific data on SBIs prevalence in participants aged 50 to 70 years old.[24] According to them, the expected prevalence should be ≈10%. Therefore, after applying the Ene 3.0 free software (GlaxoSmithKline S.A., Spain; http://sct.uab.cat/estadistica/es), with a confidence interval of 95% and an accuracy of 2%, sample size should be of ≥865 individuals, which was increased to 1000 individuals by taking into account possible losses.

Statistical analysis was performed with the SPSS 17.0 statistical package (Chicago, IL). Intergroup differences were assessed by the χ^2 or Fisher exact test for categorical variables and by the t test, ANOVA, Mann–Whitney U test, and Kruskal–Wallis test for continuous variables. The correlation between continuous variables was determined with Spearman or Pearson coefficients, as appropriate. A P value <0.05 was considered as significant. To evaluate independently associated factors of SBIs in our sample, we constructed forward stepwise logistic regression models with all variables associated with SBIs showing a P value <0.1 in the univariate analysis (model 1). Odds ratios and 95% confidence intervals were further adjusted by adding smoking habit and antihypertensive treatment to the model. In a second term (model 2), REGICOR score was used as a measure of total cardiovascular risk as covariate. Interaction terms of age and BP (model 1) and REGICOR score and microalbuminuria (model 2) were also tested.

Results

Baseline Demographical and Clinical Characteristics

Nine hundred seventy-six patients were included in this study. Demographical characteristics and cardiovascular risk profile are shown in Table 2. Median age was 64 years, and 49.4% of the sample were men. Besides hypertension, most of the participants had dyslipidemia (71.7%) and 23.5% were diabetic. Overall, 120 (12.3%) had already a history of an established cardiovascular disease. From those free of vascular disease at baseline, total cardiovascular risk was estimated by means of the REGICOR risk charts; the majority of the participants belonged to the moderate or high risk categories (median=6 [4–9]).

Regarding BP, mean systolic and diastolic BP were 141.5 and 77.5 mm Hg, respectively. All patients had been recommended to follow lifestyle recommendations to control their BP, and also the vast majority (95.4%) were taking antihypertensive drugs at the time of the study entry (40.2% monotherapy, 37.2% were on 2 drugs, 18% on ≥3 drugs). Only 54% of participants self-reported correct treatment compliance.

Table 2.   Univariate Analysis: Description of Demographic and Clinical Baseline Factors in the Total Sample and in Those With or Without SBIs

Characteristics	All Patients	Absence of SBI (n=877)	Presence of SBI (n=99)	P
Age, y*	64 (60–67)	64 (59.5–67)	65 (61.7–69)	<0.01
Sex, male*	49.4%	46.9%	71.7%	<0.01
Tobacco use	15.2%	15.3%	14.1%	0.76
Alcohol abuse	6.4%	6.7%	4.8%	0.78
Diabetes mellitus	23.5%	22.7%	30.3%	0.09
Dyslipidemia	71.7%	70.8%	79.6%	0.07
Abdominal obesity	72.7%	72.7%	72.4%	0.95
Body mass index, kg/m²	29.9 (27.1–33.2)	30.0 (27.1–33.2)	29.9 (26.9–33)	0.86
Mean office SBP, mm Hg	141.5 (132–153)	141.5 (132–153)	144 (130–155.6)	0.69
Mean office DBP, mm Hg*	77.5 (71–84)	77.5 (70.5–84)	81.5 (72.8–89.7)	0.03
Duration of hypertension, y	8.6 (5.3–12.4)	9.1 (5.7–12.8)	8.8 (4.5–12.8)	0.52
REGICOR score*	6 (4–9)	6 (4–8)	7 (5–10.75)	<0.01
Previous cardiovascular disease*	12.3%	11.2%	22.2%	<0.01
No. of antihypertensives	2 (1–2)	2 (1–2)	2 (1–2.75)	0.18
Treatment compliance	54.4%	54.8%	50.5%	0.43

Data are expressed in median (interquartile range), mean±SD, and percentage as appropriate. DBP indicates diastolic blood pressure; REGICOR, Registre Gironí del Cor; SBI, silent brain infarct; and SBP, systolic blood pressure.

*Significant results.

SBIs and Their Associated Factors

A total of 99 participants had SBIs, leading to a prevalence of 10.1% of the sample (95% confidence interval, 8.4%–12.2%). Most of the patients had a single lesion (69%), whereas 31% presented multiple lesions (ranging 2–11), accounting for a total number of 163 infarcts. The majority of lesions were located in the basal ganglia (35.6%) or subcortical white matter (28.8%), followed by the cerebellum (16%), brain stem (11%), and cortex (8.6%).

As expected, increasing age was related to the presence of SBIs but also sex differences were found. Prevalence of SBIs was gradually increased for both sexes with age, but they were more often in men than in women at any age category. However, men and women differed in the frequency of many baseline characteristics as shown in Table S1 (online-only Data Supplement).

Other baseline differences in SBI presence about vascular risk factors, total cardiovascular risk, or BP levels are shown in Table 2.

Finally, because subclinical organ damage may affect prognosis in hypertensives, we evaluated the kidney function by means of urine albumin-to-creatinine ratio and estimated GFR. After exclusion of 10 participants who showed serum creatinine levels (>132.6 μmol/L in men and 114.9 μmol/L in women) or proteinuria (urine albumin-to-creatinine ratio ≥300 mg/g at least once) suggestive of overt nephropathy, 13.7% presented microalbuminuria, 7.8% had low estimated GFR, and in 1.1% of participants both alterations were present. Also, left ventricular hypertrophy was detected as signature of hypertensive heart damage in 9.1% of the cohort.

Looking into how these markers of TOD were interrelated, we found that microalbuminuria was associated with the presence of SBIs (27.2% in those with microalbuminuria versus 12.2% in those without it, $P<0.001$), whereas finding a decreased GFR or left ventricular hypertrophy presence was not ($P=0.25$ and $P=0.22$, respectively).

In Table 3, we present results from the multivariate analyses. Increasing age, male sex, and microalbuminuria (model 1) were all independently associated with SBIs. Moreover, because current guidelines support that diagnosis and management of hypertension should be related to quantification of global (or total) cardiovascular risk, we included in the analysis the Framingham-calibrated REGICOR score (model 2) and found that it was also predictor of SBIs, in addition to microalbuminuria. A graded response was found between REGICOR risk categories and SBI, with the strongest associations corresponding to those at high or very high-risk categories.

It should be noted that despite the fact that microalbuminuria was independently associated with SBIs in both models, in our sample, still 66% of the participants with SBIs had no renal or heart involvement.

Discussion

Here, we described the prevalence of SBIs in a large Mediterranean cohort of middle- and old-aged hypertensives. SBIs were found in 10.1% of participants, a prevalence that is similar to other population-based studies but lower than that reported in hypertensive cohorts. Although this might be surprising, several differences should be noted between ours and previous studies in hypertensives, apart from ethnicity, as mentioned before. First, our population was younger and the majority of

Table 3.   Multivariate Analysis: Independent Associated Factors With the Presence of Silent Brain Infarcts

Characteristics	OR (95% CI)	*P*
Model 1		
Age, per 5 y	1.54 (1.22–1.94)	<0.01
Sex, male	2.53 (1.55–4.15)	<0.01
Microalbuminuria	2.28 (1.33–3.918)	<0.01
Model 2		
Total cardiovascular risk (REGICOR)		0.05
Low (<5%)	1 (reference)	
Moderate (5–9.9%)	1.29 (0.66–2.51)	0.46
High (10–14.9%)	2.17 (1.00–4.69)	0.05
Very high (≥15%)	3.17 (1.22–8.22)	0.02
Microalbuminuria	2.34 (1.29–4.26)	<0.01

Values represent odds ratios (OR) and their corresponding 95% confidence intervals (CI). Model 1 includes covariates age, sex, dyslipidemia, mean office diastolic blood pressure (per 1 mm Hg increase), diabetes mellitus, previous cardiovascular disease, microalbuminuria, smoking habit, antihypertensive treatment (number of drugs received), and the interaction term of age and blood pressure. Model 2 includes categorized Registre Gironí del Cor (REGICOR) score (low-risk category as reference), microalbuminuria, antihypertensive treatment, and the interaction term between REGICOR and microalbuminuria.

our participants was long-term (median 8.6 years since diagnosis) and treated hypertensives with office BP levels that were lower as compared with previous studies selecting hypertensives (Table 1).[2–17] Most importantly, the selection of participants was performed randomly from a primary care setting. The cohort was routinely treated and monitored by general practitioners, avoiding the bias that might be caused by selection in more specialized contexts, such as hospital units. Moreover, our sample size was estimated taking into account previous studies on this matter in general populations, and to date, it is almost twice larger than that of previous studies in a purely hypertensive cohort.

We found that SBIs were strongly associated with age, as it has been shown consistently before, and much more frequent in hypertensive men than women. This is also remarkable, taking into account that stroke is the leading cause of death for women in our country. Other population-based studies, such as the Rotterdam Scan Study[31] and the Cardiovascular Health Study,[32] found opposite results, with more SBIs in women than in men, although their participants were older than ours. In opposition, our results agree with those from the Northern Manhattan Study, a multiethnic community-based cohort.[33] It is well known that women have lower BP levels across the lifespan than their age-matched counterparts. However, hypertension becomes increasingly prevalent in postmenopausal women.[34] We randomized participants taking into both sex and age, but still several differences were found in the distribution of vascular risk factors, with women displaying less global vascular risk and comorbidities than men in our cohort. These differences might explain the lower prevalence of SBIs in women. It is also possible that because we did not perform ambulatory BP monitoring to select participants, some of them might have indeed a white coat effect. This condition is associated with an intermediate risk of cardiovascular events between those with sustained hypertension and normotensive individuals, and it is described to be particularly frequent in women.[35] However, we

excluded participants with suspected white coat hypertension, and the vast majority of them had been treated for a long time before inclusion, thus making this possibility less likely.

Our results, therefore, emphasize the need to uncover sex differences to better understand pathological processes associated with aging and stroke and to personalize preventive health care.

We also found an independent association between microalbuminuria and SBIs. This is important because these results extend previous knowledge on the role of microalbuminuria as predictive marker of cardiovascular events and stroke risk.[36] Less is known on how microalbuminuria is interrelated to other subclinical TOD, such as that present in the brain. Specifically, this was reported in hypertensives by Henskens et al[5] in a cohort of 192 young untreated hypertensives, in whom different TOD markers were evaluated, including microalbuminuria. Interestingly, although the proportion of subjects with damage in heart, kidney, brain, or any combination of them was higher in that study than in our population, half of the patients with brain damage (including SBIs but also other lesions such as white matter hyperintensities or microbleeds) did not present cardiorenal damage and were classified as having no-target organ involvement. Likewise, in our study, in almost 66% of those with SBIs, these lesions did not coexist with heart or kidney involvement, which are the organs routinely screened to assess risk in hypertension. Although both Henskens et al[5] and our results suggest that screening for SBI might improve risk stratification in hypertensives, longitudinal studies with stroke (and possibly other vascular events) as outcomes are needed to determine their predictive value.

Microalbuminuria is generally interpreted as an early sign of kidney disease or as a marker of endothelial dysfunction.[37] As kidney and brain display common hemodynamic properties such as low vascular resistance, as compared with other vascular beds, they might be unprotected against increased pulsatile stress occurring with aging and hypertension.[38] This could lead to endothelial damage and progress toward both the appearance of microalbuminuria and brain infarcts, even in the absence of an impaired kidney function. However, to properly address the occurrence of these events over time, prospective studies are needed.

Finally, we found that total cardiovascular risk is not only associated with the odds of symptomatic future vascular events but also related to the presence of subclinical brain disease. These results are in agreement with those reported in the Framingham Offspring cohort study,[39] but as original Framingham function scores overestimate risk in low-risk countries such as Spain,[20] we used a validated and easy-to-use tool (REGICOR) that is already extensively used by general practitioners in our area. In our study, total cardiovascular risk predicted the presence of SBIs better than any risk factor taken separately, highlighting the importance of treating patients preferably according to their estimated global cardiovascular risk, rather than based on the presence of any individual risk factor.

Strengths and Limitations

This study has some strengths and some limitations. As strengths, this is a large study, representative for a population of middle-aged hypertensives living in a low cardiovascular risk country in the Mediterranean area.

Moreover, inclusion procedures required careful review of medical records and interview with the participants to remove nonessential hypertension and rule out participants with previous stroke or dementia. We also have some limitations. Lack of ambulatory BP monitoring for selecting participants might have led to increased frequency of white coat hypertension effect. Urine albumin-to-creatinine ratio was measured in this study with a single-spot urine sample. In clinical practice, it is recommended to confirm this observation with multiple testing, to avoid false-positive results attributable to variability of the measurement. Also hypertensive heart damage could be determined with higher accuracy with the use of echocardiography or other imaging techniques.

Perspectives

This study characterizes the prevalence and risk factors of SBIs in a large hypertensive cohort, from a low cardiovascular risk country in the Mediterranean area. Other markers of TOD, such as microalbuminuria, or total cardiovascular risk are independently associated with silent brain vascular disease and might be useful to screen those at high risk of future stroke and dementia, while taking into account sex differences in the design of preventive strategies.

References
1. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol*. 2007;6:611–619.
2. Kwon HM, Kim BJ, Oh JY, Kim SJ, Lee SH, Oh BH, Yoon BW. Retinopathy as an indicator of silent brain infarction in asymptomatic hypertensive subjects. *J Neurol Sci*. 2007;252:159–162.
3. Kato T, Inoue T, Yamagishi S, Morooka T, Okimoto T, Node K. Low-density lipoprotein subfractions and the prevalence of silent lacunar infarction in subjects with essential hypertension. *Hypertens Res*. 2006;29:303–307.
4. Henskens LH, Kroon AA, van Oostenbrugge RJ, Gronenschild EH, Fuss-Lejeune MM, Hofman PA, Lodder J, de Leeuw PW. Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. *Hypertension*. 2008;52:1120–1126.
5. Henskens LH, van Oostenbrugge RJ, Kroon AA, Hofman PA, Lodder J, de Leeuw PW. Detection of silent cerebrovascular disease refines risk stratification of hypertensive patients. *J Hypertens*. 2009;27:846–853.
6. Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, Murata M, Kuroda T, Schwartz JE, Shimada K. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation*. 2003;107:1401–1406.

7. Kario K, Pickering TG, Hoshide S, Eguchi K, Ishikawa J, Morinari M, Hoshide Y, Shimada K. Morning blood pressure surge and hypertensive cerebrovascular disease: role of the alpha adrenergic sympathetic nervous system. *Am J Hypertens*. 2004;17:668–675.

8. Kario K, Eguchi K, Hoshide S, Hoshide Y, Umeda Y, Mitsuhashi T, Shimada K. U-curve relationship between orthostatic blood pressure change and silent cerebrovascular disease in elderly hypertensives: orthostatic hypertension as a new cardiovascular risk factor. *J Am Coll Cardiol*. 2002;40:133–141.

9. Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension*. 2001;38:852–857.

10. Kario K, Shimada K, Schwartz JE, Matsuo T, Hoshide S, Pickering TG. Silent and clinically overt stroke in older Japanese subjects with white-coat and sustained hypertension. *J Am Coll Cardiol*. 2001;38:238–245.

11. Kario K, Matsuo T, Kobayashi H, Hoshide S, Shimada K. Hyperinsulinemia and hemostatic abnormalities are associated with silent lacunar cerebral infarcts in elderly hypertensive subjects. *J Am Coll Cardiol*. 2001;37:871–877.

12. Kario K, Matsuo T, Kobayashi H, Imiya M, Matsuo M, Shimada K. Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Advanced silent cerebrovascular damage in extreme dippers. *Hypertension*. 1996;27:130–135.

13. Shimizu M, Ishikawa J, Yano Y, Hoshide S, Shimada K, Kario K. The relationship between the morning blood pressure surge and low-grade inflammation on silent cerebral infarct and clinical stroke events. *Atherosclerosis*. 2011;219:316–321.

14. Ishikawa J, Tamura Y, Hoshide S, Eguchi K, Ishikawa S, Shimada K, Kario K. Low-grade inflammation is a risk factor for clinical stroke events in addition to silent cerebral infarcts in Japanese older hypertensives: the Jichi Medical School ABPM Study, wave 1. *Stroke*. 2007;38:911–917.

15. Kario K, Ishikawa J, Eguchi K, Morinari M, Hoshide S, Ishikawa S, Shimada K. Sleep pulse pressure and awake mean pressure as independent predictors for stroke in older hypertensive patients. *Am J Hypertens*. 2004;17(5 Pt 1):439–445.

16. Selvetella G, Notte A, Maffei A, Calistri V, Scamardella V, Frati G, Trimarco B, Colonnese C, Lembo G. Left ventricular hypertrophy is associated with asymptomatic cerebral damage in hypertensive patients. *Stroke*. 2003;34:1766–1770.

17. Ma JF, Sun JL, Zhao J, Wei X, Wang BS, Fu Y. Relationship between nocturnal blood pressure variation and silent cerebral infarction in Chinese hypertensive patients. *J Neurol Sci*. 2010;294:67–69.

18. Ishikawa S, Kayaba K, Gotoh T, Nago N, Nakamura Y, Tsutsumi A, Kajii E. Incidence of total stroke, stroke subtypes, and myocardial infarction in the Japanese population: the JMS Cohort Study. *J Epidemiol*. 2008;18:144–150.

19. van Boxtel MPJ, Henskens LHG, Kroon AA, Hofman PAM, Gronenschild EHBM, Jolles J, de Leeuw PW. Ambulatory blood pressure, asymptomatic cerebrovascular damage and cognitive function in essential hypertension. *J Hum Hypertens*. 2006;20:5–13.

20. Marrugat J, Vila J, Baena-Díez JM, Grau M, Sala J, Ramos R, Subirana I, Fitó M, Elosua R. [Relative validity of the 10-year cardiovascular risk estimate in a population cohort of the REGICOR study]. *Rev Esp Cardiol*. 2011;64:385–394.

21. Sierra C, de La Sierra A, Mercader J, Gómez-Angelats E, Urbano-Márquez A, Coca A. Silent cerebral white matter lesions in middle-aged essential hypertensive patients. *J Hypertens*. 2002;20:519–524.

22. Zhu YC, Dufouil C, Tzourio C, Chabriat H. Silent brain infarcts: a review of MRI diagnostic criteria. *Stroke*. 2011;42:1140–1145.

23. Wardlaw JM, Smith EE, Biessels GJ, et al; STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822–838.

24. Riba-Llena I, Jarca CI, Mundet X, Tovar JL, Orfila F, López-Rueda A, Nafría C, Fernández JL, Castañé X, Domingo M, Alvarez-Sabín J, Fernández-Cortiñas I, Maisterra O, Montaner J, Delgado P. Investigating silent strokes in hypertensives: a magnetic resonance imaging study (ISSYS): rationale and protocol design. *BMC Neurol*. 2013;13:130.

25. Berger K, Hense HW, Rothdach A, Weltermann B, Keil U. A single question about prior stroke versus a stroke questionnaire to assess stroke prevalence in populations. *Neuroepidemiology*. 2000;19:245–257.

26. American Psychiatric Association. *Manual Diagnóstico y Estadístico de los trastornos mentales, DSM-IV-TR*. Barcelona: Masson; 2002.

27. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*. 1986;24:67–74.

28. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2007;28:1462–1536.

29. Gosse P, Jan E, Coulon P, Cremer A, Papaioannou G, Yeim S. ECG detection of left ventricular hypertrophy: the simpler, the better? *J Hypertens*. 2012;30:990–996.

30. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461–470.

31. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke*. 2002;33:21–25.

32. Longstreth WT Jr, Bernick C, Manolio TA, Bryan N, Jungreis CA, Price TR. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. *Arch Neurol*. 1998;55:1217–1225.

33. Prabhakaran S, Wright CB, Yoshita M, Delapaz R, Brown T, DeCarli C, Sacco RL. Prevalence and determinants of subclinical brain infarction: the Northern Manhattan Study. *Neurology*. 2008;70:425–430.

34. Bushnell C, McCullough LD, Awad IA, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Council for High Blood Pressure Research. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2014;45:1545–1588.

35. Vinyoles E, Felip A, Pujol E, de la Sierra A, Durà R, del Rey RH, Sobrino J, Gorostidi M, de la Figuera M, Segura J, Banegas JR, Ruilope LM; Spanish Society of Hypertension ABPM Registry. Clinical characteristics of isolated clinic hypertension. *J Hypertens*. 2008;26:438–445.

36. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Impact of microalbuminuria on incident stroke: a meta-analysis. *Stroke*. 2010;41:2625–2631.

37. Tsioufis C, Dimitriadis K, Andrikou E, Thomopoulos C, Tsiachris D, Stefanadi E, Mihas C, Miliou A, Papademetriou V, Stefanadis C. ADMA, C-reactive protein, and albuminuria in untreated essential hypertension: a cross-sectional study. *Am J Kidney Dis*. 2010;55:1050–1059.

38. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension*. 2005;46:200–204.

39. Das RR, Seshadri S, Beiser AS, Kelly-Hayes M, Au R, Himali JJ, Kase CS, Benjamin EJ, Polak JF, O'Donnell CJ, Yoshita M, D'Agostino RB Sr, DeCarli C, Wolf PA. Prevalence and correlates of silent cerebral infarcts in the Framingham offspring study. *Stroke*. 2008;39:2929–2935.

Novelty and Significance

What Is New?

- Silent brain infarcts are present in ≈10% of hypertensives in a low-cardiovascular-risk Mediterranean population.
- Total cardiovascular risk and microalbuminuria could be useful to determine those with subclinical brain vascular disease and, therefore, with higher risk of future stroke and dementia.

What Is Relevant?

- Our results emphasize the need of assessing total cardiovascular risk in hypertensives, to determine the burden of clinical and subclinical disease.
- Sex differences need to be further explored in stroke prevention.

Summary

Silent brain infarcts prevalence reached 10% of hypertensives between 50 and 70 years old in a low cardiovascular risk Mediterranean population, with striking sex differences. Microalbuminuria and increased total cardiovascular risk are independently associated with silent brain infarcts presence in long-term treated essential hypertensives.