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TARGET ORGAN DAMAGE

Small Vessel Disease of the Brain and Stroke: Association with Clinic and Ambulatory Blood Pressure

[1]Puneet Gupta, [2]William B White

ABSTRACT

Several potential vascular risk factors exist for the development and accumulation of small vessel disease of the brain and stroke in older people. In older people followed up for several years, we and others have reported that white matter hyperintensity lesions on magnetic resonance imaging nearly doubled in volume and were associated with alterations in neurologic function. In this article, we review blood pressure (BP) as a risk factor for the development and pathogenesis of small vessel disease and stroke in older persons. The research efforts have focused on ambulatory BP measurements, which have proven to be a stronger indicator than clinic pressures for the progression of small vessel disease in older people as well as the development of stroke. Based on relations among 24 hours systolic BP levels, the accrual of small vessel disease, and relations with cognitive function and mobility, we have designed the INFINITY trial, a novel interventional study that uses ambulatory BP to guide antihypertensive therapy addressed at improving functional decline.

Keywords: Ambulatory blood pressure, Cerebral small vessel disease, Stroke, Systolic hypertension.

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INTRODUCTION

Cerebrovascular Disease, Hypertension, and Functional Decline

Small vessel brain disease that is represented by white matter hyperintensity (WMH) lesions on magnetic resonance imaging (MRI) is associated with vascular risk factors, including hypertension, in older people.[1,2]

[1,2]Professor and Chief

[1,2]Division of Hypertension and Clinical Pharmacology, Calhoun Cardiology Center, University of Connecticut School of Medicine Farmington, Connecticut, USA

Corresponding Author: William B White, Professor and Chief Department of Medicine, Division of Hypertension and Clinical Pharmacology, Calhoun Cardiology Center, University of Connecticut School of Medicine, Farmington, Connecticut, USA Phone: +18606792104, e-mail: wwhite@uchc.edu

Postmortem histopathology of WMH shows nonspecific brain changes with gliosis, loss of myelin and axons from arteriosclerosis, tissue rarefaction, and lipohyalinosis.[3,4] Although the pathophysiology of WMH remains unclear, there are several proposed mechanisms, including hypoxia, hypoperfusion due to altered cerebrovascular auto-regulation, blood–brain barrier leakage, inflammation, degeneration, and amyloid angiopathy.[5] Marstrand and colleagues demonstrated that cerebral blood flow and cerebrovascular reactivity were reduced in areas of WMH, making tissue damage more likely during hypoperfusion states.[6]

In most instances, WMH lesions are bilateral and symmetrical on T2-weighted MRI. They are distributed in the periventricular and deep white matter regions and less frequently in the infratentorial areas of the brain. On computed tomography (CT) scan, WMH lesions appear as hypodensities.[1,7] They are commonly assessed using visual rating scales, such as Fazekas scale and Scheltens scale.[5] Another approach uses semi-automated, computerized analyses of the MRIs providing a quantitative distribution of cerebral SVD lesions suitable for longitudinal numerical comparisons and regional localizations (Fig. 1).[8]

Cognitive Function

Higher degrees of small vessel disease burden are associated with impaired cognitive function, mobility impairment, depression, and impaired urinary function.[1,9,10] The frequency of falls even in the absence of obvious neurologic deficits is more common in people with WMH lesions.[8] Cognitive dysfunction has been studied extensively in persons with WMH lesions on MRI.[9,11-18] Perceived cognitive dysfunction as measured by Cognitive Difficulties Scale was found to be worse with higher WMH burden and the annual rate of decline on the mini-mental status examination (MMSE) was 0.035 points per standard deviation increase in periventricular WMH.[19] In addition, steeper declines in performance have been found on measures of speed of processing and executive functioning, such as the Stroop Color Word test ($p = 0.04$) and the Symbol-Digit Substitution Test ($p < 0.01$) are seen with WMH lesions, whereas performances on memory tests, such as the 15-word verbal learning test are not as affected.[9,19] Over a decade, the European Leukoaraiosis

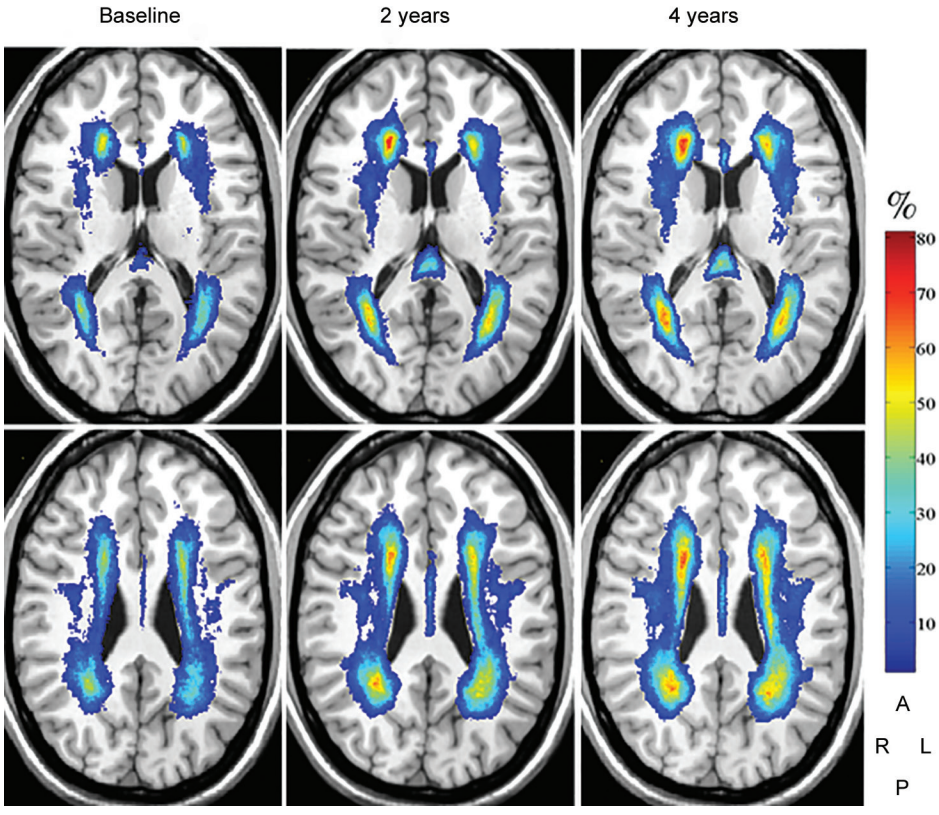

Fig. 1: The figure depicts the location and frequency of white matter hyperintensities (WMHs) captured over three time points during 4 years of prospective evaluation (baseline (left column), 2 years (center column), and 4 years (right column) in 67 older study participants. The WMHs are overlaid on the gray scale slice (0.87 mm thickness) of the common anatomical brain (International Consortium of Brain Mapping). Columns show two slices separated by 12.2 mm. The vertical color bar represents the frequency (%) of WMHs (e.g., color corresponding to 70% indicates the percent of participants with the WMH in that brain area. The lettering below the color bar indicates right (R), left (L), anterior (A), and posterior (P) brain aspects) (From Wolfson et al (2013)[8] discuss with permission from Oxford University Press on behalf of The Gerontological Society of America)

and DISability Study (LADIS) showed steeper declines in the Stroop test, Trail Making A test, verbal fluency, and MMSE among patients with cerebral small vessel disease and the group found that these abnormalities predicted a doubling of risk for dementia and transition from an autonomous to dependent state.[17]

Importantly, among patients with a history of stroke and/or transient ischemic attack in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), the dementia risk during a median follow-up period of 3.9 years was found to be 7.7 times higher in patients with white matter disease than those without it at the time of study enrollment.[16] A meta-analysis performed by Debette and Markus[20] also showed a significant association between white matter disease and risk of dementia (OR 1.9, 95% confidence intervals (CIs), 1.3 to 2.8, $p = 0.002$) as well as faster declines in global cognitive performance, executive function, and processing speeds.

Mobility and Balance

In addition to the aforementioned relationships between WMH burden and cognitive function, small vessel disease of the brain is also associated with impaired gait and balance in the older population.[8] Furthermore, severe WMH burden has been linked to increased risk of falls (relative risk (RR) = 1.63, 95% CI, 1.11–2.40).[10] In the LADIS, walking speed correlated with the white matter disease burden (1.24 ± 0.28 m/second for mild, 1.18 ± 0.32 m/second for moderate, 1.09 ± 0.31 m/second for severe categorizations respectively; $p < 0.001$).[21] Patients with mild white matter disease burden performed better with single leg stance when compared with those with moderate and severe diseases ($p < 0.001$). These findings have also been found in other studies correlating cerebral small vessel disease and mobility in the elderly and will be the subject of discussion later in this paper.[22]

Ambulatory Blood Pressure in Risk Assessment for Stroke

There has been mounting evidence for four decades on the importance of ambulatory blood pressure monitoring parameters for predicting cardiovascular events including stroke. In a meta-analysis of 17,312 persons with hypertension recently reported by the ABC-H

(Ambulatory Blood Pressure Collaboration in Patients With Hypertension) investigators,[23] reverse dippers (systolic night-to-day BP ratio > 1) had a significantly higher risk of strokes (HR 1.89, 95% CI 1.26–2.82, p < 0.01) compared to those study participants who had a more normal circadian BP rhythm (systolic night-to-day ratio < 0.9 and > 0.8). In addition, patients with reduction in nocturnal BP decline compared with those individuals with at least a 10% decline in BP during sleep, had a 27% greater risk for total cardiovascular events. Similar findings have also been reported by Verdecchia et al[24] in a longitudinal study in Italy of 3,012 hypertensive patients followed up for a mean period of 8.4 years.

The Ohasama study[25] has highlighted the additive importance of ambulatory BP measurements with home and office measurements for evaluation of stroke risk in 1,464 persons with a median follow up of 17.1 years. Using normal BP sustained over time as a reference, adjusted hazard ratios for stroke (95% CI; events/N) were 1.38 (0.82–2.32; 19/137) for white coat hypertension (isolated office hypertension), 2.05 (1.24–3.41; 23/100) for masked hypertension (both home and ambulatory hypertension with office normotension), 2.08 (1.37–3.16; 38/180) for partial masked hypertension (either home or ambulatory hypertension with office normotension), and 2.46 (1.61–3.77; 42/154) for sustained hypertension. The authors concluded that both home and 24 hours ambulatory blood pressure measurements are needed to evaluate stroke risk accurately.

Another major epidemiologic study of ambulatory BP and stroke outcomes is the International Database on Ambulatory BP and Cardiovascular Outcomes (IDACO).[26] In a recent report from the IDACO investigators[26] involving 8,341 people randomly recruited from 12 populations followed up for a median period of 11.2 years, the risks conferred by 24 hours BP were found to be age dependent. In participants above the age of 50 years, 24 hours systolic BP was a major predictor of stroke (HR 1.52, 95% CI 1.32–1.76, p < 0.001), total mortality, CV mortality, and all CV events after multivariate adjustment for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, systolic BP, and diastolic BP. Below the age of 50 years, 24 hours diastolic BP was the main driver of risk, reaching significance for total and cardiovascular mortality and for all cardiovascular end points combined. The 24 hours ambulatory systolic and diastolic BPs were also found to be independent predictors of CV events, including stroke, in another observational study of 502 patients in Finland with 16.1 years of follow up.[27]

Several other ambulatory blood pressure parameters have been studied for prediction of cardiovascular events. In a meta-analysis of 13,844 patients with hypertension[28] comprising nine cohorts from Europe, Japan, and Brazil, nocturnal (nighttime) systolic BP independently predicted higher CV risk. Each 10 mm Hg increase in nighttime systolic BP was also an independent risk factor for stroke (HR 1.95, 95% CI 1.18–3.20) in a cohort of 859 patients with type 2 diabetes[29] and in another Japanese cohort of 1,276 patients with hypertension[30] followed up for 3.2 years. A recent review from Portugal[31] found that a 10 mm Hg increase in pre-awakening BP surge, analyzed on a continuous scale, was related to a modest increased risk of stroke (HR = 1.11 for three studies). There has been some controversy regarding the impact of the early-morning surge in BP *vs* a sustained increase in nocturnal BP as the more potent risk of future stroke. Verdecchia et al[24] addressed this issue in a longitudinal study that found that a blunted pre-awakening BP surge due to high nocturnal BP was an important risk factor for an increased risk of stroke.

Resistant hypertension (lack of hypertension control on three or more antihypertensive agents) is associated with increases in hypertensive target organ disease and has become a topic of great interest. In a retrospective analysis of 217 patients with resistant hypertension, the ambulatory arterial stiffness index (AASI) was found to be an ABPM marker with the high predictive value for CV events including stroke.[32] In a meta-analysis of seven longitudinal studies that had followed up 20,505 patients with a mean follow-up of 7.8 years,[33] each standard deviation increase of AASI was associated with an age, sex, and risk factor-adjusted increase in relative risk of stroke by 30%. There is also evidence that average real variability (ARV) of 24 hours average and nocturnal systolic BP as well as BP variability during sleep may be independent predictors of subclinical cerebral small vessel disease.[34,35]

With growing evidence of increased CV risk with elevated nocturnal BP, a randomized prospective study comparing bedtime administration of antihypertensive therapy with conventional dosing time of therapy administered in the morning – the MAPEC study[36] – was undertaken. With a median follow-up of 5.6 years in 2,156 participants with hypertension, the study demonstrated a 67% reduction in major CV events (CV death, nonfatal MI, and nonfatal ischemic and hemorrhagic stroke) in subjects in the bedtime antihypertensive medication treatment group. Progressive decrease in sleep BP mean has been found to be the most significant predictor of event-free survival, a novel therapeutic target for primary prevention.[37]

Ambulatory BP Monitoring in Evaluating Outcomes for Recurrent Stroke

Hypertension is well known to be associated with increased risk of recurrent stroke in patients with a history

of a prior ischemic or hemorrhagic event.[38] A recent meta-analysis of 16 randomized controlled trials and 40,292 patients with history of stroke (ischemic, transient ischemic attack [TIA], or hemorrhagic), with and without hypertension, demonstrated that antihypertensive therapy reduced the risk of recurrent stroke (relative risk reduction, 18%; 95% confidence interval [CI], 9–26%). The meta-regression analysis also revealed that each 10 mm Hg reduction in systolic BP is associated with a 33% (95% CI, 9–51%) reduction in the risks of recurrent stroke.[39] In an observational study of 426 patients with acute cerebral infarction followed up for an average 7.6 years, daytime systolic BP on ambulatory monitoring was a significant predictor of recurrence of cerebral infarction.[40]

Ambulatory BP has demonstrated a higher sensitivity compared to office BP for evaluation of the effectiveness of antihypertensive treatment among stroke survivors.[38] In a study of 51 patients with a recent TIA syndrome and 225 clinically healthy control subjects, ambulatory BP monitoring revealed a highly significant proportion of these patients (90%) whose hypertension was not well controlled.[41] In another study of 187 consecutive first-ever hypertensive stroke survivors who underwent office and ambulatory BP measurements at 120 ± 30 days, effective BP control was documented in significantly ($p < 0.001$) fewer patients using ambulatory BP monitoring (32.1%) than those using office recordings (43.3%), whereas in 16% of the study population, there was a masked pattern (elevated ambulatory blood pressure in the presence of normal office blood pressure levels) identified.[42]

Castilla-Guerra et al[43] reported a chronic disruption of circadian rhythm of BP after the acute phase of stroke in a prospective study of 101 patients admitted within 24 hours after stroke onset and followed up for 1 year. The normal diurnal variation in BP was abolished in 87.1% of patients during the acute phase of stroke, in 76.9% after 6 months, and in 74.6% after 1 year. Another study[44] found that the nocturnal BP reduction was blunted in most (~90%) of 48 elderly bedridden hypertensive patients assessed within 1 to 3 months after stroke. In an interesting observational study,[40] a reverse dipper pattern and high nighttime heart rate in patients with acute cerebral infarction were independently associated with total mortality.

A meta-analysis of studies of acute ischemic stroke patients admitted within 24 hours of onset and undergoing ABPM within 24 hours of admission showed that both high systolic and diastolic BP levels derived from ambulatory BP monitoring were associated with poor short-, intermediate-, and long-term outcomes, but the same was not found for casual (clinic) BP measurements.[45] Additionally, in a study of 128 initial acute stroke patients who underwent ABPM within 24 hours of stroke onset and computerized tomography scans of the brain on both admission to the hospital and 5 days later, multivariate logistic regression analysis showed that each 0.1 mm Hg/minutes increase in the time rate of 24 hours SBP variation was associated with a 13.9% increased probability of presence of brain edema.[46] A longer-term study of 109 patients with stroke whose 24 hours BP variability was assessed within 24 hours of onset showed that higher systolic BP variation at baseline promoted negative outcomes at 1 year.[47]

Higher 24 hours, daytime, and nighttime systolic and diastolic BPs at baseline in patients with new lacunar infarctions have also been associated with the development of new cerebral microbleeds at 2 years follow-up.[48] A 3 months follow-up study of acute ischemic stroke patients found that mean values of systolic BP, diastolic BP, pulse pressure, and HR on day 1 of admission on ambulatory BP monitoring were inversely associated with their independence.[49]

The data mentioned before highlight the importance of ambulatory BP monitoring for potentially improving the secondary prevention of stroke using several parameters in the acute phase. Ambulatory BP monitoring not only helps in identifying patients with inadequate blood pressure control despite "apparently" well-controlled office BP, but can also help decide the appropriate timing of medications individualized to circadian rhythm. Furthermore, inadvertent excessive lowering of BP – which has been associated with recurrence of stroke[50-52] – may be avoided with assessment of 24 hours BP levels and patterns. Further research might best focus on using ambulatory BP parameters to guide antihypertensive therapy in patients with a history of stroke to facilitate further fine-tuning of secondary prevention strategies prevalent at this point.

The Importance of Blood Pressure as a Risk Factor for Cerebral Small Vessel Disease and Functional Decline in Older Persons

White matter hyperintensities and its progression, present in the MRIs of older people, have been associated with hypertension, and evidence suggests that WMHs occur as a result of arteriosclerosis within the wall of the arteriole.[53-56] Large arterial and small vessel disease of the cerebral circulation share risk factors (e.g., hypertension and diabetes) and may coexist in individuals as noted earlier. Although given the differences noted in Table 1, it is unclear if they both produce white matter tissue damage through similar mechanisms.[57,58]

White matter lesions have also been associated with deterioration of mobility, urinary control, and cognition.[59-64] Evidence of WMHs within brain pathways known to

Table 1: Comparison of some characteristics of stroke and white matter hyperintensity lesions*

Characteristic	*Stroke (large artery)*	*White matter hyperintensities*
Onset/progression	Sudden/brief if any	Ill-defined/gradual over years
Manifestations	Focal neurologic deficit	Functional limitations
Location	Vascular distribution	Grow from head/tail-lateral ventricles
Size	Stroke (cm)→ lacunae (mm)	< 1 mm
Vessel	Large to small artery	Arteriolar
Pathophysiology	Ischemic	Unclear

Note: There may be infarction due to small vessel disease that has onset/progression and manifestations that are similar to large artery stroke; *Modified from White et al[69] with permission of Elsevier, Ltd

support mobility, cognition, or voiding confirms this association.[63,64] Details seen on MRI of the brain have allowed localization and quantification of the disseminated WMHs.[65] Cross-sectional and prospective cohort studies have documented the relationships among WMHs and neurologic function in older people and the distinctive nature of the distribution and volume of brain WMHs that are responsible for deterioration of these functions, particularly in older groups. Approximately two-thirds of individuals over 75 years of age have detectable WMHs using MRI of the brain.[54] The lower limit of detection of WMH by experts in neuroradiology is approximately 0.2 to 0.3% of intracranial contents, and 0.5% is easily visible to the naked eye based on our experience.[8,54,65] Our cohort studies have demonstrated an increase of WMH volume from 0.99 to 1.47 to 1.7% of the intracranial contents volume from baseline to 2 and 4 years respectively.[8,54] This increase was even present in participants with normal mobility throughout the study period.

We have also observed that progression of WMH over time was strongly linked to the initial presence of WMH.[8,66] The accumulation of WMH often occurred by expansion of preexisting periventricular lesions in a stereotyped manner. Regional analysis of the distribution of WMH lesions demonstrated a robust link to expansion of lesions in the splenium of the corpus callosum, a posterior periventricular structure important for the integration of cortical sensorimotor function.[66]

Blood pressure and other cardiovascular risk factors have been related to brain WMH, although predictors of quantitative WMH progression and their effect on the function of older persons have not been well understood. In our past work in this area, we have evaluated the progression of WMH over 2 and 4 years in a cohort of 95 patients 75 to 90 years (mean baseline age, 82 years) who had office and ambulatory BP and volumetric MRI.[54,65] Neither clinic BP nor changes in clinic BP predicted progression of WMH, while the 24 hours ambulatory BP and changes in ambulatory BP significantly correlated with both WMH volume ($p < 0.04$) and changes in WMH ($p < 0.003$).[54] Further analyses demonstrated associations for WMH and mobility indexes with level of systolic BP based on tertiles of the cohort – i.e., those in the higher (24 hours systolic BP = 144 mm Hg) ambulatory BP group showed increases in WMH and slower mobility compared with the middle tertile (ambulatory systolic BP = 130 mm Hg) (Table 2). Furthermore, gait speed in the

Table 2: Functional parameters at 24 months of observation according to clinic and ambulatory blood pressure

Parameter	*Clinic blood pressure tertile*			
Clinic Systolic BP (mm Hg)	*Low (n = 25)*	*Middle (n = 25)*	*High (n = 24)*	*p-value*
Total WMH (%)	120.7 ± 1.2	135.9 ± 0.8	152.8 ± 1.8	
Mobility assessments	1.5 ± 0.3	1.4 ± 0.2	1.5 ± 0.2	0.935
Tinetti Gait	11.2 ± 0.2	11.6 ± 0.2	10.9 ± 0.3	0.207
Stair descent time (second)	6.7 ± 0.6	5.8 ± 0.4	6.6 ± 0.5	0.393
Maximal gait velocity (m/s)	0.69 ± 0.04	0.76 ± 0.03	0.67 ± 0.03	0.168
Walk time (second)	3.4 ± 0.2	3.0 ± 0.1	3.2 ± 0.1	0.136
	24 hours ambulatory blood pressure tertile			
24 hours Systolic BP (mm Hg)	*Low (n = 26)*	*Middle (n = 23)*	*High (n = 24)*	*p-value*
Total WMH (%)	116.7 ± 1.4	130.4 ± 0.7	144.1 ± 1.3	
Mobility assessments	1.4 ± 0.2	1.2 ± 0.2	2.03 ± 0.3	**0.034**
Tinetti Gait	11.2 ± 0.3	11.8 ± 0.1	10.8 ± 0.3	**0.025**
Stair descent time (second)	6.4 ± 0.8	5.1 ± 0.4	7.1 ± 0.4	**0.016**
Maximal gait velocity (m/s)	0.71 ± 0.04	0.78 ± 0.03	0.65 ± 0.03	**0.045**
Walk time (second)	3.1 ± 0.1	2.8 ± 0.1	3.6 ± 0.2	**0.002**

Unpublished data from our cohort study[54]; WMH: White matter hyperintensity lesions; m/s: meters/second; Significant values are bold typeface

higher ambulatory BP group decreased 0.15 m/second more than that in the low BP group and while this difference appears small, it represents a between-group change after only 2 years of observation.[54] Mobility limitation linked to WMH occurs gradually so that this decrement may be part of a long-term process that compromises gait velocity over 10 or more years. These data have suggested that an intervention using mean 24 hours systolic BP as the target could reduce progression of microvascular disease in the elderly and thus favorably impact function.

The results of our cohort studies have been supported by a larger longitudinal population-based study of 665 persons from the Rotterdam study.[55] Over a 5 years period, clinic BP and WMH lesion progression were measured 3.5 years apart, and after adjusting for baseline WMH, only systolic BP was significantly associated with progression (0.05 mL/year of standard deviation (SD) increase). Of interest, people with uncontrolled and untreated hypertension had significantly greater white matter lesion progression than people with uncontrolled but treated hypertension (Fig. 2). These studies suggest that antihypertensive treatment could reduce white matter lesion progression in uncontrolled hypertension. However, guiding therapy through the use of ambulatory BP monitoring could make this process more precise since ambulatory BP is more reproducible than clinic BP in older people[67] and ambulatory BP recordings would provide a means to target BP elevations during sleep, a period that is strongly related to WMH and cerebrovascular disease.[54,68]

The INFINITY Study

The Intensive versus Standard Ambulatory Blood Pressure Lowering to Prevent Functional DecliNe in The ElderlY (INFINITY) study[69] has been designed to evaluate the functional impact of a clinically relevant separation in 24 hours mean ambulatory systolic BP in an older population (i.e., < 130 mm Hg *vs* < 145 mm Hg). The study has been designed to evaluate these two levels of ambulatory BP control in hypertensive individuals 75 years or older with normal or mildly impaired mobility and cognition who already have detectable cerebrovascular disease (≥ 0.5% WMH fraction of intracranial volume). The key outcomes monitored over the 3 years of the trial are white matter lesion progression and measures of mobility and cognition. INFINITY is a prospective, randomized, open-label trial with blinded end points that will evaluate the changes from baseline in mobility and cognitive function and accumulation of WMH volume and changes in diffusion tensor imaging.

Our objective is to achieve a 24 hours systolic BP of ≤ 130 mm Hg in an intensively treated group or standard goal of 24 hours systolic BP of ≤ 145 mm Hg for a total of 36 months using similar classes of antihypertensive

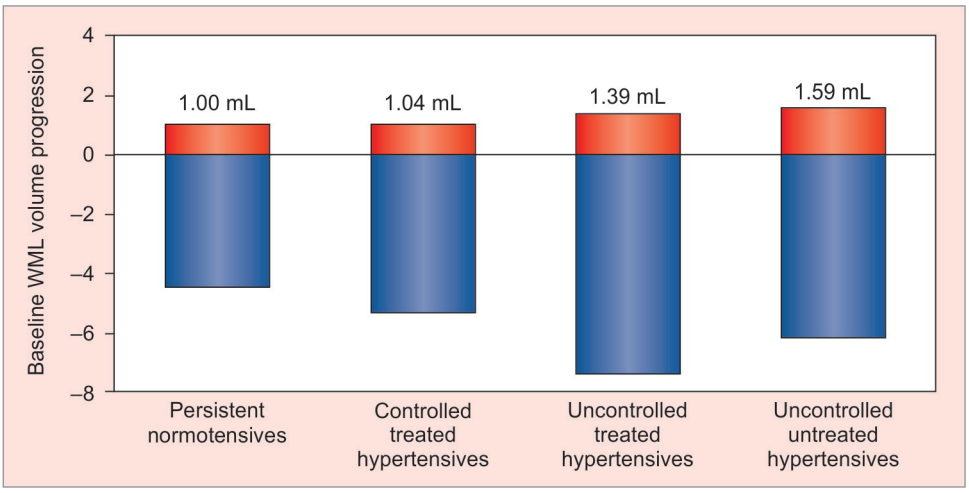

Fig. 2: Mean WML progression in mL (95% confidence interval [CI]; black bars) on top of the baseline WML volume (gray bars) for four blood pressure categories. Categories were defined as follows based on their mean blood pressure and medication use in the 5 years before the first scan: (1) Normotensives: Normal mean blood pressure and receiving no antihypertensive medication (n = 255); (2) controlled treated hypertensives: Normal mean blood pressure and receiving antihypertensive medication (n = 83); (3) uncontrolled treated hypertensives: Hypertensive mean blood pressure and receiving antihypertensive medication (n = 155); and (4) uncontrolled untreated hypertensives: Hypertensive mean blood pressure and receiving no antihypertensive medication (n = 172). Hypertensive mean blood pressure was defined as diastolic blood pressure ≥ 90 mm Hg or systolic blood pressure ≥ 140 mm Hg. A statistically significant difference in WML progression was observed between the uncontrolled untreated hypertensive group and the uncontrolled treated hypertensive group, after adjusting age, sex, intracranial volume, time between scans, and the baseline WML load ($p < 0.05$) (From Verhaaren et al (2013)[55] with permission from the American Heart Association)

therapies. Data from the Hypertension in the Very Elderly Trial (HYVET) demonstrated that antihypertensive therapy decreases stroke mortality in patients in their mid-80s.[70] In HYVET, the goal of therapy was to reduce systolic BP to < 150 mm Hg, and this intervention did result in a 39% reduction in stroke mortality that was related to a 15 mm Hg difference in systolic BP between the active treatment and placebo groups. The goal of the standard of care 24 hours mean ambulatory systolic BP in this age group is 140 to 145 mm Hg. No clinical trial in older patients with systolic hypertension has used ambulatory BP to guide therapy and to specifically assess cerebrovascular outcomes. The INFINITY trial will be the first study to guide antihypertensive therapy using ambulatory BP monitoring rather than clinic BP to reduce small vessel disease of the brain. Initiated in 2012, we project that the study will be completed in 2018.[69]

DISCLOSURES

Neither of the authors has any disclosures related to the content and topic of this manuscript.

REFERENCES

1. Longstreth WT Jr, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, Enright PL, O'Leary D, Fried L. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke 1996 Aug;27(8):1274-1282.
2. Yikoski A, Erkinjuntti T, Raininko R, Sarna S, Sulkava R, Tilvis R. White matter hyperintensities on MRI in the neurologically nondiseased elderly. Analysis of cohorts of consecutive subjects aged 55 to 85 years living at home. Stroke 1995 Jul;26(7):1171-1177.
3. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010 Jul;9(7):689-701.
4. van Dijk EJ, Prins ND, Vermeer SE, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM. C-reactive protein and cerebral small-vessel disease: the Rotterdam Scan Study. Circulation 2005 Aug;112:900-905.
5. Gouw AA, Seewann A, van der Flier WM, Barkhof F, Rozemuller AM, Scheltens P, Geurts JJ. Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. J Neurol Neurosurg Psychiatry 2011 Feb;82(2):126-135.
6. Marstrand JR, Garde E, Rostrup E, Ring P, Rosenbaum S, Mortensen EL, Larsson HB. Cerebral perfusion and cerebrovascular reactivity are reduced in white matter hyperintensities. Stroke 2002 Apr;33(4):972-976.
7. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013 Aug;12:822-828.
8. Wolfson L, Wakefield DB, Moscufo N, Kaplan RF, Hall CB, Schmidt JA, Guttmann CR, White WB. Rapid buildup of brain white matter hyperintensities over 4 years linked to ambulatory blood pressure, mobility, cognition, and depression in old persons. J Gerontol A Biol Sci Med Sci 2013 Nov;68(11):1387-1394.
9. Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Jolles J, Koudstaal PJ, Hofman A, Breteler MM. Cerebral small-vessel disease and decline in information processing speed, executive function and memory. Brain 2005 Sep;128(Pt 9):2034-2041.
10. Zheng JJ, Lord SR, Close JC, Sachdev PS, Wen W, Brodaty H, Delbaere K. Brain white matter hyperintensities, executive dysfunction, instability, and falls in older people: a prospective cohort study. J Gerontol A Biol Sci Med Sci 2012 Oct;67(10):1085-1091.
11. Debette S, Beiser A, DeCarli C, Au R, Himali JJ, Kelly-Hayes M, Romero JR, Kase CS, Wolf PA, Seshadri S. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study. Stroke 2010 Apr;41(4):600-606.
12. Kuller LH, Shemanski L, Manolio T, Haan M, Fried L, Bryan N, Burke GL, Tracy R, Bhadelia R. Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study. Stroke 1998 Feb;29(2):388-398.
13. Smith EE, Egorova S, Blacker D, Killiany RJ, Muzikansky A, Dickerson BC, Tanzi RE, Albert MS, Greenberg SM, Guttmann CR. Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. Arch Neurol 2008 Jan;65(1):94-100.
14. Silvert LC, Howieson DB, Dodge H, Kaye JA. Cognitive impairment risk: white matter hyperintensity progression matters. Neurology 2009 Jul;73(2):120-125.
15. Smith EE, Gurol ME, Eng JA, Engel CR, Nguyen TN, Rosand J. White matter lesions, cognition, and recurrent hemorrahage in lobar intracerebral hemorrhage. Neurology 2004 Nov;63(9):1606-1612.
16. Dufouil C, Godin O, Chalmers J, Coskun O, MacMahon S, Tzourio-Mazoyer N, Bousser MG, Anderson C, Mazoyer B, Tzourio C, et al. Severe cerebral white matter hyperintensities predict severe cognitive decline in patients with cerebrovascular disease history. Stroke 2009 Jun;40(6):2219-2221.
17. Jokinen H, Kalska H, Ylikoski R, Madureira S, Verdelho A, van der Flier WM, Scheltens P, Barkhof F, Visser MC, Fazekas F, et al. Longitudinal cognitive decline in subcortical ischemic vascular disease—the LADIS Study. Cerebrovasc Dis 2009;27(4):384-391.
18. Debette S, Bombois S, Bruandet A, Delbeuck X, Lepoittevin S, Delmaire C, Leys D, Pasquier F. Subcortical hyperintensities are associated with cognitive decline in patients with mild cognitive impairment. Stroke 2007 Nov;38(11):2924-2930.
19. Haley AP, Hoth KF, Gunstad J, Paul RH, Jefferson AL, Tate DF, Ono M, Jerskey BA, Poppas A, Sweet LH, et al. Subjective cognitive complaints relate to white matter hyperintensities and future cognitive decline in patients with cardiovascular disease. Am J Geriatr Psychiatry 2009 Nov;17(11):976-985.
20. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2010 Jul;341:c3666.
21. Baezner H, Blahak C, Poggesi A, Pantoni L, Inzitari D, Chabriat H, Erkinjuntti T, Fazekas F, Ferro JM, Langhorne P, et al. Association of gait and balance disorders with age-related white matter changes: the LADIS study. Neurology 2008 Mar;70(12):935-942.

22. Soumaré A, Elbaz A, Zhu Y, Maillard P, Crivello F, Tavernier B, Dufouil C, Mazoyer B, Tzourio C. White matter lesions volume and motor performances in the elderly. Ann Neurol 2009 Jun;65(6):706-715.
23. Salles GF, Reboldi G, Fagard RH, Cardoso CR, Pierdomenico SD, Verdecchia P, Eguchi K, Kario K, Hoshide S, Polonia J, et al. Prognostic effect of the nocturnal blood pressure fall in hypertensive patients: the ambulatory blood pressure collaboration in patients with hypertension (ABC-H) meta-analysis. Hypertension 2016 Apr;67(4):693-700.
24. Verdecchia P, Angeli F, Mazzotta G, Garofoli M, Ramundo E, Gentile G, Ambrosio G, Reboldi G. Day-night dip and early-morning surge in blood pressure in hypertension: prognostic implications. Hypertension 2012 Jul;60(1):34-42.
25. Satoh M, Asayama K, Kikuya M, Inoue R, Metoki H, Hosaka M, Tsubota-Utsugi M, Obara T, Ishiguro A, Murakami K, et al. Long-term stroke risk due to partial white-coat or masked hypertension based on home and ambulatory blood pressure measurements: the Ohasama Study. Hypertension 2016 Jan;67(1):48-55.
26. Li Y, Wei FF, Thijs L, Boggia J, Asayama K, Hansen TW, Kikuya M, Björklund-Bodegård K, Ohkubo T, Jeppesen J, et al. Ambulatory hypertension subtypes and 24 hour systolic and diastolic blood pressure as distinct outcome predictors in 8341 untreated people recruited from 12 populations. Circulation 2014 Aug;130(6):466-474.
27. Niiranen TJ, Mäki J, Puukka P, Karanko H, Jula AM. Office, home and ambulatory blood pressures as predictors of cardiovascular risk. Hypertension 2014 Aug;64(2):281-286.
28. ABC-H Investigators, Roush GC, Fagard RH, Salles GF, Pierdomenico SD, Reboldi G, Verdecchia P, Eguchi K, Kario K, Hoshide S, et al. Prognostic impact from clinic, daytime, and night-time systolic blood pressure in nine cohorts of 13,844 patients with hypertension. J Hypertens 2014 Dec;32(12): 2332-2340.
29. Draman MS, Dolan E, van der Poel L, Tun TK, McDermott JH, Sreenan S, O'Brien E. The importance of night-time systolic blood pressure in diabetic patients: Dublin Outcome Study. J Hypertens 2015 Jul;33(7):1373-1377.
30. Yano Y, Bakris GL, Matsushita K, Hoshide S, Shimada K, Kario K. Both chronic kidney disease and nocturnal blood pressure associate with strokes in the elderly. Am J Nephrol 2013;38(3):195-203.
31. Sheppard JP, Hodgkinson J, Riley R, Martin U, Bayliss S, McManus RJ. Prognostic significance of the morning blood pressure surge in clinical practice: a systematic review. Am J Hypertens 2015 Jan;28(1):30-41.
32. Bastos, FilipaS, Joana S, Raquel F, Polonia J. The prognostic value of ambulatory arterial stiffness index as a predictor of cardiovascular events in resistant hypertensive patients? J Hypertens 2015 Jun;33 (Suppl 1):e74.
33. Aznaouridis K, Vlachopoulos C, Protogerou A, Stefanadis C. Ambulatory systolic-diastolic pressure regression index as a predictor of clinical events: a meta-analysis of longitudinal studies. Stroke 2012 Mar;43(3):733-739.
34. Filomena J, Riba-Llena I, Vinyoles E, Tovar JL, Mundet X, Castañé X, Vilar A, López-Rueda A, Jiménez-Baladó J, Cartanyà A, et al. Short-term blood pressure variability relates to the presence of subclinical brain small vessel disease in primary hypertension. Hypertension 2015 Sep;66(3):634-640.
35. Eguchi K, Hoshide S, Schwartz JE, Shimada K, Kario K. Visit-to-visit and ambulatory blood pressure variability as predictors of incident cardiovascular events in patients with hypertension. Am J Hypertens 2012 Sep;25(9):962-968.
36. Hermida RC, Ayala DE, Smolensky MH, Fernández JR, Mojón A, Portaluppi F. Chronotherapy with conventional blood pressure medications improves management of hypertension and reduces cardiovascular and stroke risks. Hypertens Res 2016 May;39(5):277-292.
37. Hermida RC, Ayala DE, Fernández JR, Mojón A. Sleep-time blood pressure: prognostic value and relevance as a therapeutic target for cardiovascular risk reduction. Chronobiol Int 2013 Mar;30(1-2):68-86.
38. Castilla-Guerra L, Fernandez-Moreno Mdel C. Chronic management of hypertension after stroke: the role of ambulatory blood pressure monitoring. J Stroke 2016 Jan;18(1): 31-37.
39. Arima H, Chalmers J. PROGRESS: prevention of recurrent stroke. J Clin Hypertens (Greenwich) 2011 Sep;13(9):693-702.
40. Park JH, Lee HS, Kim JH, Lee JH, Kim J, Choi SW. Reverse dipper and high night-time heart rate in acute stage of cerebral infarction are associated with increased mortality. J Stroke Cerebrovasc Dis 2014 May-Jun;23(5):1171-1176.
41. Cugini P, Tubani L, Sesana G, Capodaglio PF, Laganà B, Salandri A, Petrangeli CM, Baratta L. The role and chrono-biometric study of ambulatory arterial pressure monitoring in hypertensive patients with a recent cerebral ischemia episode. Recenti Prog Med 1997 Sep;88(9):383-387.
42. Zakopoulos N, Spengos K, Tsivgoulis G, Zis V, Manios E, Vemmos K. Assessment of blood pressure control in hypertensive stroke survivors: an ambulatory blood pressure monitoring study. Blood Press Monit 2006 Oct;11(5):235-241.
43. Castilla-Guerra L, Fernández-Moreno Mdel C, Espino-Montoro A, López-Chozas JM. Ambulatory blood pressure monitoring in stroke survivors: do we really control our patients? Eur J Intern Med 2009 Dec;20(8):760-763.
44. Sasaki M, Ando H, Fujimura A. Lack of nocturnal blood pressure fall in elderly bedridden hypertensive patients with cerebrovascular disease. Chronobiol Int 2012 Feb;29(1): 62-65.
45. Kakaletsis N, Ntaios G, Milionis H, Haidich AB, Makaritsis K, Savopoulos C, Berge E, Hatzitolios AI. Prognostic value of 24-h ABPM in acute ischemic stroke for short-, medium-, and long-term outcome: a systematic review and meta-analysis. Int J Stroke 2015 Oct;10(7):1000-1007.
46. Skalidi SJ, Manios ED, Stamatelopoulos KS, Barlas G, Michas F, Toumanidis ST, Vemmos KN, Zakopoulos NA. Brain edema formation is associated with the time rate of blood pressure variation in acute stroke patients. Blood Press Monit 2013 Aug;18(4):203-207.
47. Zis P, Vemmos K, Spengos K, Manios E, Zis V, Dimopoulos MA, Zakopoulos N. Ambulatory blood pressure monitoring in acute stroke: pathophysiology of the time rate of blood pressure variation and association with the 1-year outcome. Blood Press Monit 2013 Apr;18(2):94-100.
48. Klarenbeek P, van Oostenbrugge RJ, Rouhl RP, Knottnerus IL, Staals J. Higher ambulatory blood pressure relates to new cerebral microbleeds: 2-year follow-up study in lacunar stroke patients. Stroke 2013 Apr;44(4):978-983.
49. Tomii Y, Toyoda K, Suzuki R, Naganuma M, Fujinami J, Yokota C, Minematsu K. Effects of 24 hour blood pressure and heart rate recorded with ambulatory blood pressure monitoring on recovery from acute ischemic stroke. Stroke 2011 Dec;42(12):3511-3517.

50. Castilla-Guerra L, Fernandez-Moreno Mdel C, Alvarez-Suero J, Jimenez-Hernandez MD. Can the treatment of arterial hypertension help to prevent dementia? Rev Neurol 2013 Jan;56(2):91-100.
51. Ovbiagele B, Diener HC, Yusuf S, Martin RH, Cotton D, Vinisko R, Donnan GA, Bath PM, PROFESS Investigators. Level of systolic blood pressure within the normal range and risk of recurrent stroke. JAMA 2011 Nov;306(19):2137-2144.
52. Ovbiagele B. Low-Normal systolic blood pressure and secondary stroke risk. J Stroke Cerebrovasc Dis 2013 Jul;22(5): 633-638.
53. deLeeuw FE, de Groot JC, Oudkerk M, Witteman JC, Hofman A, van Gijn J, Breteler MM. A follow-up study of blood pressure and cerebral white matter lesions. Ann Neurol 1999 Dec;46(6):827-833.
54. White WB, Wolfson L, Wakefield DB, Hall CB, Campbell P, Moscufo N, Schmidt J, Kaplan RF, Pearlson G, Guttmann CR. Average daily blood pressure, not office blood pressure, is associated with progression of cerebrovascular disease and cognitive decline in older people. Circulation 2011 Nov 22;124(21):2312-2319.
55. Verhaaren BF, Vernooij MW, de Boer R, Hofman A, Niessen WJ, van der Lugt A, Ikram MA. High blood pressure and cerebral white matter lesion progression in the general population. Hypertension 2013 Jun;61(6):1354-1359.
56. Wolfson, L. Microalbuminurea as an index of brain microvascular dysfunction. J Neurol Sci 2008;272:34-35.
57. Kuller LH, Longstreth WT Jr. Arnold AM, Bernick C, Bryan RN, Beauchamp NJ Jr. Cardiovascular Health Study Collaborative Research Group. White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. Stroke 2004 Aug;35(8):1821-1825.
58. Rosenberg GA. Matrix metalloproteinases and their multiple roles in neurodegenerative diseases. Lancet Neurol 2009 Feb;8(2):205-216.
59. Benson RR1, Guttmann CR, Wei X, Warfield SK, Hall C, Schmidt JA, Kikinis R, Wolfson LI. Older people with impaired mobility have specific loci of periventricular abnormality on MRI. Neurology 2002 Jan;58(1):48-55.
60. Baloh RW, Yue Q, Socotch TM, Jacobson KM. White matter lesions and disequilibrium in older people. I. Case-control comparison. Arch Neurol 1995 Oct;52(10):970-974.
61. Sakakibara R, Hattori T, Uchiyama T, Yamanishi T. Urinary function in elderly people with and without leukoaraiosis: relation to cognitive and gait function. J Neurol Neurosurg Psychiatry 1999;67(5):658-660.
62. Junqué C, Pujol J, Vendrell P, Bruna O, Jódar M, Ribas JC, Viñas J, Capdevila A, Marti-Vilalta JL. Leuko-araiosis on magnetic resonance imaging and speed of mental processing. Arch Neurol 1990 Feb;47(2):151-156.
63. Kuchel GA, Moscufo N, Guttmann CR, Zeevi N, Wakefield D, Schmidt J, Dubeau CE, Wolfson L. Localization of brain white matter hyperintensities and urinary incontinence in community-dwelling older adults. J Gerontol A Biol Sci Med Sci 2009 Aug;64(8):902-909.
64. Kaplan RF, Cohen RA, Moscufo N, Guttmann C, Chasman J, Buttaro M, Hall CH, Wolfson L. Demographic and biological influences on cognitive reserve. J Clin Exp Neuropsychol 2009 Oct;31(7):868-876.
65. Moscufo N, Guttmann CR, Meier D, Csapo I, Hildenbrand PG, Healy BC, Schmidt JA, Wolfson L. Brain regional lesion burden and impaired mobility in the elderly. Neurobiol Aging 2011 Apr;32(4):646-654.
66. Moscufo N, Wolfson L, Meier D, Liguori M, Hildenbrand PG, Wakefield D, Schmidt JA, Pearlson GD, Guttmann CR. Mobility decline in the elderly relates to lesion accrual in the splenium of the corpus callosum. Age 2012 Apr;34(2):405-414.
67. Campbell P, Ghuman N, Wakefield D, Wolfson L, White WB. Long-term reproducibility of ambulatory blood pressure is superior to office blood pressure in the very elderly. J Hum Hypertens 2010 Nov;24(11):749-754.
68. White WB, Mansoor GA, Tendler BE, Anwar YA. Nocturnal blood pressure epidemiology, determinants, and effects of antihypertensive therapy. Blood Press Monit 1998 Feb;3(1): 43-51.
69. White WB, Marfatia R, Schmidt J, Wakefield DB, Kaplan RW, Bohannon CB, Hall CB, Guttmann CR, Moscufo N, Fellows D, et al. INtensive versus standard ambulatory blood pressure lowering to prevent functional DeclINE in the ElderlY (INFINITY). Am Heart J 2013 Mar;165(3):258-265.
70. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008 May 1;358(18):1887-1898.