White-coat hypertension/effect is associated with higher arterial stiffness and stroke events

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WHITE COAT HYPERTENSION/EFFECT IS ASSOCIATED WITH HIGHER ARTERIAL STIFFNESS AND STROKE EVENTS

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WHITE COAT HYPERTENSION/EFFECT RISK

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ABSTRACT:

Objectives: The risk profile of white coat hypertension/effect (WCH/E) remains unclear. This study aimed to investigate the relationship between WCH/E, markers of cardiovascular risk and cerebrovascular events.

Methods: This is a sub-group analysis of The Arterial Stiffness In lacunar Stroke and Transient ischemic attack (ASIST) study, which recruited ninety-six patients aged ≥40-years-old with a diagnosis of transient ischemic attack or lacunar stroke in the preceding 14 days. Thirty-two patients with target blood pressure (clinic blood pressure <140/90mmHg and day-time ambulatory blood pressure <135/85mmHg) and thirty patients with WCH/E (clinic blood pressure ≥140/90mmHg and day-time ambulatory blood pressure <135/85mmHg) were included in the analysis.

Results: Patients with WCH/E were older and had a higher body mass index. Central systolic (145±13 vs 118±8mmHg, p<0.001) and diastolic blood pressures (82±8 vs 76±7mmHg, p=0.004) were higher in those with WCH/E. They also had higher arterial stiffness measured by carotid-femoral pulse wave velocity (11.9±3.0 vs 9.6±2.3m/s, p=0.002) and cardio-ankle vascular index (10.3±1.3 vs 9.4±1.7, p=0.027). Regression analysis showed an independent relationship between WCH/E and both measures of arterial stiffness. Lacunar strokes were more prevalent in those with WCH/E (47% vs 22%, p=0.039) and individuals in this group were more likely to have had a lacunar stroke than a transient ischemic attack (odds ratio 9.6, 95% CI 1.5-62.6, p=0.02).

Conclusion: In this cohort of patients with lacunar stroke and transient ischemic attack, WCH/E was associated with elevated markers of cardiovascular risk and a higher

prevalence of lacunar stroke. These results suggest that WCH/E is associated with adverse cardiovascular risk.

Keywords:

White Coat Hypertension, Blood Pressure, Arterial Stiffness, Stroke

INTRODUCTION

White coat hypertension (WCH) is characterised by elevated clinic blood pressure (BP) in the presence of normal ambulatory or home values. The term WCH is usually reserved for patients who are not taking anti-hypertensive medications. On the other hand, the white coat effect (WCE) describes elevated clinic BP and a lower home or ambulatory BP in both untreated and treated patients who have established hypertension.

WCH is common and has an estimated prevalence of 13%.(1) There is an existing body of evidence that has begun to establish a link between WCH and risk factors for cardiovascular disease. Individuals with WCH have elevated markers of inflammation and endothelial damage compared to those with normotension. These inflammatory markers have a positive correlation with carotid intima–media thickness, which in turn is indicative of atherosclerosis.(2,3) Those with WCH are also three-times more likely to transition to sustained hypertension than those with normal BP.(4) Cardiovascular outcomes are also thought to be worse in individuals with WCH. This is demonstrated by a meta-analysis that studied over 20,000 patients with a mixed anti-hypertensive treatment status. Compared to normotensives, those with WCH had an increased risk of cardiovascular disease and total mortality.(5)

The association between WCH and transient ischemic attack (TIA) or stroke is less understood. The largest prospective study to date has suggested that WCH is associated with an increased incidence of stroke after the sixth year of follow up.(6) The mechanism

for this is unclear, but the authors speculate that the frequent peaks in BP seen in individuals with WCH might contribute to carotid atherosclerosis and ultimately stroke. This association is in contrast with a more recent meta-analysis of 14 studies containing a total of 29,000 participants which showed no significant difference in the risk of stroke between individuals with WCH and normotension.(7) Further characterisation of the relationship between WCH and the risk of TIA or stroke is required.

Arterial stiffness is a marker of vascular structure and function.(8) There is a well characterised relationship between increased arterial stiffness and risk of coronary heart disease and stroke. This relationship is present even after adjusting for standard cardiovascular risk factors.(9) There is also some evidence suggesting that individuals with WCH have higher aortic stiffness than those with normal BP.(10) However, the actual relationship between WCH, arterial stiffness and cerebrovascular disease remains unclear.

This study aims to investigate the risk associated with white coat hypertension/effect (WCH/E) in a cohort of patients with a recent TIA or lacunar stroke by comparing: i) arterial stiffness measures and ii) clinical event type in patients with WCH/E vs. those with target blood pressure.

METHODS

This was a sub-group analysis of the arterial stiffness and lacunar stroke and TIA (ASIST) study (IRAS ID: 144157, approved by London – Harrow Research Ethics Committee, NHS REC: 14/LO/0189). Potential participants were identified from rapid access TIA clinics and inpatient wards. Ninety-six patients aged >40 years with a confirmed diagnosis of TIA (focal neurological deficit resolving within 24 hours of onset) or lacunar stroke (focal neurological deficit not resolving within 24 hours accompanied by ischemic changes on brain imaging) in the preceding 14 days were recruited. Patients were excluded if they were undergoing treatment for malignancy, were unable to give informed consent or if they lost capacity during the trial period (data collected until the time of loss of capacity was included in all analyses). Informed consent was given by each of the patients in line with the principles set out by the Declaration of Helsinki.

Classification of BP phenotypes

Clinic (Omron 705IT, Omron Corporation, Kyoto – Japan) and ambulatory BP (Diasys Integra II, Novacor SA, Paris – France) were measured in accordance with national guidelines.(11) Of the 96 participants recruited, six participants declined ambulatory blood pressure monitoring (ABPM) and were excluded. Those with masked hypertension (n=3, clinic BP <140/90 mmHg, day-time ABPM ≥135/85) and sustained hypertension (n=25, clinic BP ≥140/90, day-time ABPM ≥135/85) were also excluded from the analysis. These exclusions left a cohort of patients with target BP (n=32, clinic BP <140/90 mmHg, day-time ABPM <135/85) and a cohort with white coat hypertension/effect (n=30, clinic

BP ≥140/90, day-time ABPM <135/85) (Figure 1). Participants taking anti-hypertensive medication were classified according to their treated BP, meaning both groups included untreated and treated individuals (Table 1).

Assessment of vascular health

Measurements of arterial stiffness were performed at room temperature, with the participant in a supine position and having rested for 10 minutes. Participants were asked to avoid the consumption of alcohol for 10 hours before assessment, and to avoid smoking, eating or caffeinated drinks for 3 hours before assessment. Arterial stiffness was measured using two techniques. Carotid-femoral pulse wave velocity (PWV) is the gold standard method for quantification of large artery stiffness.(12) It was measured using the Complior device (ALAM Medical, Saint Quentin Fallavier – France). Cardio-ankle vascular index (CAVI) is an alternative technique, which quantifies total arterial stiffness from the heart to the ankle. Unlike PWV, this measure is theoretically independent of BP.(13) CAVI was measured using the VaSera VS-1500N (Fukuda Denshi, Tokyo – Japan). Measurements were taken on the left and right side of the body and the mean of these values was used for analysis.

Central aortic pressures were captured non-invasively using radial artery applanation tonometry (SphygmoCor, AtCor Medical, Naperville – Illinois – USA), as described in full by Chen et al.(14) A generalised transfer function was applied to the radial pulse waveform to reconstruct the central aortic waveform from which aortic systolic and diastolic blood pressure are derived.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 25.0 (IBM Corp, Armonk – New York – USA). The Shapiro-Wilk test and Q-Q plots were used to assess data distribution. Comparison of continuous variables was performed using independent samples t-test for normally distributed data, or Mann-Whitney U test for non-normally distributed data. Comparison of categorical variables was performed using the chi-square test, or Fisher's exact test if >20% of cells had expected frequencies < 5. Multiple linear and binary logistic regression was then carried out to adjust for the influence of established cardiovascular and cerebrovascular risk factors (the presence of WCH/E, number of anti-hypertensive medications, 24-hour systolic BP [mmHg], age [years], male sex, body mass index [kg/m^2], current smoker, diabetes, total cholesterol [mmol/L], serum creatinine [μmol/L] and previous TIA/stroke). This allowed us to assess whether WCH/E was an independent determinant of vascular risk. All variables included in the regression analysis had a low degree of collinearity (tolerance value > 0.5).

RESULTS

In this study cohort, patients with WCH/E were older (75.7±9.3 vs 69.9±11.5 years, p=0.033), had a higher body mass index (28±4 vs 25±4 kg/m^2, p=0.014) and more commonly had a previous TIA/lacunar stroke (17 vs 9, p=0.023) when compared to those with target BP. As expected, both clinic systolic (155±13 vs 125±9 mmHg, p<0.001) and diastolic BP (81±8 vs 75±7 mmHg) were higher in WCH/E. Although ambulatory BP values remained within the normal range, those with WCH/E had significantly higher systolic BP in the day-time (121±10 vs 114±10 mmHg, p=0.007), night-time (113±14 vs 103±13 mmHg, p=0.007) and over 24-hours (119±9 vs 112±9 mmHg, p=0.003) (Table 2).

Prevalence of Lacunar Stroke/TIA

There was a greater prevalence of lacunar stroke amongst individuals with WCH/E (16 TIAs [53%] and 14 [47%] lacunar strokes). In comparison, individuals with target BP had 25 TIAs (78%) and 7 (22%) lacunar strokes (p=0.039) (Table 3). Binary logistic regression was used to investigate whether WCH/E was an independent predictor of lacunar stroke (Nagelkerke R^2=0.364) (Table 4). After adjusting for other cardiovascular risk factors in the model, patients with WCH/E were over 9 times more likely to have had a lacunar stroke than a TIA (odds ratio 9.6, 95% CI 1.5 - 62.6, p=0.02). All other variables had a statistically non-significant influence on the odds ratio for lacunar stroke.

Arterial stiffness

Participants with WCH/E had higher arterial stiffness than those with target BP, as measured by both PWV (11.9±3.0 m/s vs 9.6±2.3 m/s, p=0.002) and CAVI (10.3±1.2 vs 9.4±1.7, p=0.027) (Table 3). In the regression model for PWV (R^2=0.522), WCH/E was an independent determinant of PWV (unstandardized β co-efficient 2.0, 95% CI 0.3 - 3.8, p=0.02) (Table S1). Age was the only other variable with a statistically significant effect on PWV (unstandardized β co-efficient=0.1, 95% CI 0.01 - 0.17, p=0.03). WCH/E was a statistically significant determinant of CAVI after adjusting for the other variables included in the model (R^2=0.742; unstandardized β co-efficient=0.8, 95% CI 0.1 - 1.5, p=0.03) (Table S2). CAVI was also positively associated with 24-hour systolic BP (unstandardized β co-efficient 0.05, 95% CI 0.01 - 0.08, p=0.01), age (unstandardized β co-efficient 0.1, 95% CI 0.02 - 0.08, p<0.001) and male sex (unstandardized β co-efficient 1.4, 95% CI 0.7 - 2.1, p<0.001). CAVI was inversely related to body mass index (unstandardized β co-efficient=-0.2, 95% CI -0.3 - -0.1, p<0.001) and previous TIA or stroke (unstandardized β co-efficient -0.9, 95% CI -1.6 - -0.2, p=0.01).

Central blood pressure

Individuals with WCH/E had significantly higher central systolic (145±13 vs 118±8 mmHg, p<0.001) and central diastolic BP (82±8 vs 76±7 mmHg, p=0.004) (Table 3). Multiple linear regression was carried out using central systolic BP (R^2=0.779) and central diastolic BP (R^2 = 0.328) as dependent variables. WCH/E was a significant predictor of central systolic BP (unstandardized β co-efficient 21.1, 95% CI 14.3 - 28.0, p<0.001) and central

diastolic BP (unstandardized β co-efficient 7.1, 95% CI 1.4 - 12.8, p=0.02) (Tables S3 and S4). Central systolic BP was also affected by 24-hour systolic BP (unstandardized β co-efficient 0.7, 95% CI 0.3 - 1.0, p<0.001) and central diastolic BP was also affected by age (unstandardized β co-efficient -0.3, 95% CI -0.52 - -0.02, p=0.04).

DISCUSSION

In this study, we found a significantly higher prevalence of lacunar stroke in individuals with WCH/E compared to those with target BP. The association between WCH/E and lacunar stroke was independent of established cardiovascular and cerebrovascular risk factors. We also demonstrated higher arterial stiffness in the WCH/E cohort. Further analysis showed that WCH/E was an independent predictor of these risk markers.

WCH/E and prevalence of TIA/lacunar stroke

Lacunar stroke was significantly more prevalent in individuals with WCH/E compared to those with target BP. The association between these two variables was independent of established cardiovascular risk factors such as age, BMI, smoking status or total cholesterol. These findings are in agreement with a prospective study of over 4,000 patients.(6) In this study, those with WCH had an increased risk of stroke after six years of follow up and the risk exceeded that of sustained hypertension after the ninth year. When the entire study period was analysed (median of 5.4 years), they found no significant difference in the hazard ratio for stroke in WCH compared to normotension. This finding does not completely exclude the possibility that WCH is a risk factor for stroke, as the wide 95% confidence interval (0.61 - 2.16) suggests that the study may have been statistically underpowered. More recently, analysis of ambulatory BP databases and a meta-analysis did not find a significant association between WCH and increased risk of stroke.(7,15) Compared to our study, the studies outlined above

contain a much higher number of total participants. However, their findings were based on strokes which occurred during the follow up period meaning that conclusions are based on relatively few events. For example, the previously cited ambulatory BP database had just 30 stroke events in a cohort of over 2,000 individuals.(15) Our study only included patients with a recent diagnosis of TIA (n=41) or lacunar stroke (n=21) so the number of events is comparable to much larger studies.

One explanation of the association between WCH/E and TIA/Lacunar stroke may be that individuals with WCH/E exhibit similar BP surges throughout the day as they would in clinic. This is particularly evident during anxiety provoking events and may contribute to BP variability and therefore increased cardiovascular risk.(16)

WCH/E and central aortic blood pressure

One previous study has compared central BP in WCH and normotension. The investigators recruited 18 normotensives and 18 white coat hypertensives. Central BP was derived from radial artery applanation tonometry and aortic pulse wave analysis. Overall, they found a trend similar to ours, with central systolic BP being raised in subjects with WCH vs normotension (115.2 ± 2.9 vs 97.9±2.5 mmHg, $p<0.05$). However, it is difficult to draw a direct comparison. Firstly, they recruited only treatment naïve individuals, whereas our study included a mixed group of treated and untreated patients. Secondly, their participants were disease free at the time of recruitment, whereas all participants in our study had sustained a neurological insult.(17) It is known

that a neurological insult, such as a TIA or stroke, can impair cerebral autoregulation of BP. In the acute phase, there is a rise in systolic and diastolic BP, which gradually returns to a physiological baseline within 2 weeks.(18,19) This finding offers a plausible explanation as to why the average central systolic BP is 30 mmHg higher amongst our WCH/E cohort than that previously reported. (17)

WCH/E and arterial stiffness

Arterial stiffness measured by PWV and CAVI was significantly higher in the WCH/E group compared to the target BP group. These findings agree with a meta-analysis performed in a population with mixed anti-hypertensive treatment status. They found elevated PWV in individuals with WCH compared to those with normal BP (95% confidence interval: 0.61 – 1.05).(10) The absolute PWV values in each group are also worthy of consideration. European Society of Hypertension guidelines state that a carotid femoral PWV >10 m/s indicates arterial stiffness.(12) In our study, those with target BP fell below this threshold and those with WCH/E exceeded it (9.6±2.3 m/s and 11.9±3.0 m/s, respectively). This is particularly notable given the high proportion that were prescribed anti-hypertensive medication in this group (77%). Overall, these findings add to the growing evidence that WCH/E is associated with aortic stiffening measured by PWV. Aortic stiffening is indicative of greater cardiovascular and cerebrovascular risk.

CAVI was a previously unexplored parameter in cohorts of adult patients with WCH/E. We found that CAVI was significantly higher in those with WCH/E compared to patients with target BP. The reference values for individuals aged 70-74 with established risk factors are 9.8±1.1 in men and 9.3±1.0 in women.(20) In this study, mean CAVI in the WCH/E group (10.3±1.2) exceeded these values. The strong association between these variables is also illustrated by regression analysis, which showed WCH/E was an independent determinant of CAVI after adjusting for established vascular risk factors. In contrast to other studies, current smoking status did not have a statistically significant effect on CAVI.(21) This is likely to be because of the relatively small sample size of our study. To the best of our knowledge, this study is the first to suggest that arterial stiffness measured by CAVI is higher in adults with WCH/E compared to those with target BP. When considered alongside the existing evidence showing heightened aortic stiffness in WCH/E, this forms a strong argument that the vasculature of individuals with target BP and WCH/E differs. This may be due to early arterial aging.(22)

Limitations

There were several limitations to this study. Firstly, the cross-sectional study design meant that we could only identify association not causation. Secondly, the strength of the conclusions drawn from this study were limited by the small sample size. This also prevented the undertaking of subgroup analysis, such as by gender. Thirdly, we studied a mixed population in which 77% of the WCH/E group were on anti-hypertensive medication and the remainder were untreated. International guidelines state that the

term WCH should be applied to untreated patients only.(12) It is well documented that untreated and treated individuals with WCH differ in terms of their baseline characteristics and clinical outcomes.(23) It is therefore undesirable to combine these patients into the same group. In addition, treated individuals included in the group with target BP may in reality have had controlled sustained hypertension. This group has a much greater cardiovascular risk than untreated normotensives, meaning that ideally these patients should not be considered as a single group.(23) However, several other large studies of WCH have included both treated and untreated individuals, correcting for antihypertensive treatment in the analysis.(5, 6) We corrected for this in our model so we do not believe this affects the validity of our results.

Drug therapy and participant characteristics were similar for patients with target BP and WCH/E, however some differences could not be accounted for (Tables 1 and 2). Anti-hypertensive use did not differ significantly between groups, but we cannot exclude differences in the use of other drug classes that would affect the risk of stroke events, such as statins. However, the proportion of patients with a past medical history of hyperlipidaemia was similar between groups and all patients would be offered a statin following a TIA or lacunar stroke. Additionally, we were unable to adjust for clinic BP in our regression model due to collinearity with the presence of WCH/E. This is particularly a limitation in the interpretation of PWV which is dependent on BP at the time of measurement. However, as we have also shown higher arterial stiffness in the WCH/E group using CAVI (which is independent of BP), we believe our findings are still valid.

Lastly, the WCH/E group was older, had a higher body mass index, more commonly had a previous TIA or lacunar stroke and had significantly higher 24-hour systolic BP. These differences may be confounding the observed relationship between WCH/E and stroke in our study. We used regression analysis to adjust for their influence and WCH/E remained a significant predictor of all variables (prevalence of lacunar stroke, central systolic and diastolic blood pressure, pulse wave velocity and Cardio-Ankle Vascular Index). This suggests that the presence of WCH/E confers additional risk.

Future directions

In this cohort, WCH/E was associated with adverse markers of vascular function and a greater prevalence of lacunar stroke. These findings are in agreement with other studies showing higher vascular risk in patients with WCH. The application of this information to clinical practice is currently limited because we do not know whether the risk conferred by WCH can be attenuated by active management. This topic has been explored in two clinical trials that did not primarily intend to study WCH. The first of these trials suggested that active management of WCH conferred no benefit over placebo, but the second suggested that it reduced total mortality and cardiovascular events.(24,25) Evidently, a large prospective randomised controlled trial that investigates the effects of pharmacological treatment on the outcomes of patients with WCH is warranted to inform clinical guidelines for the management of WCH.

Conclusion

The risk-profile of WCH/E in relation to cardiovascular events is incompletely understood. We explored this topic using risk markers and clinical events (TIA vs lacunar stroke). Individuals with a recent TIA/stroke and WCH/E had higher central blood pressure and arterial stiffness than those with target BP, and they were more likely to have had a lacunar stroke. The association between WCH/E and these variables was independent of established vascular risk factors. Our findings add to the existing evidence that WCH/E is associated with increased vascular risk.

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REFERENCES

1. Fagard R, Cornelissen V. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis. Journal of Hypertension. 2007;25(11):2193-8.

2. Yavuzer S, Yavuzer H, Cengiz M, Erman H, Altıparmak M, Korkmazer B, et al. Endothelial damage in white coat hypertension: Role of lectin-like oxidized low-density lipoprotein-1. Journal of Human Hypertension. 2015;29(2):92–8.

3. Yavuzer H, Cengiz M, Yavuzer S, Altıparmak M, Korkmazer B, Balci H, et al. Procalcitonin and Pentraxin-3: Current biomarkers in inflammation in white coat hypertension. Journal of Human Hypertension. 2016;30(7):424–9.

4. Sivén SSE, Niiranen TJ, Kantola IM, Jula AM. White-coat and masked hypertension as risk factors for progression to sustained hypertension. Journal of Hypertension. 2016;34(1):54–60.

5. Huang Y, Huang W, Mai W, Cai X, An D, Liu Z, et al. White-coat hypertension is a risk factor for cardiovascular diseases and total mortality. Journal of hypertension. 2017;35(4):677–88.

6. Verdecchia P, Reboldi G, Angeli F, Schillaci G, Schwartz J, Pickering T, et al. Short- and Long-Term Incidence of Stroke in White-Coat Hypertension. Hypertension. 2005;45(2):203–8.

7. Briasoulis A, Androulakis E, Palla M, Papageorgiou N, Tousoulis D. White-coat hypertension and cardiovascular events. Journal of Hypertension.

2016;34(4):593–9.

8. Chen Y, Shen F, Liu J, Yang GJ. Arterial stiffness and stroke: de-stiffening strategy, a therapeutic target for stroke. BMJ. 2017;2(2):65–72.

9. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson S, Benjamin E, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. Journal of the American College of Cardiology. 2014;63(7):636–46.

10. Cai P, Peng Y, Wang Y, Wang X. Effect of white-coat hypertension on arterial stiffness. Medicine. 2018;97(42):e12888.

11. Hypertension in adults: diagnosis and Hypertension in adults: diagnosis and management management. Clinical guideline [Internet]. 2011. Available from: https://www.nice.org.uk/guidance/cg127/resources/hypertension-in-adults-diagnosis-and-management-pdf-35109454941637.

12. Williams B, Mancia G, Spiering W, Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal. 2018;39(33):3021–104.

13. Miyoshi T, Ito H. Assessment of Arterial Stiffness Using the Cardio-Ankle Vascular Index. Pulse. 2016;4(1):11–23.

14. Chen C-H, Nevo E, Fetics B, Pak P, Yin F, Maughan W, et al. Estimation of Central Aortic Pressure Waveform by Mathematical Transformation of Radial

Tonometry Pressure. Circulation. 1997;95(7):1827–36.

15. Tocci G, Presta V, Figliuzzi I, Attalla El Halabieh N, Battistoni A, Coluccia R, et al. Prevalence and clinical outcomes of white-coat and masked hypertension: Analysis of a large ambulatory blood pressure database. The Journal of Clinical Hypertension. 2018;20(2):297–305.

16. Mena LJ, Felix VG, Melgarejo JD, Maestre G. 24-Hour Blood Pressure Variability Assessed by Average Real Variability: A Systematic Review and Meta-Analysis. Journal of the American Heart Association. 2017;6:e006895.

17. Wimmer NJ, Sathi K, Chen TL, Townsend R, Cohen D. Comparison of Pulse Wave Analysis Between Persons With White Coat Hypertension and Normotensive Persons. The Journal of Clinical Hypertension. 2007;9(7):513–7.

18. Dawson SL, Blake MJ, Panerai RB, Potter J. Dynamic But Not Static Cerebral Autoregulation Is Impaired in Acute Ischaemic Stroke. Cerebrovascular Diseases. 2000;10(2):126–32.

19. Sugimori H, Ibayashi S, Fujii K, Yao H, Sadoshima S, Fujishima M. Brain Infarction Developed in Hypertensive and Normotensive Patients During Hospitalization—Hemodynamic Factors. Angiology. 1995;46(6):473–80.

20. Namekata T, Suzuki K, Ishizuka N, Shirai K. Establishing baseline criteria of cardio-ankle vascular index as a new indicator of arteriosclerosis: a cross-sectional study. BMC cardiovascular disorders. 2011;11:51.

21. Hata K, Nakagawa T, Mizuno M, Yanagi N, Kitamura H, Hayashi T, et al.

Relationship between smoking and a new index of arterial stiffness, the cardio-ankle vascular index, in male workers: a cross-sectional study. Tobacco induced diseases. 2012;10(1):11.

22. Sung S-H, Cheng H-M, Wang K-L, Yu W-C, Chuang S-Y, Ting C-T, et al. White coat hypertension is more risky than prehypertension: important role of arterial wave reflections. Hypertension. 2013 Jun;61(6):1346–53.

23. Stergiou G, Asayama K, Thijs L, Kollias A, Niiranen T, Hozawa A, et al. Prognosis of White-Coat and Masked Hypertension. Hypertension. 2014;63(4):675–82.

24. Fagard R, Staessen J, Thijs L, Gasowski J, Bulpitt C, Clement D, et al. Response to antihypertensive therapy in older patients with sustained and nonsustained systolic hypertension. Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Circulation. 2000;102(10):1139–44.

25. Bulpitt C, Beckett N, Peters R, Staessen J, Wang J-G, Comsa M, et al. Does White Coat Hypertension Require Treatment Over Age 80? Hypertension. 2013;61(1):89–94.

Table 1: Anti-hypertensive drug treatment in individuals with target BP and WCH/E.

	With target BP	**WCH/E**
	(n=32)	**(n=30)**
Receiving any anti-hypertensive drug	19 (59.4)	23 (76.7)
Mean number of anti-hypertensive drugs used amongst treated participants	1.6	1.4
Anti-hypertensive drug class		
ACE inhibitor or ARB	13 (40.6)	12 (40.0)
β-blocker	7 (21.9)	6 (20.0)
Calcium channel blocker	8 (25.0)	9 (30.0)
Diuretic	2 (6.3)	3 (10.0)
α-antagonist	1 (3.1)	1 (3.3)

Data displayed as number of participants (percentage of participants in that group).

Abbreviations: ACE=angiotensin-converting enzyme; ARB=angiotensin-II receptor blocker.

Table 2. Participant characteristics.

	With Target BP (n=32)	WCH/E (n=30)	P value
Demographics			
n (%)	32(52)	30 (48)	…
Age (years)	69.9±11.5	75.7±9.3	0.033
Male, n (%)	21(66)	22(73)	NS
Blood pressure variables			
Anti-hypertensive use, n (%)	19(59)	23(77)	NS
Clinic systolic BP (mmHg)	125±9	155±13	<0.001
Clinic diastolic BP (mmHg)	75±7	81±8	0.003
Day-time systolic BP (mmHg)	114±10	121±10	0.007
Day-time diastolic BP (mmHg)	73±7	72±7	NS
Night-time systolic BP (mmHg)	103±13	113±14	0.007
Night-time diastolic BP (mmHg)	65±7	67±8	NS
24-hour systolic BP (mmHg)	112±9	119±9	0.003
24-hour diastolic BP (mmHg)	72±6	71±6	NS
Past medical history			
Previous TIA/stroke, n (%)	9(28)	17(57)	0.023
Ischemic heart disease, n (%)	2(6)	6(20)	NS
Hyperlipidemia, n (%)	21(66)	19(63)	NS

Atrial fibrillation, n (%)	9(28)	5(17)	NS
Heart failure, n (%)	4(13)	1(3)	NS
Cardiovascular risk factors			
Body mass index (kg/m^2)	25±4	28±4	0.014
Current smoker, n (%)	5(16)	4(13)	NS
Diabetes, n (%)	6 (19)	9 (30)	NS
Total cholesterol (mmol/litre)	5.0±1.2	4.8±1.4	NS
HDL (mmol/litre)	1.6±0.5	1.6±0.5	NS
Serum creatinine (μmol/litre)	84.0±24.3	89.0±23.3	NS

Past medical history represents diagnoses made prior to the preceding 14 days and recruitment into the ASIST trial. Data expressed as mean ± standard deviation unless otherwise stated. An independent t test was carried out between participants with target BP vs WCH/E with a p value of ≤ 0.05 considered statistically significant.

Abbreviations; n = number of participants, NS = non-significant, BP = Blood pressure, TIA = Transient ischemic attack, HDL = high density lipoprotein.

Table 3. Comparison of surrogate markers of cardiovascular risk and cerebrovascular accidents.

	With target BP (n=32)	WCH/E (n=30)	P value
Prevalence of TIA/Lacunar stroke			
Transient ischemic attack, n (%)	25 (78)	16 (53)	0.039
Lacunar stroke, n (%)	7 (22)	14 (47)	
Central blood pressure			
Central systolic BP (mmHg)	118±8	145±13	< 0.001
Central diastolic BP (mmHg)	76±7	82±8	0.004
Arterial stiffness			
Pulse wave velocity (m/s)	9.6±2.3	11.9±3.0	0.002
Cardio-ankle vascular index	9.4±1.7	10.3±1.2	0.027

Data expressed as mean ± standard deviation unless otherwise stated. A p value of ≤ 0.05 is considered statistically significant. Abbreviations; TIA = Transient ischemic attack, BP = Blood pressure, n = number of participants.

Table 4. Binary logistic regression analysis with lacunar stroke as the dependent variable.

Variables	Odds ratio	95% CI	P value
WCH/E	9.6	1.5 - 62.6	0.02
Number of anti-hypertensives	2.3	0.9 - 6.2	NS
24-hour systolic BP (mmHg)	1.0	0.9 - 1.1	NS
Age (years)	0.9	0.9 - 1.0	NS
Male	1.7	0.2 - 13.8	NS
Body mass index (kg/m^2)	1.0	0.8 - 1.2	NS
Current smoker	2.3	0.3 - 17.5	NS
Diabetes	0.4	0.1 - 2.0	NS
Total cholesterol (mmol/L)	0.8	0.4 - 1.6	NS
Serum creatinine (μmol/L)	1.0	1.0 - 1.0	NS
Previous TIA/Stroke	1.1	0.2 - 6.0	NS

A p value of ≤ 0.05 is considered statistically significant. Abbreviations; CI = confidence interval, WCH/E = White coat hypertension/effect, NS = non-significant.

Please see Supplemental Digital Content for:

- Table S1: Multi-variable linear regression analysis with carotid-femoral PWV as the dependent variable.
- Table S2: Multi-variable linear regression analysis with CAVI as the dependent variable.
- Table S3: Multi-variable linear regression analysis with central systolic BP as the dependent variable.
- Table S4: Multi-variable linear regression analysis with central diastolic BP as the dependent variable.