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Effect of visit-to-visit blood pressure variability on cognitive and functional decline in mild to moderate Alzheimer's disease.

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Abstract

Introduction: Visit-to-visit blood pressure (BP) variability (VVV) is increasingly recognized as a marker of cardiovascular risk. Although implicated in cognitive decline, few studies are currently available assessing its effects on established dementia.

Objective: To investigate if VVV is associated with one-year rate of decline in measures of cognition and function in patients with mild to moderate Alzheimer's disease (AD) in the Doxycycline And Rifampicin for Alzheimer's Disease study.

Methods: Patients were included if ≥3 BP readings were available (n=392). VVV was defined using different approaches including the coefficient of variation (CV) in BP readings between visits. Outcomes included rates of decline in the Standardized Alzheimer's Disease Assessment Scale–Cognitive Subscale (SADAS-cog), Standardised MMSE, Clinical Dementia Rating Scale, the Quick Mild Cognitive Impairment screen and the Lawton-Brody activities of daily living (ADL) scale.

Results: Half of the patients (196/392) had a ≥4-point decline in the SADAS-cog over one-year. Using this cut-off, there were no statistically significant associations between any measures of VVV, for systolic or diastolic BP, with and without adjustment for potential confounders including treatment allocation, history of hypertension and use of anti-hypertensive and cognitive enhancing medications. Multiple regression models examining the association between systolic BP CV by quartile and decline over one-year likewise showed no clinically significant effects, apart from a U-shaped pattern of ADL decline of borderline clinical significance.

Conclusions: This observational study does not support recent research showing that VVV predicts cognitive decline in AD. Further studies are needed to clarify its effects on ADL in AD.

Key words: Visit-visit-variability, blood pressure variability, blood pressure, cognition, Alzheimer's disease

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Registration: The trial is registered at www.controlled-trials.com –ISRCTN15039674.

Introduction

Hypertension is associated with cerebrovascular disease and cognitive impairment [1,2], particularly among older people [3]. While there is some evidence that treatment of high blood pressure (BP) in those without cerebrovascular disease can prevent cognitive decline [4,5], there is growing evidence that raised and fluctuating BP are linked with a higher burden of white matter changes and subsequent cognitive decline [6,7]. While unclear, the mechanism is likely to be multifactorial, relating to the development of small vessel ischemia, compromised cerebral autoregulation [6] and the abnormal accumulation of amyloid beta [7].

Visit-to-visit blood pressure variability (VVV), fluctuations in BP readings across outpatient visits [8], is linked to atherosclerosis [9,10] and coronary heart disease [11]. A recent systematic review and meta-analysis of the effect of VVV suggests there are also associations with cardiovascular disease and all-cause mortality, albeit these are modest and limited by available data [12]. Persons with dementia have greater variability in VVV than aged-matched controls [13]. More recently, high VVV has also been associated with cognitive decline in Alzheimer's disease [14,15] and in those without established dementia [16] but not in fronto-temporal dementia [15] or with incident all-cause dementia [17] in community-dwelling older adults. Similar to its effects on stroke, it is implicated in the development of atherosclerosis and arterial stiffness that may ultimately lead to cognitive decline [18,19].

However, studies examining the effects of hypertension and BP variability on cognition are limited in number [20] and by the sensitivity and specificity of the instruments used to measure change, particularly the Mini-Mental State Examination (MMSE) [21], which has ceiling effects and is influenced by age, ethnicity, and education [22,23,24]. Data available are confined to observational cohort studies [14,15] or in samples without clearly established dementia. Further, to our knowledge, no studies have examined the effects of VVV on functional outcomes such as personal and instrumental activities of daily living (ADL) and global measures of socialisation, community affairs and hobbies in those with dementia, which are considered more important patient-centred outcomes that are frequently under-reported in dementia trials [25, 26].

Given these concerns, the aim of this study is to examine the effect of VVV on detailed, validated cognitive, ADL and global functional measures in those with established dementia using data from a completed randomised controlled trial (RCT) of patients with mild to moderate stage Alzheimer's disease (AD), followed over one year called the Doxycycline And Rifampicin for Alzheimer's Disease (DARAD) RCT [27].

Methods

Overview of the DARAD trial

Data collection

This analysis included data from the DARAD trial [27]. The methods of the DARAD have been reported elsewhere [27,28] but in summary, the DARAD was a multi-centre, blinded, RCT, conducted in 14 geriatric outpatient clinics in Canada between

2006 and 2010, comparing two antibiotics, doxycycline and rifampicin, to placebo to investigate if these can delay progression in mild to moderate stage AD over one year. AD was diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke criteria [27]. Those with established AD, aged ≥50 years, with adequate English language literacy and a Standardised MMSE (SMMSE) score between 14–26 out of 30 points (inclusive) were included. Neuroimaging with computed tomography (CT), ECG and laboratory testing were conducted to support inclusion and exclusion criteria. A sub-study, the DARAD-MRI, recruited 58 participants comparing magnetic resonance imaging (MRI) pre and post-treatment (ClinicalTrials.gov – NCT00692588). Only those with significant cerebrovascular disease or multi-infarct dementia, which is demonstrable on CT, were excluded. In total, 406 participants were randomized of whom 365 completed follow-up [27]. Full details of participant recruitment are available at www.controlled-trials.com –ISRCTN15039674 [24].

Outcome measures included in the DARAD

Assessments in the DARAD were performed at baseline, 3, 6, 9 and 12 months. Systolic and diastolic BP readings were recorded by a trained, dedicated research nurse at each visit, while sitting after five minutes rest using the same standard mercury sphygmomanometer. Available data included participants' age, gender, years of education and use of anti-hypertensives, cholinesterase inhibitors and or memantine. The co-primary outcomes were the Standardized Alzheimer's Disease Assessment Scale–Cognitive Subscale (SADAS-cog) [29] and the Clinical Dementia Rating Scale Sum of the Boxes (CDR-SB) [30]. Secondary outcomes included the Lawton-Brody ADL scale [31], the Quick Mild Cognitive Impairment (Q*mci*) screen [32], the Geriatric Depression Scale (GDS) [33], and the Cornell Scale for Depression in Dementia (CSDD) [34]. The SADAS-cog, CDR-SB, Q*mci* screen, SMMSE and Lawton-Brody scale were used in this analysis.

The SADAS-cog is composed of 11 subtests providing a score from 0–70; results ≥13 suggest impaired cognitive function. Elements include naming, commands, construction, orientation, word recognition, language, comprehension, word finding and recall. A four-point change in the SADAS-cog at six-months is taken by the US Food and Drug Administration to be the minimal important change required to confirm the benefit of any new medication [35]. The CDR-SB is a global cognitive measure incorporating memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care domains. It is scored from 0–18 with higher scores indicating greater cognitive impairment [30]. The Lawton-Brody ADL scale combines basic (ability to toilet, feed, dress, groom, bathe and walk) and instrumental (ability to shop, prepare food, perform housekeeping, wash laundry, arrange transport, administer medication, use a telephone and manage finances) ADLs across 14 categories and is scored from 14–64 points, where higher scores denote greater independence. The Q*mci* screen is a short cognitive screen, sensitive and specific in differentiating mild cognitive impairment and mild dementia from normal cognition, scored from 0–100 points, where lower scores indicate cognitive impairment incorporating six subtests: orientation, working memory,

verbal fluency, clock drawing, delayed recall and logical memory [36,37]. It can be substituted for SADAS-cog in clinical trials [38] and is widely validated [37, 39-43].

Analysis in this study

Visit-to-visit blood pressure variability

This study examined the effect of VVV on outcomes recorded within the DARAD trial. As no single approach to measuring VVV is currently accepted [8], we compared five recognized models [8] including the: (1) Standard Deviation (SD); (2) Coefficient of Variation in BP readings between visits (CV) calculated as the SD divided by mean BP over all available visits expressed as a percentage; (3) variation in BP independent of the mean (VIM), a transformation of SD uncorrelated to mean BP; (4) Average real variability (ARV); the average of absolute differences between successive BP measurements; (5) Delta BP defined as the maximum BP minus minimum BP. [8]. In general, these measures are strongly correlated and it is recommended that at least one metric of overall BP variability (SD, CV or VIM), variability between concentric visits (ARV) and of single extreme values (Delta BP) be included in the analysis [44]. These were calculated for both systolic and diastolic BP readings. Only participants with three or more interval BP readings available were included in this analysis. Missing data were not imputed.

Main analysis

Data were analysed using SPSS V25.0 (SPSS Inc., Chicago IL, USA). Data were normally distributed and analysed with parametric statistical approaches. Cognitive decline was calculated based on the change in each instrument over one year based on the difference between baseline and last available follow-up scores. Each measure of VVV was examined in turn as the independent variable. First, binary logistic regression was used to examine the association between SADAS-cog data, dichotomized into <4 or ≥4 points, considered a clinically important change [35], categorical outcomes and measures of VVV. Second, linear regression analysis was performed to explore the association between VVV and change in cognitive and functional scores as continuous variables. Cognitive and functional outcome measures were taken as the dependent variable (Model one).

Sensitivity analysis

Results were then adjusted for potential covariates in a sensitivity analysis; Model 2 controlling for sex, age, and educational level (<12 or ≥12 years) and Model 3 for the GDS, investigational product received (i.e. treatment allocation of either rifampicin and/or doxycycline or placebo), anti-hypertensive treatment, patient's average BP and use of cholinesterase inhibitors and/or memantine. An alternative sensitivity analysis (Model 3b), adjusting for baseline SMMSE, treatment allocation, depression (GDS and CSDD), the use of cognitive enhancers (cholinesterase inhibitors and/or memantine) and the use of centrally-acting angiotensin converting enzyme receptor inhibitors (ACEi) versus none, was conducted (see Appendix). The later was added as ACEis were the most commonly prescribed anti-hypertensive in this sample and our previous study showed that centrally-acting ACEi slowed functional and cognitive decline in this cohort [28]. There were insufficient numbers of other classes of anti-hypertensives available including Angiotensin II receptor blockers (ARBs), to conduct

a similar sensitivity analysis with these agents. To investigate the differential effects of minimum and maximum BP, participants were divided into mutually exclusive quartiles (Q) based on their systolic BP CV values: Q1 ≤5.9; Q2 6.0 – 8.3; Q3 8.4 – 10.7; Q4 ≥10.8. Multiple regression using ANOVA analysis was performed for Model 1, and ANCOVA for Models 2, 3 and 4. In a further sensitivity analysis, CV values were also divided into quintiles. CV was selected for this sub-analysis as it is independent of mean BP and is consistent with other studies allowing comparison [11,17].

Results

Characteristics of patients included in this analysis

Of the 406 participants available from the DARAD trial, 392 (97%) had at least three BP measurements over follow-up and were included in this analysis. The mean age of these was 77.67 years, standard deviation (SD) ±7.09 years; 49% were female. In all, 219 (56%) were hypertensive, 357 (91%) taking cholinesterase inhibitors and 60 (15%) memantine. There were no statistically significant differences in potentially cognitively enhancing medications, cholinesterase inhibitors (p=0.61) or memantine (p=1.0), gender (p=0.60) or years in education (p=0.93) between those included and those excluded from the analysis. Excluded participants were significantly older (p=0.004) but this was not clinically meaningful, both with a mean age of 77 years. The characteristics of participants included compared to those excluded and all patients recruited to the DARAD trial are presented in Table 1. The mean number of BP readings per participant included was 5.53 ±0.88. Mean systolic BP at baseline was 134.17 ±16.12 mmHg and 132.39 ±17.29 mmHg at the last available follow-up. Mean diastolic BP was 72.92 ± 10.30 mmHg at baseline compared to 72.59 ±10.59 mmHg at end-point. The mean CV of systolic BP was 8.77 ±3.85 versus 10.52 ±5.11 for diastolic BP.

Effect of VVV on cognitive and functional outcomes

At one year, 196/392 (50%), half of the sample had an increase of ≥4 points in the SADAS-cog (denoting cognitive decline). Binary logistic regression using the SADAS-cog as the categorical dependent variable, taking a deterioration of four points as clinically important [35], showed that there were no statistical associations between any of the measures of VVV, for either systolic or diastolic BP, with and without adjustment, and decline in the SADAS-cog during follow-up. The odds ratio for each was close to or equal to 1.0 as can be seen in Table 2. Examining the mean CV systolic and diastolic BP by quartile on change in the SADAS-cog showed no gradient effect with 95% CI all including the null. Using linear regression, examining each of the outcomes of interest in turn (i.e. SADAS-cog, CDR-SB, Lawton-Brody ADL scale, Q*mci* screen and SMMSE scores as continuous variables), similarly showed no statistically significant association with any of the measures of VVV. Sensitivity analysis showed that variables including the use of cholinesterase inhibitors, memantine and anti-hypertensives (any versus none), see models 2 and 3 above, did not influence these results, except for a weak but statistically significant association between reduced decline in Lawton-Brody ADL scale scores and systolic BP using Delta BP as a marker of VVV in model 3. All other reported coefficients were non-significantly different from 0, see Table 3. Adjusting for baseline cognition based on

SMMSE scores and centrally versus non-centrally acting ACEis in Model 3b reaffirmed that there were no significant associations (see Appendix).

Proportions of cognitive and functional decline

To assess the effects of minimal and maximal systolic BP we compared participants according to systolic BP CV values by quartiles using Q1 as the reference. The proportion with a ≥4 points increase in the SADAS-cog by BP CV quartile is presented in Figure 1; no statistically significant differences were seen for either systolic (p=0.54) or diastolic (p=0.27) readings (Table 2). Although Q2 of diastolic BP CV quartile was found to approach significance in model 1 (p=0.054) it was not statistically significant in model 2 (p=0.056) or model 3 (p=0.057) either. Multiple linear regression models showed no association between systolic blood pressure CV quartiles and each cognitive and functional outcome except for those in the third quartile with a CV in systolic BP of between 8.4 – 10.7, who had a significantly greater rate of decline in ADL compared to those in Q1. These data are presented in Table 4 and in Figure 2. However, there were no overall statistically significant differences in the rate of decline in ADL scores comparing all quartiles and this effect was lost when BP was divided into quintiles (see Table 5 in the Appendix). Otherwise, for unadjusted and adjusted models, no other significant results were found for any of the cognitive or functional outcome measures assessed.

Discussion

Overview

This study presents an examination of VVV in patients with established dementia participating in a RCT investigating rate of cognitive and functional decline after treatment with doxycycline or rifampin, alone or in combination, over one year. The findings of this observational secondary analysis do not suggest that VVV is associated with either cognitive or functional decline in those with mild to moderate stage AD. Similarly, the results do not suggest that low or high VVV predicts one-year change in scores. Irrespective of the approach to calculating VVV, no clinically significant association with rate of decline using a selection of validated outcome measures was consistently found for either systolic or diastolic BP. Sensitivity analysis showed that a wide variety of independent variables including use of any anti-hypertensive medication and cholinesterase inhibitors or memantine, did not influence associations. Data were also adjusted for depression as this may interact with systolic BP variability to hasten cognitive decline [45]. A small difference in rates of decline in ADL (for overall systolic BP delta and CV in the third quartile when these were examined by quartile) were of statistical significance. This may suggest that further research is needed to explore the effects of VVV on ADL, particularly as there is some evidence that higher VVV in systolic but not diastolic BP is associated with an increased rate of functional decline in ADL in older adults without established dementia [46]. Further, the results suggest a possible U-shaped association with more marked decline in ADL in those with higher and lower quartiles compared to the middle quartile (Q3), similar to a recent study showing this increases mortality in patients with cardiovascular disease [47]. However, as these changes were not seen for cognition and were lost when CV values were examined as quintiles, it is probable that they relate to multiplicity, although further exploration is needed.

Results in context

These results differ from those found in other observational studies of persons with mild-moderate stage AD with a similar age profile, which have found that BP VVV (specifically systolic BP variability) was associated with significant differences in decline in the MMSE over one year [14,15]. However, this to our knowledge is one of only a few studies investigating this and the first to examine the impact of VVV on cognition using more detailed neuropsychological testing including the standardized ADAS-cog, used by many regulatory authorities including the Food and Drug Administration in the United States to denote clinically meaningful change in dementia trials [35]. It is also the first to examine the effect on ADL. Other possible reasons that may account for the differences include the MMSE score at entry and differences in patient selection. While these results differ from the studies by Lattanzi et al [14,15], they do reflect the current lack of certainty regarding the significance of VVV for all cardiovascular outcomes [12]. To date, while there is data from meta-analysis showing that VVV is associated with increased mortality and incidence of cardiovascular disease and stroke, samples are heterogenous [12, 48,49], only modest supportive evidence is available [12, 49] and further studies are recommended to determine its significance [14] and confirm if there is any effect in established AD [20] or other dementia subtypes. Some recent studies including a post hoc analysis of the Systolic Blood Pressure Intervention (SPRINT) RCT have found no association between VVV in office BP and a composite end-point of fatal and nonfatal cardiovascular events, though these did not look at the effects of cognition [50]. Finally, it is suggested that older patients with established cerebrovascular disease and more cardiovascular co-morbidity may already be too advanced to detect the effects of VVV on dementia [17, 20].

Strengths and limitations

The strengths of this study include the RCT design with a relatively large sample size compared to other studies examining rate of cognitive decline in dementia, the standardisation of measurements, high rates of compliance with medications and measurement and relatively low loss to follow-up [27]. Further, the study included a range of cognitive and functional measures including the CDR-SB, allowing for more detailed investigation of the effects of VVV on those with mild to moderate AD than existing studies [14,15]. While the inclusion of a range of dependent variables, which were shown to have moderate to strong correlation with each other [38], could have increased the possibility of chance findings of significance, that it did not, serves to highlight the lack of association between VVV and decline in these patients. Limitations include the observational nature of the study and the relatively short-period of follow-up, one year (the duration of the DARAD trial was informed by a pilot RCT that showed possible benefits at one year [51]); it is possible that significant associations could be demonstrated over longer periods. This said, most studies in this area have used an observational design [20] and the only two comparable studies included smaller numbers, approximately 240 patients with AD in each, followed over a similar period, with patients who were not recruited within the framework of a rigorously controlled RCT [14,15]. In addition, the diagnosis of AD, while robust, did not include the routine use of MRI or biomarkers meaning that

some patients with concomitant mild cerebrovascular changes could have been included. That said, patients underwent a comprehensive work-up including neuroimaging with CT in all cases, laboratory testing and detailed neuropsychological testing meeting established clinical criteria for AD at the time of testing [27] and a proportion had an MRI pre and post treatment as part of the DARAD-MRI sub-study [52]. The co-existence of AD and minor cerebrovascular changes is common, does not appear to affect rate of progression [53] and is often acceptable for inclusion in trials of AD where it does not affect the diagnostic classification [54]. This is arguably more naturalistic and representative of 'real-life' clinical practice. The study was conducted in a single country, Canada, and no data on ethnicity were available, reducing the generalizability of results. However, Canada is a large, multi-ethnic country, where in 2011 the majority were Caucasian, 19.1% were visible minorities (South Asian, Chinese, Black) and 4.3% Aboriginal Canadians [55]. Those with clinically significant comorbidities including poorly controlled diabetes were excluded, further, restricting generalizability. The adjustment for anti-hypertensives is limited to the presence or absence of any agent or central versus non-centrally acting ACEis. Insufficient numbers of other anti-hypertensives including ARBs, which were less commonly prescribed during the recruitment window of this trial, were available for analysis. However, adjusting for multiple anti-hypertensives may lead to collinearity and some of the most robust data exists for agents targeting the renin angiotensin aldosterone system [56]. Further, details of historical anti-hypertensive therapy were not available. Finally, the number and timing of visits and device used to measure BP can affect VVV, potentially influencing results and comparability between studies [57].

Conclusion

In summary, this observational study showed that there were few statistically significant effects of VVV or high VVV, irrespective of the approach used to define it, on a range of cognitive and functional outcomes in those with confirmed AD recruited to a RCT over one-year. Further studies are now required using prospective longitudinal cohort designs following patients over longer periods of time and examining different populations to confirm whether VVV is a marker of risk of decline in those with established dementia, if it results in worse cardiovascular outcomes and whether treatment could be beneficial.

Acknowledgments

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Tables

Table 1. Baseline characteristics of participants included in this analysis from the Doxycycline And Rifampicin for Alzheimer's Disease (DARAD) study (n=392) compared to all (n=406) included in the DARAD trial.

Variable	Total (N=406) (Mean±SD or %)	Included (n=392) (Mean±SD or %)	Not included (n=14) (Mean±SD or %)	*p-value
Age (years)	77.86 ± 7.13	77.67 ± 7.09	83.21 ± 6.41	0.004
Gender (% female)	49%	49%	57%	0.60
Education (years)	12.31 ± 3.47	12.31 ± 3.48	12.00 ± 0.00	0.93
Hypertension (%)	54%	56%	50%	1.00
Systolic Blood pressure (mmHg)	134.20 ± 16.01	134.17 ± 16.12	135.00 ± 12.84	0.86
Diastolic Blood pressure (mmHg)	73.05 ± 10.27	72.92 ± 10.30	76.92 ± 8.79	0.17
CV of Systolic BP (expressed as (%)	8.61 ± 3.94	8.77 ± 3.85	4.21 ± 4.00	< 0.001
CV of Diastolic BP (expressed as %)	10.34 ± 5.20	10.52 ± 5.11	5.50 ± 5.51	< 0.001
Use of anti-hypertensive (%)	94%	94%	100%	1.00
Use of metformin (%)	6.5%	6.4%	7.1%	1.00
Cholinesterase inhibitor use (%)	91%	91%	100%	0.61
Memantine use (%)	15%	15%	14%	1.00
SADAS-cog	21.68 ± 7.89	21.67 ± 7.86	22.00 ± 8.85	0.88
CDR-SB	5.89 ± 2.50	5.83 ± 2.47	7.54 ± 2.61	0.012
SMMSE	22.15 ± 3.12	22.15 ± 3.14	22.21 ± 2.69	0.94
Q*mci* screen	38.47 ± 12.86	38.52 ± 12.81	37.00 ± 14.66	0.66
Lawton-Brody ADL	50.03 ± 6.82	50.28 ± 6.65	42.93 ± 8.10	< 0.001
CSDD	3.53 ± 3.12	3.52 ± 3.13	4.00 ± 0.00	0.88
GDS	1.79 ± 1.87	1.78 ± 1.87	4.00 ± 0.00	0.24

ADL= Activities of daily living; BP = Blood pressure; CDR-SB; CSDD = Cornell Scale for Depression in Dementia; CV = Coefficient of variation; GDS = Geriatric Depression Scale; Q*mci* screen = Quick Mild Cognitive Impairment screen; SADAS-cog =; SMMSE = Standardised Mini-Mental State Examination;

* Comparison of patients included in this analysis compared to the total included in the DARAD

Table 2. Binary logistic regression models (adjusted and unadjusted) showing the association between measures of Visit-Visit BP (Blood Pressure) Variability (VVV) and change (increase ≥ 4 points) in the Standardized Alzheimer's Disease Assessment Scale–Cognitive Subscale.

VVV		**Model 1** (unadjusted) OR with 95% CI	**Model 2** (adjusted*) OR with 95% CI	**Model 3** (adjusted**) OR with 95% CI
Systolic BP	**CV**	0.99 (0.93 to 1.05)	1.00 (0.94 to 1.06)	0.99 (0.93 to 1.05)
	SD	0.99 (0.95 to 1.03)	0.99 (0.95 to 1.04)	0.99 (0.95 to 1.04)
	VIM	0.99 (0.95 to 1.03)	1.00 (0.95 to 1.04)	0.99 (0.95 to 1.04)
	ARV	1.00 (0.97 to 1.03)	1.00 (0.97 to 1.04)	1.00 (0.97 to 1.04)
	Delta	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)
Diastolic BP	**CV**	1.01 (0.97 to 1.06)	1.02 (0.97 to 1.06)	1.01 (0.97 to 1.06)
	SD	1.02 (0.96 to 1.08)	1.02 (0.96 to 1.08)	1.02 (0.96 to 1.09)
	VIM	1.02 (0.96 to 1.08)	1.02 (0.96 to 1.08)	1.02 (0.96 to 1.09)
	ARV	1.01 (0.97 to 1.06)	1.01 (0.97 to 1.06)	1.02 (0.97 to 1.07)
	Delta	1.00 (0.98 to 1.03)	1.00 (0.98 to 1.03)	1.00 (0.98 to 1.03)
Systolic BP CV quartiles	**Q1 (≤ 5.9)**	reference	reference	reference
	Q2 (6.0 - 8.3)	1.29 (0.71 to 2.37)	1.27 (0.69 to 2.34)	1.27 (0.68 to 2.38)
	Q3 (8.4 - 10.7)	1.33 (0.72 to 2.43)	1.41 (0.76 to 2.60)	1.36 (0.72 to 2.56)
	Q4 (≥ 10.8)	0.95 (0.51 to 1.77)	1.03 (0.55 to 1.94)	0.96 (0.51 to 1.81)
Diastolic BP CV quartiles	**Q1 (≤ 6.9)**	reference	reference	reference
	Q2 (7.0 - 9.8)	1.83 (0.99 to 3.38) ^	1.83 (0.98 to 3.39)	1.86 (0.98 to 3.51)
	Q3 (9.9 - 12.9)	1.55 (0.84 to 2.85)	1.55 (0.84 to 2.87)	1.46 (0.78 to 2.73)
	Q4 (≥ 13)	1.42 (0.77 to 2.62)	1.44 (0.78 to 2.69)	1.38 (0.73 to 2.62)

CV = Coefficient of Variation; SD = Standard Deviation; VIM = Variation Independent of Mean; ARV = Average real variability;
^ Borderline statistical significance (p = .054)
*Model 2: adjusted for sex, age, education (<12 or ≥12 years).
**Model 3: adjusted for anti-hypertensive, treatment group (placebo, rifampicin and/or doxycycline), use of cholinesterase inhibitors or memantine, Geriatric Depression Scale, patient's average blood pressure.
Note: Reported as Odd Ratio (OR) with 95% Confidence Intervals (CI).

Table 3. Linear regression models (adjusted and unadjusted) for an association between measures of Visit-Visit BP Variability and change in scores of the Standardized Alzheimer's Disease Assessment Scale–Cognitive Subscale (SADAS-cog), Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB), Quick Mild Cognitive Impairment (Q*mci*) Screen and Lawton-Brody Activities of Daily Living Scale and Standardised Mini-Mental State Examination (SMMSE).

Instrument	Visit-Visit BP Variability		Model 1 (unadjusted)	Model 2 (adjusted*)	Model 3 (adjusted**)
SADAS-cog	**Systolic BP**	**CV**	0.02 (-0.20 to 0.24)	0.05 (-0.17 to 0.27)	0.02 (-0.20 to 0.24)
		SD	-0.01 (-0.17 to 0.15)	0.01 (-0.15 to 0.17)	-0.01 (-0.15 to 0.18)
		VIM	0.003 (-0.16 to 0.17)	0.02 (-0.14 to 0.19)	0.02 (-0.15 to 0.18)
		ARV	-0.01 (-0.12 to 0.11)	0.01 (-0.11 to 0.13)	0.02 (-0.10 to 0.13)
		Delta	0.01 (-0.05 to 0.07)	0.02 (-0.04 to 0.08)	0.02 (-0.04 to 0.08)
	Diastolic BP	**CV**	-0.02 (-0.18 to 0.14)	-0.02 (-0.18 to 0.15)	0.001 (-0.16 to 0.16)
		SD	-0.001 (-0.22 to 0.22)	-0.002 (-0.22 to 0.22)	0.02 (-0.21 to 0.24)
		VIM	-0.01 (-0.24 to 0.21)	-0.01 (-0.24 to 0.21)	0.01 (-0.22 to 0.23)
		ARV	0.01 (-0.16 to 0.18)	0.02 (-0.15 to 0.19)	0.04 (-0.13 to 0.21)
		Delta	0.01 (-0.07 to 0.10)	0.01 (-0.07 to 0.10)	0.02 (-0.06 to 0.11)
CDR-SB	**Systolic BP**	**CV**	0.04 (-0.04 to 0.12)	0.03 (-0.05 to 0.11)	0.02 (-0.06 to 0.10)
		SD	0.02 (-0.04 to 0.07)	0.01 (-0.05 to 0.07)	0.02 (-0.04 to 0.08)
		VIM	0.02 (-0.04 to 0.08)	0.02 (-0.04 to 0.08)	0.02 (-0.04 to 0.08)
		ARV	0.01 (-0.03 to 0.05)	0.01 (-0.04 to 0.05)	0.01 (-0.03 to 0.06)
		Delta	0.01 (-0.01 to 0.03)	0.01 (-0.01 to 0.03)	0.01 (-0.01 to 0.03)
	Diastolic BP	**CV**	0.02 (-0.05 to 0.08)	0.01 (-0.04 to 0.07)	0.01 (-0.05 to 0.07)
		SD	0.01 (-0.07 to 0.09)	0.01 (-0.07 to 0.09)	0.02 (-0.06 to 0.10)
		VIM	0.02 (-0.07 to 0.10)	0.01 (-0.07 to 0.09)	0.02 (-0.07 to 0.10)
		ARV	0.04 (-0.02 to 0.10)	0.04 (-0.02 to 0.10)	0.05 (-0.02 to 0.11)
		Delta	0.01 (-0.02 to 0.04)	0.01 (-0.02 to 0.04)	0.01 (-0.02 to 0.04)
Lawton-Brody ADL Scale	**Systolic BP**	**CV**	-0.14 (-0.33 to 0.04)	-0.14 (-0.33 to 0.04)	-0.14 (-0.33 to 0.04)
		SD	-0.09 (-0.23 to 0.04)	-0.09 (-0.23 to 0.05)	-0.11 (-0.25 to 0.03)
		VIM	-0.10 (-0.24 to 0.03)	-0.10 (-0.24 to 0.04)	-0.11 (-0.25 to 0.03)
		ARV	-0.04 (-0.14 to 0.06)	-0.05 (-0.15 to 0.05)	-0.06 (-0.16 to 0.04)
		Delta	-0.05 (-0.09 to 0.004)	-0.04 (-0.09 to 0.006)	**-0.05 (-0.10 to -0.002)*** **
	Diastolic BP	**CV**	0.02 (-0.12 to 0.16)	0.03 (-0.11 to 0.16)	0.04 (-0.10 to 0.18)
		SD	0.04 (-0.14 to 0.23)	0.05 (-0.14 to 0.24)	0.04 (-0.15 to 0.23)
		VIM	0.04 (-0.15 to 0.23)	0.04 (-0.15 to 0.23)	0.05 (-0.14 to 0.24)
		ARV	0.05 (-0.10 to 0.19)	0.05 (-0.10 to 0.19)	0.04 (-0.11 to 0.18)
		Delta	0.01 (-0.06 to 0.08)	0.02 (-0.06 to 0.09)	0.01 (-0.06 to 0.08)
Q*mci* Screen	**Systolic BP**	**CV**	-0.12 (-0.41 to 0.17)	-0.18 (-0.47 to 0.10)	-0.18 (-0.47 to 0.12)
		SD	-0.09 (-0.31 to 0.12)	-0.13 (-0.34 to 0.08)	-0.13 (-0.35 to 0.09)
		VIM	-0.09 (-0.31 to 0.12)	-0.14 (-0.35 to 0.08)	-0.13 (-0.35 to 0.09)
		ARV	-0.05 (-0.20 to 0.10)	-0.07 (-0.23 to 0.08)	-0.07 (-0.23 to 0.08)
		Delta	-0.04 (-0.12 to 0.04)	-0.06 (-0.13 to 0.02)	-0.06 (-0.14 to 0.02)
	Diastolic BP	**CV**	0.01 (-0.20 to 0.23)	0.001 (-0.21 to 0.21)	-0.02 (-0.24 to 0.19)
		SD	-0.02 (-0.31 to 0.28)	-0.02 (-0.32 to 0.27)	-0.03 (-0.33 to 0.27)
		VIM	-0.004 (-0.30 to 0.29)	-0.01 (-0.31 to 0.28)	-0.03 (-0.33 to 0.27)
		ARV	0.02 (-0.21 to 0.25)	-0.003 (-0.23 to 0.22)	-0.01 (-0.24 to 0.22)
		Delta	-0.03 (-0.14 to 0.09)	-0.03 (-0.14 to 0.08)	-0.03 (-0.14 to 0.08)
SMMSE	**Systolic BP**	**CV**	-0.05 (-0.16 to 0.06)	-0.06 (-0.17 to 0.05)	-0.05 (-0.16 to 0.06)
		SD	-0.02 (-0.10 to 0.06)	-0.02 (-0.11 to 0.06)	-0.03 (-0.11 to 0.05)
		VIM	-0.03 (-0.11 to 0.06)	-0.03 (-0.12 to 0.05)	-0.03 (-0.12 to 0.05)
		ARV	0.02 (-0.04 to 0.08)	0.01 (-0.05 to 0.07)	0.01 (-0.05 to 0.07)
		Delta	-0.01 (-0.04 to 0.02)	-0.02 (-0.05 to 0.02)	-0.02 (-0.05 to 0.01)
	Diastolic BP	**CV**	0.03 (-0.05 to 0.12)	0.03 (-0.05 to 0.11)	0.03 (-0.06 to 0.11)
		SD	0.04 (-0.07 to 0.16)	0.04 (-0.07 to 0.16)	0.03 (-0.08 to 0.15)
		VIM	0.05 (-0.07 to 0.16)	0.05 (-0.07 to 0.16)	0.04 (-0.08 to 0.15)
		ARV	0.03 (-0.06 to 0.12)	0.03 (-0.06 to 0.11)	0.02 (-0.07 to 0.11)
		Delta	0.01 (-0.03 to 0.05)	0.01 (-0.03 to 0.05)	0.01 (-0.04 to 0.05)

CV = Coefficient of Variation; SD = Standard Deviation; VIM = Variation Independent of Mean; ARV = Average real variability;

*Model 2: adjusted for sex, age, education (<12 or ≥12 years).

**Model 3: adjusted for anti-hypertensive, treatment group (placebo, rifampicin and/or doxycycline), use of cholinesterase inhibitors or memantine, Geriatric Depression Scale, patient's average blood pressure.

Note: Reported values are linear regression coefficients with 95% confidence intervals, all values are non-significant different from 0, except for one coefficient marked with *** ($p < 0.05$).

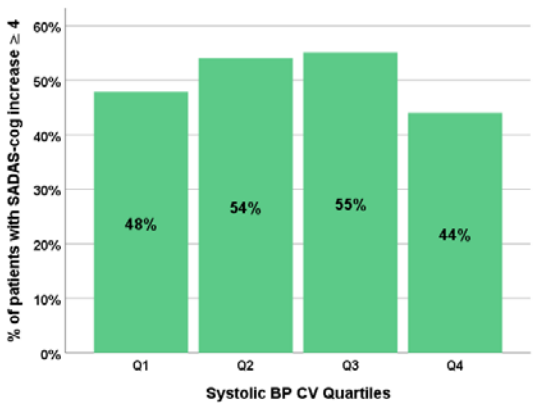
Table 4. Multiple linear regression models (adjusted and unadjusted) for an association between systolic blood pressure coefficient of variation (CV) quartiles (Q) taking Q1 as the reference value and change in scores of the Standardized Alzheimer's Disease Assessment Scale–Cognitive Subscale (SADAS-cog), Clinical Dementia Rating Scale- Sum of Boxes (CDR-SB), Quick Mild Cognitive Impairment (Q*mci*) Screen and Lawton-Brody Activities of Daily Living Scale.

Dependent variable		**Systolic Blood Pressure CV quartiles**				**p value**
		Q1 ≤ 5.9	**Q2** 6.0 – 8.3	**Q3** 8.4 – 10.7	**Q4** ≥ 10.8	
SADAS-cog change	**Model 1**	0 (ref)	0.36 (-1.90 to 2.63)	-0.10 (-2.37 to 2.17)	0.10 (-2.22 to 2.42)	0.75
	Model 2*	0 (ref)	0.33 (-1.93 to 2.59)	0.13 (-2.14 to 2.41)	0.40 (-1.93 to 2.74)	0.73
	Model 3**	0 (ref)	0.16 (-2.12 to 2.44)	-0.32 (-2.63 to 1.99)	0.002 (-2.34 to 2.35)	0.79
Q*mci* Screen change	**Model 1**	0 (ref)	-0.29 (-3.26 to 2.67)	2.69 (-0.29 to 5.66)	-1.59 (-4.63 to 1.46)	0.08
	Model 2*	0 (ref)	-0.15 (-3.09 to2.78)	2.35 (-0.61 to 5.31)	-2.22 (-5.25 to 0.82)	0.12
	Model 3**	0 (ref)	-0.06 (-3.05 to 2.94)	2.68 (-0.36 to 5.72)	-2.12 (-5.20 to 0.96)	0.08
Lawton-Brody ADL change	**Model 1**	0 (ref)	-0.72 (-2.61 to 1.18)	**-1.86*** (-3.76 to -0.01)**	-0.93 (-2.88 to 1.02)	0.046
	Model 2*	0 (ref)	-0.78 (-2.68 to 1.12)	**-1.94*** (-3.85 to -0.03)**	-0.97 (-2.93 to 0.99)	0.047
	Model 3**	0 (ref)	-0.75 (-2.67 to 1.17)	**-2.03*** (-3.98 to -0.08)**	-0.99 (-2.97 to 0.98)	0.041
CDR-SB change	**Model 1**	0 (ref)	0.21 (-0.61 to 1.03)	0.18 (-0.64 to 1.00)	0.30 (-0.54 to 1.14)	0.48
	Model 2*	0 (ref)	0.25 (-0.57 to 1.06)	0.16 (-0.67 to 0.98)	0.27 (-0.58 to 1.11)	0.53
	Model 3**	0 (ref)	0.18 (-0.65 to 1.01)	0.05 (-0.79 to 0.88)	0.13 (-0.72 to 0.98)	0.67
SMMSE change	**Model 1**	0 (ref)	0.04 (-1.10 to 1.17)	0.38 (-0.76 to 1.52)	-0.41 (-1.57 to 0.76)	0.49
	Model 2*	0 (ref)	0.06 (-1.08 to 1.20)	0.32 (-0.83 to 1.46)	-0.54 (-1.71 to 0.63)	0.36
	Model 3**	0 (ref)	0.26 (-0.89 to 1.40)	0.57 (-0.59 to 1.73)	-0.35 (-1.52 to 0.82)	0.33

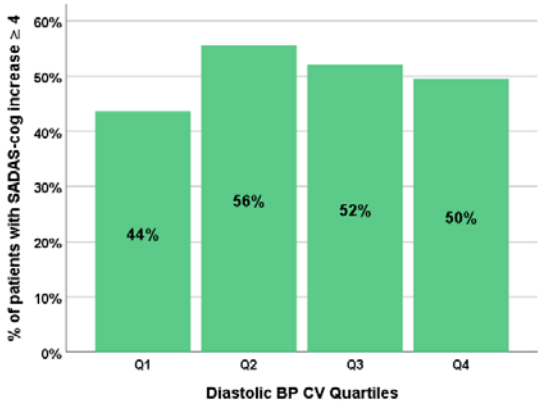
*Model 2: adjusted for sex, age, low education (<12 years).
**Model 3: adjusted for anti-hypertensive, treatment group (placebo, rifampicin and/or doxycycline), use of cholinesterase inhibitors or memantine, Geriatric Depression Scale, patient's average systolic blood pressure.
*** p<0.05
Note: Reported values are linear regression coefficients with 95% Confidence Intervals (CI).

Figures

Figure 1. Proportion of patients with a deterioration (≥4 points increase over follow-up) in the Standardized Alzheimer's Disease Assessment Scale–Cognitive Subscale (SADAS-cog) according to (a) quartiles of systolic BP CV, (b) quartiles of diastolic BP CV.

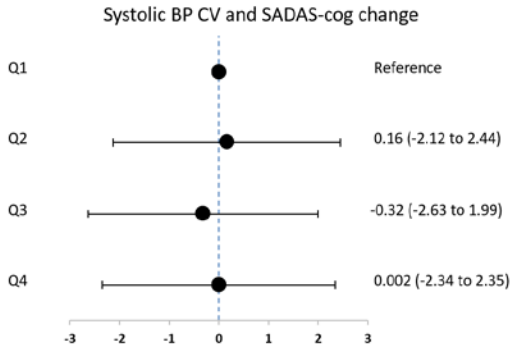


a.

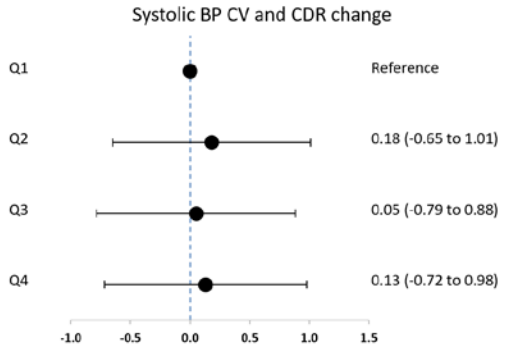


b.

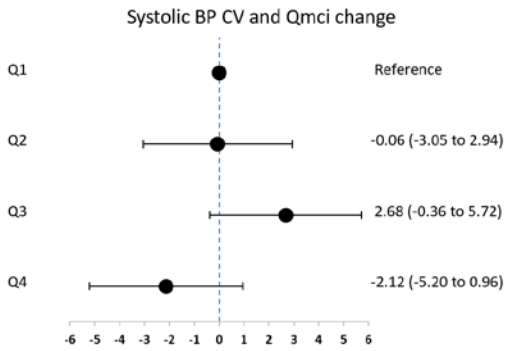
Figure 2. Development of deterioration in cognition and activities of daily living (ADL) according to systolic blood pressure (BP) coefficient of variation (CV) quartiles: decline in (a) Standardized Alzheimer's Disease Assessment Scale–Cognitive Subscale SADAS-cog, (b) Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB), (c) Quick Mild Cognitive Impairment (Q*mci*) screen, (d) ADL change during one-year follow-up and (e) Standardised Mini-Mental State Examination (SMMSE).



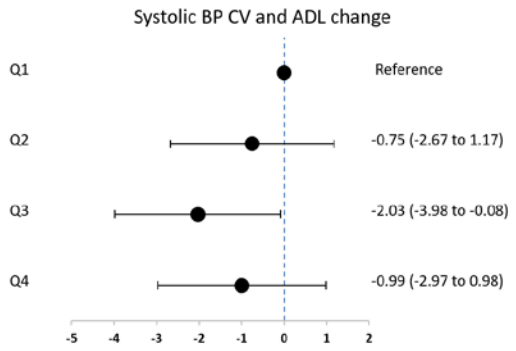
a.



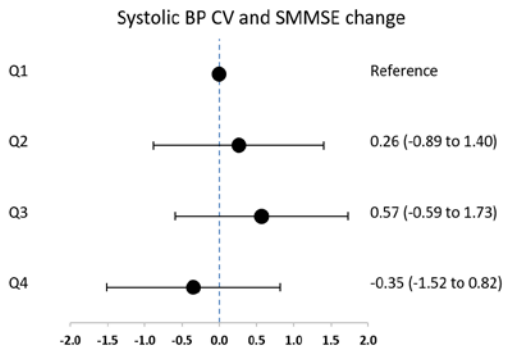
b.



c.



d.



e.

Note: results based on linear regression are presented as linear regression with 95% confidence intervals adjusted for sex, age, education, randomization group, Geriatric Depression Scale, Standardised Mini-Mental State Examination use of anti-hypertensives, cholinesterase inhibitors and memantine, patient's average systolic blood pressure.

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