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Antihypertensive drug use and risk of cognitive decline in the very old: an observational study, The Newcastle 85+ Study

Short title: Antihypertensives cognitive decline

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Abstract

Objectives

Older adults are a fast growing group in society and are at high risk of hypertension, cognitive decline and dementia. Antihypertensive drugs, particularly Calcium Channel Blockers (CCB), have been associated with a decreased risk of cognitive decline and dementia. We used observational data to examine the association between antihypertensive drug class and change in cognitive function.

Methods

The Newcastle 85+ Study is a population based cohort study recruiting individuals aged 85 (born in 1921) via general/family practices in Newcastle/North Tyneside (UK). Data, including blood pressure, antihypertensive drug use and cognitive function (assessed using the Standardised Mini-Mental State Exam [SMMSE]), was collected at baseline and three year follow up.

Results

The study population comprised 238 participants with a diagnosis of hypertension, prescribed antihypertensive drug treatment and with baseline and follow up SMMSE assessment. There was an association between CCB use and less cognitive decline over three years (rate of decline was lower by 1.29 SMMSE points (95% Confidence Interval (CI) 0.16 to 2.42; P=0.03) compared to those taking other antihypertensive classes after adjustment for age, sex, years of education, baseline SMMSE score, smoking, body mass index, baseline blood pressure, and incident cerebrovascular event. This finding was even stronger in the cognitively intact (SMMSE>24), where rate of cognitive decline was lower by 1.33 SMMSE points (95% CI 0.30 to 2.37); P=0.01), but was not seen for other antihypertensive classes.

Conclusions

Findings provide support for an association between CCB use and a lower rate of cognitive decline in very old adults with hypertension.

Condensed abstract

Antihypertensive drugs, particularly Calcium Channel Blockers(CCB), have been associated with a decreased risk of cognitive decline and dementia. Using a population based cohort study, the Newcastle 85+ Study, we examined the association between antihypertensive drug class and change in cognitive function. CCB users showed less cognitive decline over three years (rate of decline lower by 1.29 Mini-Mental State Exam(SMMSE) points (95% Confidence Interval (CI)0.16 to 2.42; P=0.03) compared to those taking other antihypertensive classes. Findings suggest a potential role of CCBs in reducing cognitive decline in adults aged 85 and over with hypertension.

Key words

Background

The risks of hypertension and dementia increase with age, with hypertension also being a risk factor for dementia [1,2]. Relationships between blood pressure lowering and dementia risk are less well understood [3-22], particularly in very old age [3]. Systematic reviews (10-12), clinical trials (13,14,19) and observational studies (15-18,20-22) variably report antihypertensive drug use as associated with decreased risk of dementia/cognitive decline [14-21], increased risk [22], or no impact [10-13]. The majority of double blind randomised placebo controlled trials show no relationships. However, two trials in the young old (below age 70) report reductions in incident dementia: from an Angiotensin Converting Enzyme-Inhibitor (ACE-I) plus optional diuretic, but only in those with prior stroke/transient ischaemic attack and concurrent stroke, mean age 64 years [14]; and from Calcium Channel Blockers (CCB), mean age 69.9 years [19,20]. Observational literature shows Beta blockers (BB), CCBs, ACE-I and diuretics as associated with some positive cognitive outcomes, again mostly in the younger old (mean age at baseline ranged from ~68-78 years) [15-18]. Evidence is strongest for CCBs with the suggestion that their impact may be independent of blood pressure lowering [11,12].

Global hypertension guidelines now recommend treatment for hypertensive individuals ≥80 years and it is important to understand the impact of such treatment on cognition. Only one trial, the Hypertension in the Very Elderly Trial (HYVET), looked specifically at the very old using a thiazide like diuretic plus optional ACE-I [10-11,13]; blood pressure fell without reducing incident dementia [13]. Two observational studies in the very old report conflicting results: the Leiden 85+ study found CCBs to be associated with decelerated cognitive decline, whilst the Canadian Study of Health and Aging (CSHA) reported increased risk of decline [21,22]. Given this discrepancy, further studies in the very old are warranted.

We analysed data from the Newcastle 85+ Study with the hypothesis that CCBs, rather than other antihypertensive drug classes, would be associated with a decreased risk of cognitive decline.

Methods

The protocol for the Newcastle 85+ Study and the baseline characteristics of the recruited cohort have been published elsewhere [23-25]. In brief, the Newcastle 85+ Study is a population-based observational cohort study which recruited people born in 1921, aged 85 when the study commenced in 2006, and who were registered with a participating General Practice (GP) in the Newcastle/North Tyneside area of the UK [23-25]. People living in institutions were included. Participants were visited in their own homes and underwent a battery of tests and questionnaires at baseline, 18 months, three years and five years of follow up [23]. GP records were examined to extract data on pre-existing diagnoses and prescribed medication. Cognitive function was tested at baseline and three year follow up using the standardised Mini-Mental State Exam (SMMSE)[26]. These analyses are based on baseline and three year follow up data.

Standard Protocol Approvals, Registrations and Patient Consents.

The study was approved by the Newcastle & North Tyneside Local Research Ethics Committee One. Participants provided written informed consent; consultee approval was used where participants had significant cognitive impairment.

Antihypertensive Medication and inclusion criteria

Because the reasons for receiving specific medication were not collected, and because antihypertensive drugs may not always be prescribed primarily for hypertension, only those participants prescribed CCBs, centrally acting antihypertensives, thiazide and related diuretics, ACE-Is, Angiotensin Receptor Blockers (ARB), vasodilators, BB and alpha adrenoreceptor blocking drugs (except for preparations specific to phaeochromocytoma) were classified as having been prescribed

antihypertensives. Prescription of loop diuretics or potassium sparing diuretics were considered more likely to be related to heart failure therapy, and were excluded from the antihypertensives list.

To examine the impact of a specific antihypertensive class (compared to other antihypertensive classes) on change in global cognitive function over time, the sample for analysis comprised those participants who had a diagnosis of hypertension, were prescribed antihypertensive drugs according to the list specified above and had both baseline and three year follow up SMMSE scores i.e. the population who had been exposed to the risk factor (hypertension), had received treatment (antihypertensives) and had data available with regard to cognitive change over time.

Confounding factors

Models were adjusted for key variables thought to have a relationship with cognitive decline: baseline systolic and diastolic blood pressure; age in years; sex; smoking behaviour (never, former occasional, former regular, current); years of education; BMI (underweight<18.50 kg/m^2, normal range 18.5 to 24.99, pre obese 25.00 to 29.99, obese 30.00 to 39.99, morbidly obese ≥40.00). Additional adjustment for change in blood pressure over 3 years and blood pressure control (defined as a systolic blood pressure <150mm Hg and a diastolic pressure<80mm Hg at both baseline and follow-up assessments), presence of atrial fibrillation, diagnosis of heart failure and baseline physical activity level was also carried to assess any further impact on results.

Data on systolic and diastolic blood pressure (mean of second and third recordings measured on the same occasion using an OMRON HEM 705-IT), height and weight (allowing calculation of Body Mass Index (BMI)), self-reported smoking behaviour and years of education were collected at study visits [23-25]. Details of co-morbidity including cerebrovascular disease (and recorded stroke or transient ischaemic attack) and heart failure were collated from review of GP records. The presence of atrial fibrillation was determined from a 12 lead ECG (Automated coding: Minnesota code 8-3-1).

Statistical analysis

Baseline characteristics of the study sample were compared to those excluded using T tests, Chi squared and Wilcoxon non-parametric tests depending on the nature of the variables. SMMSE scores are presented both as Mean (M) and Standard Deviation (SD), in order to allow comparability to other studies, and as median and interquartile range since data are skewed.

Cross-sectional analyses were performed to establish relationships between baseline SMMSE and antihypertensive drug class (see drug classes above), firstly unadjusted (by T Tests) and then adjusted for confounders (by multilevel linear regression models with participants' general practice as a random effect to account for within-practice similarities).

The effect of antihypertensive drug class on change in cognitive function over time (baseline to three year follow up) was also examined. The mechanism by which antihypertensives impact on cognitive function is thought to be independent from blood pressure lowering, therefore participants taking a particular class of antihypertensive drug were compared to those taking other antihypertensive classes. Exposure to the drug was classified as present if it was recorded as prescribed at both baseline and three year follow up, regardless of concurrent exposure to other antihypertensive types. Analyses were carried out both unadjusted and adjusted for key variables thought to have an influence on cognitive decline (baseline SMMSE and incident stroke or transient ischaemic attack during three year follow up, in addition to those listed above). SMMSE was analysed in three ways: (i): change in SMMSE score over time as a continuous variable, by multilevel linear regression models; (ii): a decline in SMMSE score of >4 points (indicating cognitive decline), by logistic regression [13]; (iii): a decline in SMMSE score greater than that calculated as likely to be a reliable change (using the published methods for calculating this, the Reliable Change Index (RCI) [27]), by logistic regression. Residuals were plotted where appropriate for the linear regression models and the fit examined.

Because antihypertensive use may have a different relationship with cognitive function in those already suffering from cognitive impairment, these analyses were repeated for the subset of

participants who were considered to be more cognitively intact at baseline, i.e. baseline SMMSE score >24 and not taking cognitive enhancing medication (i.e. acetylcholinesterase inhibitors) at baseline or three years.

Sensitivity analyses

Further analyses were carried out to investigate whether exposure to either the risk factor (hypertension) or intervention (antihypertensive treatment) was related to cognitive change by examining change in SMMSE firstly with antihypertensive medication, with or without a diagnosis of hypertension (i.e. exposed to the intervention regardless of exposure to the risk factor), and secondly with a diagnosis of hypertension with or without treatment (exposed to the risk factor regardless of intervention). Analyses were repeated to compare each antihypertensive class in turn to the untreated population. Mortality rates were also examined in order to examine whether particular classes of antihypertensive had a disproportionate association with death prior to the three year visit (which might therefore mask an effect on cognitive decline).

Complete case analysis was used as levels of missing baseline data were largely less than one percent.

Results

Of the 1453 people eligible to participate in the Newcastle 85+ study (registered with participating

GP and still alive when contact was established), 851 consented to both home based assessment and

review of GP records at baseline. Two participants then withdrew requesting that all data be

destroyed and 4 had incomplete GP records, leaving 845 available for analysis. Of these, 483

underwent the home based assessment and review of GP records at three year follow up. Loss was

mainly due to deaths (63%, 232/368) with the remainder due to withdrawal.

A total of 415 participants at baseline had a diagnosis of hypertension and were taking

antihypertensive medication. Of these, 147 died and 27 withdrew prior to the three year follow up

and a further three had missing follow-up SMMSE data, leaving 238 participants with a diagnosis of

hypertension, taking antihypertensive medication and with baseline and follow up SMMSE data

(analytic sample). Figure 1 shows the flow chart for the analytic sample.

Baseline characteristics

The characteristics of the Newcastle 85+ study population have been published [23-25]. The

characteristics of the analytic sample selected here (n=238, mean age 85.5 (SD0.4)) are shown in

Table 1. This study population did not differ statistically from the rest of the baseline Newcastle 85+

cohort (n=607) in terms of sex (P=0.89), BMI (P=0.10), diastolic blood pressure (P=0.12), previous

cerebrovascular disease (P=0.69), level of education (P=0.28) or patterns of smoking (P=0.51). The

analytic sample were significantly more likely to have higher systolic blood pressures (Mean (M)

151.9mmHg (SD22.0) compared to 147.8 (SD25.3); P=0.02) and better cognitive function than the

rest of the cohort (mean baseline SMMSE 27.5 (SD2.8) compared to 25.2 (SD5.9); P<0.0001).

When the analytic sample was compared to those who would have been eligible for inclusion i.e. had

hypertension and were receiving antihypertensive treatment but who did not complete both baseline

and follow up SMMSE assessment (n=177), those not included were found to have a significantly

lower baseline SMMSE (M 25.2 (SD5.3) compared to M 27.5 (SD2.8); P<0.001), and a slightly

lower diastolic blood pressure (M 72.2 (SD12.4) compared to M 74.8 (SD11.0); P=0.03) but did not

differ in terms of sex, BMI, systolic blood pressure, smoking, level of education or diagnosis of previous cerebrovascular disease.

The mean number of antihypertensive drugs prescribed was 1.9 (SD 0.9), range 1-5. Thirty six percent of participants were taking one antihypertensive, 40% two and 19% three drugs. Where just one antihypertensive drug was prescribed it was most likely to be an ACE-I (N=21) whilst for two or more antihypertensive drugs the most common combinations were CCB/ACE-I (N=38), CCB/BB (N=36), BB/ACE-I (N=36), CCB/thiazide and related diuretics (N=33) and BB/thiazide and related diuretics (N=31). Overall there were 78 participants prescribed BBs, 74 CCBs, 60 prescribed thiazide and related diuretics, 60 ACE-I and 33 prescribed ARBs. Numbers reporting alpha blockers (n=24), centrally acting antihypertensives (n=5) and vasodilator (n=0) use were lower and these categories were not explored further. The characteristics of those prescribed BBs, CCBs, thiazide and related diuretics, ACE-I and ARBs were broadly similar with the exception of sex (Table 1); whilst women formed 63% of the study population, they formed 43% and 48% of the CCB and ACE-I groups respectively compared to 85% for ARB, 77% for thiazide and related diuretics and 72% for BB.

Antihypertensive use and baseline cognitive function

Exposure to thiazide and related diuretics was associated with a slightly higher baseline SMMSE compared to non-exposure in a multilevel linear regression adjusted for baseline blood pressure (systolic and diastolic), age, sex, smoking, educational level and BMI (ß=0.35, (95% Confidence Intervals (CI) 0.04 to1.50), P=0.04). There was no association between any other antihypertensive class and baseline SMMSE. There was also no statistically significant association between baseline SMMSE and baseline blood pressure (systolic or diastolic), age, sex, smoking, educational level or BMI.

Antihypertensive use and cognitive change over three years

Unadjusted analysis of change in SMMSE score (baseline minus three year follow up score, i.e. a positive value represents a fall) separately by antihypertensive class suggested less cognitive decline was associated with CCB use and ARB use only (Table 2). After adjustment for confounders these associations were confirmed for CCB use but not for ARB use (Table 3); those taking CCBs showed less cognitive decline (i.e. their rate of decline was 1.29 SMMSE points lower, 95% CI 0.16 to 2.42, P=0.03) compared to those who were not taking CCBs. In comparison, the decline in SMMSE for those taking ARBs, compared to those not taking ARBs, was 0.97 points (95%CI -0.58 to 2.52, P=0.20). Results for CCB use were in the same direction, though not statistically significant, when cognitive decline was defined as a fall of >4 SMMSE points over three years (OR= 0.37, 95% CI 0.13 to 1.06; P=0.06) or decline in SMMSE greater than the RCI (OR=0.35, 95% CI 0.10 to1.20, P=0.09). Use of BBs was associated with a1.33 SMMSE points higher rate of cognitive decline (95% CI 0.22 to 2.45, P=0.02); and an increased risk of a decline >4 points (OR=2.88, 95% CI 1.24 to 6.70, P=0.01). No significant associations were found for thiazide and related diuretics or ACE-I use.

Further analyses were carried out adding all drug exposure variables into the model at the same time (i.e. CCB use present/absent, BB use present/absent, ARB use present/absent etc.) with adjustment for confounders. These again supported the lower rate of cognitive decline with CCB use of 1.20 SMMSE points (95% CI 0.08 to 2.32), P=0.04). The direction of the relationship with other antihypertensive types remained consistent i.e. thiazide, ACE-I and ARB use was associated with less decline and BB use with greater decline. Neither the direction nor overall significance of the findings changed when analyses were repeated with additional adjustments for: change in systolic and diastolic blood pressure over three years (n=220/238 without missing data); achievement of controlled blood pressure (defined as a systolic blood pressure <150mm Hg and a diastolic pressure<80mm Hg at both baseline and follow-up assessments [28] (224/238 without missing data); baseline physical activity levels (n=223/238 without missing data); and presence of atrial fibrillation (n=28), diabetes (n=40) or heart failure (n=16) (n=222/238 without missing data). Residuals were checked for all linear regression models and model fits were satisfactory.

Analysis of participants who were cognitively intact at baseline.

The analyses were repeated in the 204 individuals who were cognitively intact (SMMSE>24) at baseline and were not taking any prescribed cognition enhancing medication. Similar patterns emerged (Table 3). CCB use remained associated with less cognitive decline over three years (rate of decline 1.33 SMMSE points lower, 95% CI 0.30 to 2.37, P=0.01) and when cognitive decline was defined as a fall of >4 SMMSE points over three years (OR= 0.16, 95% CI 0.03 to 0.79; P=0.02) or a decline in SMMSE greater than the RCI (OR=0.38, 95% CI 0.15 to1.00, P=0.05). The direction of relationship remained the same for BBs, but was no longer significant. When adjusted analyses were repeated including all drug exposure variables, CCB use remained associated with a lower rate of cognitive decline by 1.35 points (95% CI 0.31 to 2.38, P=0.01).

Sensitivity analyses

Change in SMMSE (between baseline and three year follow up) was available for 470 participants. Neither presence of a diagnosis of hypertension (treated or untreated) (n=269/470) nor prescription of any type of antihypertensive treatment (irrespective of a diagnosis of hypertension) (n=296/470) had a significant relationship with change in SMMSE score over three years. Decline in SMMSE was largest for those without hypertension and on no treatment and smallest for those who were on antihypertensive treatment but without a hypertension diagnosis. The median decline in SMMSE score was 1.0 point in all groups.

Further analyses of each antihypertensive class comparing treated (with that antihypertensive) to untreated (ie without any antihypertensive treatment) participants found the SMMSE fall was smaller in the treated groups, although overall numbers were lower. T tests were statistically significant in favour of CCBs, ARBs and thiazide and related diuretics but, although the direction of relationships remained the same, they were no longer significant after adjustment for confounders. Examining the treatment characteristics of the 147 participants who died prior to the three year follow-up revealed that this group were most likely to be taking a single antihypertensive (N=67 (45.6%)) and that this was most likely to be a BB (N=22) or an ACE-I (N=19). There were 53 (36.1%) participants taking two antihypertensives, most commonly CCB/ACE-I (N=28) or BB/ACE

(N=22) combinations. Of the 180 taking CCBs at baseline, alone or in combination, 79 (43.8%) died before the three year follow-up, with similar proportions seen for ACE-I (N=79/167: 47.3%) and BB (N=77/169: 45.6%) and slightly lower proportions for thiazide and related diuretics (N=52/138: 37.7%) and ARBs (N=21/63: 33.3%). Cox proportional hazard regression using time from study entry until death or three year follow-up date showed no relationship between antihypertensive drug types and death either separately by drug class or when all drug classes were included in the model.

Discussion

Our findings from the Newcastle 85+ Study suggest an association between CCB use and lower global cognitive decline (assessed by SMMSE) in very old adults treated with antihypertensive medication, particularly in those who were cognitively intact at baseline (SMMSE>24). This association was independent of blood pressure lowering and was apparent when change in SMMSE was evaluated both as a continuous and as a categorical variable (a decline of >4 points). It was further supported by analyses using a Reliable Change Index [27] to identify a reliable change (decline) in SMMSE. There was also weak evidence for an association between BB use and an increased risk of SMMSE decline, although this was not present in the cognitively intact population. These results did not appear to be due to differential mortality between antihypertensive drug classes.

Our findings on CCB use and lower cognitive decline generally agree with the literature [11,12,19-21,29-31]. Our results, however, differ from those of the Canadian Study of Health and Aging which reported an increased risk of incident cognitive decline with CCB use, compared to other antihypertensives, over five years follow up in participants with a mean baseline age of 77.8(SD7.5) [22]. Possible explanations for this disparity may include variation in CCB types, population characteristics, length of follow up or unknown confounding factors. Interestingly our findings agree with the dementia outcome from a double blind placebo controlled trial, the Syst-Eur trial [19,20] , albeit in a younger population (mean age~69.9 years). Syst-Eur reported a significant reduction in incident dementia associated with CCB use (nitrendipine) compared to placebo; Hazard Ratio 0.43

(95% CI 0.25-0.74). Other observational studies have also reported point estimates for dementia related outcomes and CCB use that suggest the possibility of reduced dementia incidence with CCB use but without statistical significance [11,12].

We found a stronger association between CCB use and lower cognitive decline in those with SMMSE>24 (cognitively intact) at baseline, and it may be that any influence of CCB use lessens once decline has progressed beyond a certain point, or that use of more sensitive cognitive assessments may be needed to detect cognitive change in a population with lower SMMSE scores. Numbers were too small to investigate associations in the Newcastle 85+ participants with SMMSE=<24, however, a Cochrane review has concluded that there is some evidence for use of nimodipine (a CCB) in treating dementia, i.e. in those already showing decline [32]. The potential mechanisms proposed to explain any protective effect exerted by CCB use, which include protecting against calcium dysregulation, neuronal influx of calcium and consequent neuronal damage, could plausibly operate at differing levels of cognitive function [29,30]. Additionally, reversal of structural alternations in the microvasculature (i.e. inward eutrophic remodelling) as a result of essential hypertension has been reported in intervention studies of patients treated with CCBs and ACE inhibitors [33], and in trials using combinations of these two drugs [34], but not in those using BBs and diuretics. CCBs may therefore exert an additional beneficial effect on peripheral and brain vasculature by ameliorating the structural damage and increased vascular resistance [35] that leads to impaired microcirculation.

A potential association between BB use and accelerated cognitive decline has been postulated [36]. However, our result is contrary to recent findings from the Honolulu Asia Ageing Study (HAAS) which reported a lower risk of cognitive impairment in BB users compared to those not taking any antihypertensives and found this to be even stronger in older participants (>75 years)[15]. Potential explanations for the difference in results could include variations in population type (the HAAS includes only Japanese American men), duration of follow up, baseline cognitive function (our

findings were attenuated and significance lost when only those with SMMSE >24 were included (although the numbers available for analysis were smaller), and types of BB used.

When we compared decline in SMMSE with use of different antihypertensive types to decline in untreated participants (irrespective of diagnosis of hypertension) we found a similar pattern in favour of treatment, albeit not statistically significant possibly because untreated participants had less exposure to the risk factor (hypertension), although again the numbers available were small.

Strengths of the Newcastle 85+ Study include: representative recruitment from the general population via GP, including residents in institutions and those with cognitive impairment; data collection via home visits; breadth of data collection; and longitudinal follow up. The use of follow up data to examine cognitive change is vital but by necessity results in a more selective population. In our analysis, the selected analytic population had higher SMMSE scores than those excluded, regardless of whether the comparator group included those with or without three year follow up data. In addition, the number of participants in the analytic group was small so it was not possible for us to separate out pure CCB use from other antihypertensive classes as the majority of participants took more than one type. Therefore, a beneficial, synergistic effect of treatment interaction on cognitive functioning cannot be ruled out. Unmeasured confounders (e.g. duration of hypertension) may also exist and may have impacted on our results, although we adjusted for the key factors associated with cognitive decline. Inferring more widely from the Newcastle data is hampered to an extent by the ethnic homogeneity of the population (100 percent white); albeit currently representative of the very old in the UK, this ethnic composition may differ in other parts of the world. Furthermore, detailed comparison between the results from the Newcastle 85+ Study and those from other population studies is limited by the large variation present in the literature where study populations, comparator groups, follow up times and types of CCB all vary [11,12,19-21,29-32,37].

Conclusions

In conclusion, these analyses add to the literature suggesting that CCB use in hypertension might reduce the risk and rate of cognitive decline, and by extrapolation, incident dementia. If cognitive decline or incident dementia could be delayed, even by a relatively short time, the global impact could be significant [38]. This would likely have a proportionally greater impact in the very old age group with competing mortality and limited life expectancy. This area warrants further investigation in order to understand what roles CCB, and specific types of CCB, may have in the preservation of cognitive function in older adults.

Author disclosure

The authors report no disclosures relevant to the manuscript

Author contributions

RP proposed and drafted the manuscript and carried out the analyses. Statistical analysis carried out by RP advised by CJ.

JC provided advice and comment regarding the manuscript and was responsible for study design and execution; study funding; supervision of data collection; data preparation; and the development and writing of the paper

AG provided advice and comment regarding the manuscript and was involved in critical evolution of the manuscript.

KD provided advice and comment regarding the manuscript and was responsible for: study design; execution of study; management of participant and general practice recruitment; supervision of data collection; data preparation; critical review of paper drafts.

TK & CJ provided advice and comment regarding the manuscript and were responsible for the generation, funding and inception of the Newcastle 85+ study.

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Table 1 Characteristics of study population (n=238) by prescribed class of antihypertensive.

Key characteristics	All participants with diagnosis of hypertension, antihypertensive use at both baseline and follow up and both baseline and follow up SMMSE,	Participants prescribed specific antihypertensive drug class				
		Calcium Channel Blockers N=74[H]	Angio-tensin receptor Blockers N=33[H]	Thiazide & related diuretics N=60[H]	Beta Blockers N=78[H]	Angio-tensin Converting Enzyme-Inhibitors N=60[H]
	All data are mean(standard deviation) unless otherwise stated.					
Female %(N)	63(149)	43(32)	85(28)	77(46)	72(56)	48(29)
Age	85.5(0.4)	85.5(0.4)	85.5(0.4)	85.5(0.4)	85.5(0.4)	85.6(0.5)
Ethnic group %(N) White British	100%	100%	100%	100%	100%	100%
Systolic blood pressure, baseline	151.8(22.0)	153.5(21.2)	150.2(22.3)	150.4(18.0)	153.6(25.8)	152.1(23.9)
Diastolic blood pressure, baseline	74.8(11.0)	76.0(11.4)	74.8(11.7)	77.1(10.5)	73.6(10.1)	72.9(10.4)
Systolic blood pressure, 36 months	144.2(20.5)	146.9(18.5)	140.1(18.2)	148.1(17.2)	140.9(20.3)	141.6(20.8)
Diastolic blood pressure, 36 months	71.1(10.7)	72.5(11.0)	68.6(10.3)	74(9.9)	68.8(9.8)	69.9(10.5)
History cerebrovascular disease %(N)*	20(48)	16(22)	8(24)	9(15)	12(15)	13(22)
Number of antihypertensives	1.9(0.8)	2.2(0.9)	2.2(0.9)	2.3(0.9)	2.3(0.9)	2.2(0.9)
Years of education	10.9(1.9)	9.9(1.9)	10.3(2.7)	9.8(1.7)	10.1(1.9)	10.0(2.1)

Count of chronic diseases**		4.9(1.5)	4.7(1.2)	5.3(1.3)	4.4(1.4)	5.0(1.5)	4.9(1.6)
Diabetes %(N)		17(40)	15(11)	21(7)	10(6)	23(18)	20(12)
Atrial fibrillation %(N)		11.9(28)	8.1(6)	18.2(6)	8.6(5)	11.5(9)	13.3(8)
Smoking %(N)	Never	40(95)	28(38)	15(45)	26(43)	30(38)	25(42)
	Former occasional	2(5)	2(3)	1(3)	0(0)	0(0)	0(0)
	Former regular	52(124)	41(55)	15(45)	32(53)	42(54)	29(49)
	Current	6(13)	3(4)	2(6)	2(3)	6(8)	5(8)
Body Mass Index (kg/m^2) %(N)^1	<18.50	4(9)	6(4)	3(1)	2(1)	4(3)	3(2)
	18.5 to 24.99	48(109)	47(33)	38(12)	47(27)	41(31)	50(29)
	25.00 to 29.99	38(88)	40(28)	44(14)	40(23)	36(27)	33(19)
	30.00 to 39.99	10(22)	7(5)	13(4)	11(6)	17(13)	14(8)
Baseline SMMSE	Mean(SD)	27.5(2.8)	27.4(2.8)	27.7(2.4)	27.9(3.0)	27.6(2.5)	27.7(3.1)
	Median(IQR)	28(27-29)	28(26-29)	28(27-29)	29(28-30)	28(27-29)	29(27-30)
Follow-up SMMSE	Mean(SD)	25.9(4.7)	26.6(4.3)	27(2.7)	26.9(4.2)	25.3(5.2)	26.2(5.4)
	Median(IQR)	27(24-29)	28(25-29)	27(26-29)	28(26-29)	26.5(24-29)	28(25-29)
SMMSE change (baseline – follow up)		1.6(6.6)	0.9(2.8)	0.7(1.6)	0.9(3.0)	2.3(4.6)	1.6(3.4)

*Diagnosis of prior stroke, transient ischaemic attack or carotid endarterectomy, as recorded in General Practice records.

**Ischaemic heart disease, hypertension, cerebrovascular disease, peripheral vascular disease, heart failure, arthritis, osteoporosis, chronic obstructive pulmonary disease, other respiratory disease, diabetes, hyper/hypoactive thyroid, cancer in the last 5 years (excluding non-melanoma skin cancer), eye disease, dementia, Parkinson's disease, atrial fibrillation or flutter, renal impairment or anaemia (23-25).

ȾOnly one participant had a BMI >39.99

ⱧParticipants could be prescribed more than one antihypertensive type

Table 2 Mean decline in SMMSE over three years by antihypertensive drug class

Antihypertensive drug class	Mean change in SMMSE (Standard Deviation)		
	Prescribed	Not prescribed	P value (t test*)
Calcium Channel Blockers (CCB) (N=74)	0.9**(2.8)	2.0(3.9)	0.02
Angiotensin receptor Blockers (ARB) (N=33)	0.7(1.6)	1.8(3.8)	<0.01
Thiazide and related diuretics (N=60)	0.9(3.0)	1.9(3.8)	0.05
Beta blockers(BB) (N=78)	2.3(4.6)	1.3(3.1)	0.12
Angiotensin Converting Enzyme Inhibitors (ACE-I)(N=60)	1.6(3.4)	1.7(3.7)	0.81

*t test is a comparison of specified class of antihypertensive against all other antihypertensive treatments.

**Change in SMMSE (baseline SMMSE minus three year follow up SMMSE), i.e. a positive value represents a fall

Table 3

Relationship between antihypertensive class use and cognitive change over three years

		Dependent variable					
		Change in SMMSE score (baseline-three year score)* Slope(95% Confidence Interval (CI))**		Decline of SMMSE by >4 points Odds Ratio(OR)(95%CI)*		Decline of SMMSE greater than the reliable change index OR(95%CI)*	
Those with hypertension and antihypertensive treatment (n=238)	CCB	-1.29(-2.42:-0.16),	P=0.03	0.37(0.13:1.06),	P=0.06	0.35(0.10:1.20),	P=0.09
	ARB	-0.97(-2.52:0.58),	P=0.20	Numbers too small		0.29(0.03:2.43),	P=0.25
	Thiazide and related diuretics	-1.18(-2.41:0.05),	P=0.06	0.57(0.18:1.80),	P=0.34	0.72(0.19:2.76),	P=0.63
	BB	1.33(0.22:2.45),	P=0.02	2.88(1.24:6.70),	P=0.01	2.60(0.97:6.99),	P=0.06
	ACE-I	-0.45(-1.69:0.80),	P=0.47	0.67(0.24:1.84),	P=0.44	0.83(0.26:2.65),	P=0.76
Those with hypertension, antihypertensive treatment and baseline SMMSE>24 (n=204)	CCB	-1.33(-2.37:-0.30),	P=0.01	0.16(0.03:0.79),	P=0.02	0.38(0.15:1.00),	P=0.05
	ARB	-0.44(-1.84:0.95),	P=0.51	Numbers too small		Numbers too small	
	Thiazide and related diuretics	-0.69(-1.80:0.41),	P=0.21	0.70(0.21:2.34),	P=0.56	0.72(0.28:1.86),	P=0.49
	BB	0.91(-0.15:2.00),	P=0.09	2.60(0.96:7.07),	P=0.06	1.68(0.74:3.83),	P=0.21

ACE-I	-0.63(-1.78:0.51),	P=0.27	0.41(0.11:1.57),	P=0.19	0.71(0.28:1.79),	P=0.47

*Change in SMMSE calculated by baseline minus 3 year follow up score.

**compared to no use of respective antihypertensive, adjusted for age, sex, years of education, baseline SMMSE score, smoking, body mass index, baseline systolic and diastolic blood pressure, and incident cerebrovascular event including transient ischemic attack.

Figure 1: Flow chart for the analytic sample

Sampling Frame

People born in 1921 from 53 participating
~~general practices~~

→ **Excluded by GP**   **n=11**

Invited to participate

→ **Excluded**
- Not at last known address   **n=24**
- ~~Uncontactable~~   ~~n=~~

Contact established

→ **Declined**   **n=358**

→ **No capacity to consent and consultee
uncontactable**   **n= 9**

Recruited

**Health assessment (HA)
only**

**Health assessment (HA) plus

review of general practice
(GP) medical records**

GP record review only

→ **Excluded**
- Withdrew and requested
  data destroyed   **n=2**

Baseline HA and GP records data available

**Baseline diagnosis of hypertension and taking
antihypertensive medication**

→ **Excluded**
- Died before 3 year follow-up **n=147**
- Withdrew before 3 year follow-up **n=27**

Analytic sample

**(Baseline diagnosis of hypertension, taking
antihypertensive medication and had both baseline and
~~three year follow-up SMMSE scores)~~**

**Baseline SMMSE >24 & not taking cognitive enhancing
medication**