TITLE PAGE

Manuscript Title

Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis.

First Author's Surname

Hughes

Authors' names, academic degrees, and affiliations

Diarmaid Hughes, M.B., BEng. (1)

Conor Judge, M.B., BEng. (1) (2) (3)

Robert Murphy, M.B. (1)

Elaine Loughlin, M.B. (1)

Maria Costello, M.B. (1)

William Whiteley, Ph.D. (4)

Jackie Bosch, Ph.D. (5)

Martin J. O'Donnell, Ph.D. (1) (5)

Michelle Canavan, Ph.D. (1)

Author affiliations

(1) HRB-Clinical Research Facility, NUI Galway, Galway, Ireland

(2) Translational Medical Device Lab, NUI Galway, Galway, Ireland

(3) Wellcome Trust – HRB, Irish Clinical Academic Training, Dublin, Ireland

(4) Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh, Scotland

(5) Population Health Research Institute, Hamilton, Canada

Name, and complete contact information for corresponding author

Michelle Canavan

michelle.canavan@hse.ie

0035391544860HRB Clinical Research Facility, Galway University Hospital, Newcastle Road, Galway, Ireland, H91YR71

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Key Points

Question

Is there an association between blood pressure lowering with antihypertensive therapy and the incidence of dementia or cognitive impairment?

Findings

In this meta-analysis that included 12 trials with 92 135 participants for the primary outcome measure, blood pressure lowering with antihypertensive agents compared to control, was associated with the development of a composite dementia or cognitive impairment outcome in 7.0% vs 7.5% of patients over a median follow-up of 4.1 years, a difference that was statistically significant.

Meaning

Lowering blood pressure may be associated with a lower risk of dementia or cognitive impairment.

Abstract

Importance

The benefit of blood pressure lowering for the prevention of dementia or cognitive impairment is unclear.

Objective

To determine the association of blood pressure lowering with dementia or cognitive impairment.

Data Sources and Study Selection

Pubmed, Embase and CENTRAL were searched from database inception through December 31, 2019 for randomised clinical trials evaluating the association of blood pressure lowering on cognitive outcomes. The control groups consisted of either placebo, alternate antihypertensive agents or higher blood pressure targets.

Data Extraction and Synthesis

Data were screened and extracted independently by two authors. Random-effects meta-analysis models were used to report pooled treatment effects and confidence intervals.

Main Outcomes and Measures

The primary outcome was dementia or cognitive impairment. The secondary outcomes were cognitive decline and changes in cognitive testing scores. PROSPERO Registration Number CRD42019125088.

Results

Fourteen randomised clinical trials were eligible (96 158 participants), of which twelve reported the incidence of dementia (or composite of dementia and cognitive impairment, 3 trials) on follow-up and were included in the primary meta-analysis, eight reported cognitive decline, and eight reported changes in cognitive test scores. The mean (Standard Deviation [SD]) age of trial participants was 69 (5.4) years; 40 617 (42.2%) were female and the mean baseline blood pressure was 154 (14.9) mmHg systolic and 83.3 (9.9) mmHg diastolic. Mean duration of follow-up was 49.2 months. Blood pressure lowering with antihypertensive agents compared to control was significantly associated with a reduced risk of dementia or cognitive impairment (n=12 trials) (7.0% in the intervention group vs 7.5% of patients in the control group over a median of 4.1 years) (odds ratio [OR], 0.93; 95% confidence interval [CI]: 0.88 to 0.98, absolute risk

reduction, 0.39% [95% CI, 0.09%-0.68%]; I^2=0.0%) and cognitive decline (n=8 trials) (20.2% in the intervention group vs 21.1% of patients in the control over a median of 4.1 years) (OR, 0.93; 95% CI: 0.88-0.99, absolute risk reduction, 0.71% [95% CI, 0.19%-1.2%]; I^2=0.0%). Blood pressure lowering was not significantly associated with a change in cognitive score testing.

Conclusions and Relevance

In a meta-analysis of randomized clinical trials, blood pressure lowering with antihypertensive agents compared to control was significantly associated with a lower risk of incident dementia or cognitive impairment.

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Introduction

Hypertension, especially in mid-life, is associated with dementia and cognitive impairment in later life (1–4). Some randomised clinical trials have reported a lower risk of dementia with blood pressure lowering treatment (5–7). However, previous meta-analyses of randomised clinical trials that have evaluated the association of antihypertensive therapy with the risk of neurocognitive syndromes, in either primary or secondary prevention populations, have been inconclusive (8–11). Two additional clinical trials have been recently published (12,13). SPRINT MIND reported a lower risk of mild cognitive impairment in those randomised to an intensive blood pressure target. Conversely, HOPE-3 reported no significant reduction in the risk of cognitive impairment or dementia with combination antihypertensive therapy compared to placebo. An updated meta-analysis was performed, given the addition of these recent large randomised clinical trials, to determine whether blood pressure lowering was associated with a reduced risk of dementia or cognitive impairment.

Methods

We performed a systematic review and meta-analysis which are reported according to the *Preferred Reporting for Systematic Reviews and Meta-analyses* (PRISMA) guidelines (14). The protocol was registered with PROSPERO (Registration Number CRD42019125088).

Data Sources and Searches

We developed the search strategy without language restriction for Pubmed, Embase and CENTRAL from database inception to December 31, 2019. The search terms included *dementia*, *cognitive decline*, *cognitive impairment*, *blood pressure*, *hypertension*, *anti-hypertensive* and *randomised controlled trials*. The search strategy was peer-reviewed by a second information specialist. The full search strategy is included in the supplementary appendix (eMethods 1). Three reviewers (DH, CJ and RM) independently screened titles and abstracts. Full texts were sourced for relevant articles. Inclusion criteria were assessed independently, and inconsistencies were resolved by consensus. The reference lists of included trials and other published meta-analyses were also reviewed.

Eligibility Criteria

Trials were considered eligible if they: (1) were randomised clinical trials; (2) compared blood pressure lowering with antihypertensive agents with a control; (3) had at least one year of follow-up; (4) included over 1000 participants; and (5) provided information on any of the prespecified outcomes. Control was defined as placebo, alternate antihypertensive agent or higher blood pressure target (Table 1). Trials were required to report at least one of the following outcomes: dementia, cognitive impairment, cognitive decline, or change in cognitive test scores (Table 1). Trials that specifically recruited participants with known dementia or cognitive impairment at the start of the trial were excluded.

Data extraction

Data were extracted independently by two authors (DH and CJ) using a standardised data extraction form. This was entered into a dedicated database and checked independently by RM, MC, EL and MC. We extracted the following data: study characteristics, baseline demographics of participants, description of the intervention, cumulative blood pressure changes, incidence of dementia and cognitive impairment, and

cognitive test scores. The cumulative blood pressure change (net change in systolic blood pressure from baseline to longest follow-up between groups) was reported in 10 trials and the other trials reported the difference between the systolic blood pressure of the groups at trial end. We reported outcomes at the point of longest follow-up (15). Majority primary prevention populations were defined as those where greater than 50% of participants had no history of cardiovascular events. All others were considered majority secondary prevention populations.

Outcomes

The primary outcome of this meta-analysis was dementia or cognitive impairment. For our primary analysis, we used a hierarchical approach where we included trials that reported incident dementia, or a composite of dementia or cognitive impairment (if dementia alone was not reported) on follow-up. Dementia was criterion referenced in 7 trials, (International Classification of Diseases (ICD) criteria, the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, or adjudicated panel), clinically based in two trials and diagnosed using a composite in the remainder (Table 1). We chose this approach to maximise the number of clinical trials included in our primary analysis. In addition, cognitive impairment and dementia represent a continuum of the same neurocognitive syndrome and we expected blood pressure lowering using antihypertensives to have a consistent association with both.

The secondary outcomes were cognitive decline and mean change in cognitive test scores. The definition of cognitive decline varied among trials, and we used a definition of cognitive decline when the cognitive score decreased by an absolute value within the study period (e.g. 3 points in MMSE), alone or combined with below a cut-point in cognitive score. All studies reported a cognitive test score.

Risk of Bias Assessment

We used the Cochrane Risk of Bias Tool (16) to assess methodological quality of eligible trials. Trials were assessed on random sequence generation, allocation concealment, blinding of participants and health care personnel, blinded outcome assessment, completeness of outcome data, evidence of selective reporting, and other biases. Risk of bias assessments were performed independently by two reviewers (DH, RM), and

disagreements were resolved by a third reviewer (CJ). If two of the domains were rated as high, the study was considered at high risk of bias. A risk of bias summary table was created in Review Manager 5.3. Details are included in the Supplementary Appendix (eTable 1, eFigure 1 and eFigure 2).

Data synthesis and analysis

A descriptive analysis of each individual trial is reported in Table 1. Baseline, follow-up and mean difference in blood pressure for each trial is reported in Table 2. For dichotomous outcomes (dementia, cognitive impairment and cognitive decline), odds ratios (OR) and 95% confidence intervals (CI) were estimated for each trial. Weighted pooled treatment effects were calculated using Restricted maximum likelihood (REML) estimation to fit a random effects meta-analysis model. The variability across studies due to heterogeneity was investigated using forest plots and I^2 statistic. Publication bias was assessed using a funnel plot (eFigure 3). For continuous outcomes (e.g. mini-mental state examination (MMSE)), the mean change from baseline to follow-up was analysed. If this was not reported, the mean difference reported at follow-up was used. 95% CIs were converted to the Standard Error using the formula, SD=√N*(Upper Bound of Confidence Interval – Lower Bound of Confidence Interval)/3.92 (17). Two trials had dual treatment groups with a common control group (18,19). To prevent double counting and a unit of analysis error, we split the common control group into two equal groups (17). The difference in MMSE change between the intervention and control group was calculated unless the difference was specifically reported. In addition, a pooled mean difference using a random-effects meta-analysis was calculated. A positive mean difference implies that the intervention compared to the control had a smaller magnitude of decrease in MMSE score between baseline and follow-up (i.e. reduced cognitive decline on testing). For additional cognitive test scores, we calculated a pooled mean standardised difference (Cohen's d) using a random-effects meta-analysis.

A priori sub-group sensitivity analyses were performed assessing pooled estimates for trials above and below the median cumulative blood pressure change, above and below median years of follow-up, and a product of both (mmHg years). We tested for an interaction between subgroup relative risks by dividing the difference in log relative risk by its standard error (20). We completed meta-regression analyses to evaluate

the association of on-treatment effect estimates, including baseline mean systolic blood pressure, years of follow-up, or cumulative systolic blood pressure change. Post hoc, absolute risk reductions (ARR) were calculated for each study, the Mantel-Haenszel method was used to obtain a pooled estimate of the risk difference and boot strapping was used to estimate the absolute risk reduction for trials reporting dementia only. In addition, sensitivity analysis only including studies at low risk of bias was performed and fragility index was calculated for the primary outcome. Statistical analyses were performed using the Metafor package (21) on R Statistical Software (V3.5.3 "Great Truth"). Comparisons were 2-tailed using a $P \leq 0.05$ threshold for all analyses apart from subgroup interactions where we used a $P \leq 0.1$ threshold (22).

Results

The systematic search of articles published before December 31, 2019, identified 1543 records. Following title and abstract screening, 163 were considered potentially relevant. Fourteen studies, available as 22 reports, were included after full text review (eFigure 4). Twelve studies reported the incidence of dementia (n=9) or composite of dementia or cognitive impairment (n=3) on follow-up and were included in the primary meta-analysis (5–7,12,13,23–28). Two studies were used for secondary outcomes only (19,29).

Study Characteristics

In total, 96 158 participants were enrolled, comprising 394 558 participant-years of follow-up. The mean (SD) age of trial participants was 69 (5.4) years; 40 617 (42.2%) were female and the mean baseline blood pressure was 154 (14.9) mmHg systolic and 83.3 (9.9) mmHg diastolic. The median (range) duration of follow-up was 49.24 (26.4-68.4) months. Publication year ranged from 1994 to 2019 (Table 1). Nine trials were in a majority primary prevention population (5,6,12,13,19,23,25,26,29), three trials were in a post-stroke secondary prevention population (24,27,28), and two trials were in participants with cardiovascular disease (18,30). Ten trials were placebo-controlled (5–7,13,19,23–27), three trials compared different blood pressure targets (12,28,29) and one trial compared two anti-hypertensive agents, alone or in combination (resulting in two comparisons, combination antihypertensive agents, and single new agent versus standard of care) (18).

Risk of Bias

Risk of bias was assessed in all 14 trials (eTable 1, eFigure 1 and 2). The overall risk of bias was deemed low in 11 trials, unclear in one trial, and high in two trials. The majority (n=13) of trials were double blinded randomised clinical trials with pre-specified outcomes and one was single-blinded (19). Randomisation sequence was adequately generated in 13 studies and 13 adequately concealed allocation. Reporting bias was noted in one trial. There was no evidence of publication bias for the primary outcome (Egger test: −0.53; P = 0.61).

Blood pressure lowering and dementia or cognitive impairment

Twelve trials reported dementia or cognitive impairment on follow-up (92 135 participants) (5–7,12,13,23–28). Dementia or cognitive impairment was diagnosed in 2992 participants in the intervention group and 2558 participants in the control group. Blood pressure lowering with antihypertensive agents compared to control was significantly associated with a reduction in dementia or cognitive impairment (7.0% in the intervention group vs 7.5% of patients in the control over a median of 4.1 years) (OR, 0.93; 95% CI, 0.88-0.98; ARR 0.39% [95% CI, 0.09%-0.68%]) (Figure 1). Heterogeneity was low (I^2=0.0%). For trials that employed criterion-reference for diagnosis of dementia (7 trials, 41 719 participants), blood pressure lowering was significantly associated with a reduction in dementia (OR, 0.87; 95% CI, 0.78-0.97; ARR 0.20% [95% CI, 0.05%-0.70%]). Sensitivity analysis only including studies at low risk of bias did not materially alter the findings (OR, 0.94; 95% CI, 0.877-0.997) (eFigure 5). The fragility index for meta-analysis of the primary outcome was 9 (31). Sensitivity analysis by cumulative change in blood pressure (above and below median) showed an association with dementia or cognitive impairment for trials with cumulative blood pressure change above the median (OR, 0.88; 95% CI, 0.80-0.96) but P for interaction was non-significant (P-interaction=0.13) and there was no significant association with dementia or cognitive impairment for cumulative blood pressure change below the median (OR, 0.96; 95% CI, 0.90-1.03). (Figure 2, eFigure 6). Sensitivity analysis by baseline blood pressure above and below the median was also non-significant for subgroup interaction (P-interaction=0.36) (Figure 2, eFigure 7). Meta-regression analysis showed no significant association between age, baseline systolic blood pressure, cumulative systolic blood pressure or years of follow-up and incidence of dementia or cognitive impairment (eFigure 8).

Blood pressure lowering and cognitive decline

Eight trials reported cognitive decline on follow-up (67 476 participants) (6,12,13,18,24,25,27,30). Cognitive decline was reported in 5513 participants in the intervention group and 4468 participants in the control group. Blood pressure lowering with antihypertensive agents compared to control was significantly associated with a reduction in cognitive decline (20.2% in the intervention group vs 21.1% of patients in the control over a median of 4.1 years) (OR, 0.93; 95% CI, 0.88-0.99; ARR, 0.71%; 95% CI, 0.19%-1.2%) (Figure 3). Heterogeneity was low (I^2=36.1%). Sensitivity analysis by cumulative change in blood pressure (above and below median) showed a significant association for cumulative blood pressure change above the median (OR, 0.89; 95% CI, 0.82-0.96) and non-significant association for cumulative blood pressure change below the median (OR, 0.98; 95% CI, 0.92-1.05) (P for interaction = 0.07) (Figure 2, eFigure 9). Sensitivity analysis by baseline blood pressure above and below the median reported no significant subgroup interaction (P for interaction=0.74) (Figure 2, eFigure 10). Meta-regression analysis showed no significant association between age, baseline systolic blood pressure, cumulative systolic blood pressure or years of follow-up and cognitive decline (eFigure 11).

Blood pressure lowering and change in cognitive score

Eight trials reported a change in cognitive score as an outcome (5,6,13,19,24,25,28,29). Five trials reported change in MMSE (5,6,24,25,29), two reported change in Trail Making Test (TMT) score (13,19) and one reported change in Cognitive Abilities Screening Instrument (CASI) Z score (28). Three studies reported baseline cognitive scores but not follow up scores and these data were insufficient to include in the meta-analysis (7,27). Blood pressure lowering with antihypertensive agents compared to control was not significantly associated with a difference in the standardised mean cognitive score (n=8) (0.25; 95% CI,-0.10 to 0.61) (eFigure 12). The P for heterogeneity was P<0.01, I^2=99.5%, Q=853.24. For trials reporting change in MMSE, blood pressure lowering with antihypertensive agents compared to control was not significantly associated with a difference in mean MMSE score (0.44; 95% CI, -0.22 to 1.10) (eFigure 13). I^2=98.5%, Q=143.17.

Discussion

This meta-analysis, including 12 trials with 92 135 participants, found that blood pressure lowering with antihypertensive agents compared to control was significantly associated with a lower risk of dementia or cognitive impairment.

This study builds on previous meta-analyses and includes the largest number of randomized clinical trials. A pooled analysis, combining randomised clinical trials and observational studies in 2013, reported a similar risk reduction with treatment of hypertension to this analysis, but no significant association in trials alone (10). A meta-analysis by van Middelar reported a similar, but non-significant, magnitude of association of blood pressure lowering and included two trials evaluating multi-component lifestyle interventions, rather than blood pressure lowering alone. Both these meta-analyses, and Cochrane reviews, were published before the SPRINT MIND and HOPE-3 trials (11,32,33). The most recent meta-analysis, by Peters et al, which included of the SPRINT MIND trial, reported an association of blood pressure lowering with reduced risk of dementia (OR 0.93, 95% CI, 0.86-1.00), which included fewer trials than this meta-analysis (8 trials) due to different selection criteria. In an analysis that selected trials with greater than 10 mmHg difference between treatment groups, they reported an odds ratio of 0.88 (95% CI, 0.78-0.98) but did not report a P-interaction. The approach taken in this study resulted in inclusion of larger numbers of clinical trials, reported a more extensive panel of outcome measures (e.g. cognitive decline and mean change of cognitive test scores), and completed a meta-regression for pre-selected variables. While the increased number of clinical trials resulted in a statistically significant summary estimate, the upper bound of the confidence interval was close to 1.0, which should prompt some caution in interpreting the findings as definitive evidence of an association of blood pressure lowering with dementia or cognitive impairment.

While observational studies report hypertension to be an important risk factor for dementia (1,3,4,34), the benefit of blood pressure lowering on dementia in clinical trials is modest (relative risk reduction [RR] 0.93, 95% CI; 0.86-1.00) (11), and lower than the risk reduction for stroke (5,6,19,23–25). The causes of neurocognitive syndromes are more heterogenous than stroke, including Alzheimer’s disease, and other causes, and the population attributable fraction of hypertension for dementia is lower than that reported for

stroke, based on indirect comparison of studies (35,36). In addition, the association of hypertension with neurocognitive syndromes, mediated through chronic covert vascular damage (ischemia, microhaemorrhage or atrophy (37)) appears to have an extended time-lag between cause and clinical consequence, although dementia may be a complication of acute stroke. Observational studies relating blood pressure to neurocognitive outcomes have required follow-up periods exceeding 20 years. Therefore, large sample sizes, with extended follow-up, are required to identify an effect of antihypertensive treatment on neurocognitive outcomes. These considerations, may explain why most individual randomized clinical trials have failed to demonstrate a treatment effect.

Epidemiologic studies have reported a stronger association of hypertension in mid-life with neurocognitive outcomes in later life, than hypertension in later-life, where a null or inverse association has been reported in some studies (38,39). These findings have led some investigators to speculate that populations included in some blood pressure trials may have been in an age range that may not benefit from blood pressure lowering to prevent cognitive outcomes. These meta-analyses would not fully support this contention, as baseline age was not a determinate of treatment effect, and mean age of included trials was 69 years at baseline.

These findings have the potential to inform public health strategies to reduce the burden of dementia globally. Effective screening and treatment of hypertension is essential for reducing premature dependence from dementia. Although the lower risk associated with blood pressure treatment is modest for an individual, the effect at a population level, given the incidence of dementia in an ageing population, may be considerable. Rates of blood pressure control are low, even in high-income countries, but especially in middle and low-income countries, which carry the largest burden of dementia (40). The World Health Organisation's global action plan on the public health response to dementia recommend management of hypertension in mid-life to reduce the risk of dementia, a recommendation supported by these results (41).

While there was a significant reduction of clinically important neurocognitive syndromes, there was no significant difference in mean change in cognitive testing, contrasting from the clinical outcomes. This finding supports the need for large simple trials with clinically important outcomes to evaluate preventative interventions in populations (42). None of the included clinical trials reported dementia as their primary

outcome measure. When dementia was reported, it was as a secondary outcome with differences in outcome definition. When the analyses were confined to clinical trials that reported criterion-referenced dementia, the association of blood pressure lowering and dementia was most evident (Figure 1).

Limitations

This study has several limitations. First, the inherent challenges in performing, and interpreting, a meta-analysis with heterogenous populations, interventions and definitions of the outcomes of dementia, cognitive impairment and cognitive decline. Second, the low incidence of dementia in all clinical trials despite the large number of participants reduced power to detect differences in treatment effect and limited exploration of subgroups or meta-regression. Third, under-detection of dementia in clinical trials due to preferential loss to follow-up of participants with dementia, and the potential effect of survival bias (where participants with blood pressure reductions are more likely to be alive) are unmeasured sources of potential error.

Conclusion

In a meta-analysis of randomized clinical trials, blood pressure lowering with antihypertensive agents compared to control was significantly associated with a lower risk of incident dementia or cognitive impairment.

Contributors

DH, CJ, MC, RM and EL were responsible for data collection. DH and CJ performed the analysis. All authors contributed to data interpretation and critical revision of the report.

Acknowledgments

The corresponding author certifies that no other persons have made substantial contributions to the research and/or manuscript. Dr Hughes and Dr Judge had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Hughes and Dr Judge conducted and are responsible for the data analysis. Dr John Ferguson (HRB CRF Galway) contributed to the updated analysis (boot strapping method for applying relative risk reduction to baseline risk of dementia). Dr Hughes and Dr Judge take full responsibility as first authors.

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Disclosures

All authors declare no competing interests.

Affiliations

The authors' affiliations are as follows: Health Research Board–Clinical Research Facility, Galway University Hospital, National University of Ireland, Galway (DH, CJ, MC, EL, RM, MO'D, MC). Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh, Scotland (WW). Population Health Research Institute, Hamilton, Canada (JB).

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Figures

Figure 1 – Blood Pressure Lowering and Dementia or Cognitive Impairment

Figure 1 - Forest plot showing the association of blood pressure lowering and dementia or cognitive impairment. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no association. * Composite of dementia and cognitive impairment (Table 1). BP-Blood Pressure, RE-Random Effect, CI-Confidence Interval

Figure 2 – Blood Pressure Lowering and Dementia or Cognitive Impairment/Cognitive Decline by Cumulative Systolic Blood Pressure Change and Baseline Systolic Blood Pressure

Figure 2 - Forest plot showing the association of blood pressure lowering on dementia or cognitive impairment and cognitive decline by cumulative systolic blood pressure change and baseline systolic blood pressure. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no association. BP-Blood Pressure, RR-Risk Ratio, CI-Confidence Interval.

Figure 3 – Blood Pressure Lowering and Cognitive Decline

Figure 3 - Forest plot showing the association of blood pressure lowering and cognitive decline. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no association. * Composite of dementia and cognitive impairment (Table 1). BP-Blood Pressure, RE-Random Effect, CI-Confidence Interval.

Tables

Table 1 – Study Characteristics

Trial	No. Participants	Trial design	Study Population	Prevention	Intervention	Control	Follow up (mths)	Testing	Baseline Cognitive Scores Intervention (SD or IQR)	Baseline Cognitive Scores Control (SD or IQR)	Primary Outcome (Dementia or Cognitive Impairment)	Secondary Outcome (Cognitive decline)	Seco Outc (Cogn score
Dementia (Criterion-referenced)													
SHEP, 1994	4736	Randomized, double-blind, placebo control	Age >60; SBP 160-219mmHg and DBP<90mmHg	MPP	Diuretic +/- Beta blocker	Placebo	60	Short-Care	0.37 (0.65)	0.38 (0.69)	Adjudicated panel	Not reported	Not repor
PROGRESS, 2001	6105	Randomized, double-blind, placebo control	Stroke / TIA in preceding 5 years	SP	ACEi +/- Diuretic	Placebo	46.8	MMSE	29 (27-30)	29 (27-30)	DSM-IV criteria	Decrease in MMSE of ≥3	Chan MMS
Syst-Eur, 2002	2902	Open label extended follow-up of randomized trial	Age >60; SBP 160-219mmHg and DBP <95mmHg	MPP	CCB +/- ACEi +/- Diuretic	Placebo	46.8	MMSE	29 (27-30)	29 (27-30)	DSM-III-R criteria	Not reported	Chan MMS
SCOPE, 2003	4937	Randomized, double-blind, placebo control	Age 70-89; SBP 160-179mmHg and/or DBP 90-99mmHg	MPP	ARB +/- Diuretic	Placebo	44.6	MMSE	28.5 (1.6)	28.5 (1.5)	ICD-10 criteria	Decrease in MMSE ≥4	Chan MMS
HYVET-COG, 2008	3336	Randomized, double-blind, placebo control	Age >80; Sitting SBP 160-200mmHg and DBP <110mmHg	MPP	Diuretic +/- ACEi	Placebo	26.4	MMSE	26 (15-30)	26 (15-30)	DSM-IV criteria	Decrease in MMSE ≥3 or MMSE ≤24	Chan MMS

ADVANCE, 2009	11 140	Randomized, double-blind, placebo control (2x2 factorial design)	Age ≥55; Diagnosis of Type II DM at age ≥30 with history/risk factor for CVD	MPP	ACEi and Diuretic	Placebo	51.6	MMSE	29 (28-30)	29 (28-30)	DSM-IV criteria	Not reported	Not repor
SPRINT MIND, 2019	8563	Randomized, open label trial	Age ≥50; SBP between 130 - 180mmHg	MPP	SBP <120mmHg	SBP <140mmHg	61.2	MoCA DSCT LMFII	23 (20-26) 51 (41-60) 8 (6-11)	23 (20-25) 51 (41-61) 8 (6-11)	Adjudicated panel	MCI by adjudicated panel	Not repor
Dementia (Clinical-based)													
PRoFESS, 2008	17 270	Randomized, double-blind, placebo control (2x2 factorial design)	Participants with ischaemic stroke in previous 90 days	SP	ARB	Placebo	30	MMSE	28 (26-30)	28 (26-30)	Investigator reported	Two outcomes reported: 1. Decrease in MMSE ≥3; 2. MMSE ≤24	Not repor
HOPE-3, 2019	1626	Randomized, double-blind, placebo control (2x2 factorial design)	Age ≥70 with CVD risk	MPP	ARB +/- Diuretic	Placebo	68.4	mMoCA TMT-B DSST	10.8 (1.7) 150.6 (90.7) 32.8 (18.3)	10.7 (1.8) 152.8 (87.3) 32.6 (18.3)	Investigator reported	Decrease of ≥2 points mMoCA, ≥10% on TMT-B and ≥5 points DSST	Chan mMC
Dementia and Cognitive Impairment (Composite)													
TRANSCEND, 2011	5383	Randomized, double-blind, placebo control	Participants who were ACEi intolerant with CVD / stroke or diabetes	MSP	ARB	Placebo	56	MMSE	29 (27-30)	29 (27-30)	Investigator reported, specilaist confirmed or MMSE ≤23	Decrease in MMSE ≥3	Not repor

ON-TARGET, 2011	23 469	Randomized, double-blind, placebo control	Participants with CVD / stroke or diabetes	MSP	ACEi & ARB or ARB	ACEi	56	MMSE	29 (27-30)	29 (27-30)	Investigator reported, specilaist confirmed or MMSE ≤23	Decrease in MMSE ≥3	Not repor
SPS3, 2014	2668	Randomized, open label (2x2 factorial design)	Lacunar Stroke within 6 months (confirmed on MRI)	SP	SBP <130mmHg	SBP 130-149mmHg	36	CASI Z score	-0.63 (1.47)	-0.56 (1.39)	MCI by cognitive score	MCI by cognitive score	Chan CASI- score
Change in cognitive score only													
MRC-Diuretic, 1996	2584	Randomized, single-blind	Age 65-74; SBP 160-209mmHg and DBP <115mmHg	MPP	Diuretic or Beta Blocker	Placebo	54	PALT TMT	17.0 (16.9-17.1) 59.9 (57.7-62.1)	17.0 (16.9-17.1) 61 (59.3-62.8)	Not reported	Not reported	Chan TMT
MRC-BB, 1996								PALT TMT	17.0 (16.8-17.1) 59.5 (57.7-62.0)	17.0 (16.9-17.1) 61 (59.3-62.8)			
ACCORD-MIND, 2014	1439	Randomized, open label (2x2 factorial design)	Age ≥55; SBP 130-180mmHg Participants with Type II DM	MPP	SBP <120mmHg	SBP <140mmHg	40	DSST MMSE	52.28 (15.7) 27.25 (26-29)	52.28 (15.7) 27.25 (26-29)	Not reported	Not reported	Chan MMS

Abbreviations: INT, Intervention; mnths, months; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; TIA, Transient ischaemic attack; CVD, Cardiovascular disease; Type II DM, Type II Diabetes Mellitus; MRI, Magnetic Resonance Imaging; MPP, Majority Primary Prevention; SP, Secondary Prevention; MSP, Majority Secondary Prevention; BB, Beta Blocker; ACEi, ACE inhibitor; CCB, Calcium Channel Blocker; ARB, Angiotensin II receptor blockers; SD, standard deviation; IQR, interquartile range; PALT, Paired Associate Learning Test; TMT, Trail making test; MMSE, Mini-Mental State

Examination; DSST, Digit Symbol Substitution Test; CASI, Cognitive Abilities Screening Instrument; MoCA, Montreal cognitive assessment; DSCT, Digit Symbol Coding Test; LMF II, Logical Memory form II; mMoCA, modified 12-item Montreal Cognitive Assessment; TMT-B, Trail Making Test Part B; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD – WHO International Classification of Diseases; MCI, Mild Cognitive Impairment

506 Table 2 – Participant Characteristics

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Trial	Country	Age at entry (SD or IQR), y	Female Participants No., (%)	Intervention Baseline BP mean (SD), mmHg	Intervention Follow-up BP mean (SD), mmHg	Intervention Difference BP mean (SD), mmHg	Control Baseline BP mean (SD), mmHg	Control Follow-up BP mean (SD), mmHg	Control Difference BP mean (SD), mmHg	Difference In BP Difference
Dementia (Criterion-referenced)										
SHEP, 1994	United States	72 (6.7)	2700 (57)	170.5 (9.5) 76.7 (9.6)	144.0 (19.3) 67.7 (10.2)	NR NR	170.1 (9.2) 76.4 (9.8)	155.1 (20.9) 71.1 (12.8)	NR NR	-11.1 -3.4
PROGRESS, 2001	Asia, Australasia, United Kingdom and Europe	64 (10)	1831 (30)	147 (19) 86 (11)	NR NR	NR NR	147 (19) 86 (11)	NR NR	NR NR	-9 -4
Syst-Eur, 2002	Europe	68 (60-92)	1918 (66)	173.8 (9.9) 85.5 (5.8)	149.1 (9.7) 79.4 (6.1)	23 (16) 7 (8)	173.9 (10.1) 85.5 (5.9)	156.1 (12) 82.5 (6)	13(17) 2(8)	-7 -3.2
SCOPE, 2003	Europe, United Kingdom, United States	76.4	3177 (65)	166 (8.9) 90.3 (6.6)	145.2 (16.1) 79.9 (8.7)	NR NR	166.5 (9.0) 90.4 (6.6)	148.5 (16.8) 81.6 (8.8)	NR NR	-3.2 -1.6
HYVET-COG, 2008	Europe, China, Tunisia, southeast Asia, and Australia	83.5 (3.1)	2017 (61)	173.0 (8.4) 90.8 (8.5)	143.4 (NR) 77.7 (NR)	29.6 (15.3) 13.1 (9.6)	173.0 (8.6) 90.8 (8.5)	155.4 (NR) 83.6 (NR)	14.6(18.5) 7.2 (10.5)	-15 -5.9
		67 (6)	4735 (43)	145 (NR)	136 (NR)	NR	145 (NR)	140 (NR)	NR	-5.6

ADVANCE, 2009	Asia, Australasia, Europe, and North America.			81 (NR)	73 (NR)	NR	81 (NR)	73 (NR)	NR	-2.2
SPRINT MIND, 2019	United States	67.9 (9.4)	3332 (35.5)	139.7 (15.8)	121.6 (120.8-122.3)	NR	139.7 (15.4)	134.8 (134.1-135.6)	NR	-13.3
				78.2 (11.9)	NR	NR	78.0 (12.0)	NR	NR	NR
Dementia (Clinical-based)										
PRoFESS, 2008	35 countries worldwide	66.1 (8.6)	7310 (36)	144 (17)	135.7 (NR)	8.3	144 (17)	141.1 (NR)	2.9	-5.4
				84 (11)	NR	NR	84 (11)	NR	NR	NR
HOPE-3, 2019	21 countries worldwide	74 (3.5)	963 (59.2)	139.7 (15.0)	NR	NR	139.7 (15.0)	NR	NR	-6
				79.4 (9.6)	NR	NR	79.4 (9.6)	NR	NR	NR
Dementia and Cognitive Impairment (Composite)										
TRANSCEND, 2011	40 countries worldwide	67 (7.3)	2547 (43)	140.7 (16.8)	NR	NR	141.3 (16.4)	NR	NR	-4
				81.8 (10.1)	NR	NR	82.0 (10.2)	NR	NR	-2.2
ON-TARGET (Dual)	40 countries worldwide	66 (7.2)	6831 (27)	141.9 (17.6)	NR	NR	141.8 (17.4)	NR	NR	-2.4
				82.1 (10.4)	NR	NR	82.1 (10.4)	NR	NR	-1.4
ON-TARGET (ARB), 2011				141.7 (17.2)	NR	NR	141.8 (17.5)	NR	NR	-0.9
				82.1 (10.4)	NR	NR	82.1 (10.5)	NR	NR	-0.6
SPS3, 2014		63 (11)	1088 (37)	144 (19)	127 (2.97)	NR	142 (19)	137 (3.4)	NR	-11

	North America, Latin America, and Spain			79 (11)	NR	NR	78 (10)	NR	NR	NR
Change in cognitive score only										
MRC-Diuretic, 1996	United Kingdom	70	1498 (58)	184.9 (183.9-185.9)	NR	NR	183.5 (182.8-184.2)	NR	NR	-17.1
				90.3 (89.4-91.2)	NR	NR	90.5 (89.9 to 91.2)	NR	NR	NR
MRC-BB, 1996				184.2 (183.2-185.2)	NR	NR	183.5 (182.8-184.2)	NR	NR	-14.5
				90.7 (89.9-91.6)	NR	NR	90.5 (89.9 to 91.2)	NR	NR	NR
ACCORD-MIND, 2014	North America	62 (5.8)	670 (46.6)	138.8 (17.0)	119 (14.7)	NR	139.2 (15.7)	133.2 (14.8)	NR	-13.8
				76.0 (10.4)	64 (10.1)	NR	76.3 (10.3)	70.2 (9.9)	NR	-5.9

Abbreviations: SBP, Systolic blood pressure; DBP, Diastolic blood pressure; SD, standard deviation; IQR, interquartile range; NR, not reported.