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FASTTRACK CLINICAL RESEARCH
Clinical trials

Blood pressure lowering and prevention of dementia: an individual patient data meta-analysis

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Abstract

Aims Observational studies indicate U-shaped associations of blood pressure (BP) and incident dementia in older age, but randomized controlled trials of BP-lowering treatment show mixed results on this outcome in hypertensive patients. A pooled individual participant data analysis of five seminal randomized double-blind placebo-controlled trials was undertaken to better define the effects of BP-lowering treatment for the prevention of dementia.

Methods and results Multilevel logistic regression was used to evaluate the treatment effect on incident dementia. Effect modification was assessed for key population characteristics including age, baseline systolic BP, sex, and presence of prior stroke. Mediation analysis was used to quantify the contribution of trial medication and changes in systolic and diastolic BP on risk of dementia. The total sample included 28 008 individuals recruited from 20 countries. After a median follow-up of 4.3 years, there were 861 cases of incident dementia. Multilevel logistic regression reported an adjusted odds ratio 0.87 (95% confidence interval: 0.75, 0.99) in favour of antihypertensive treatment reducing risk of incident dementia with a mean BP lowering of 10/4 mmHg. Further multinomial regression taking account of death as a competing risk found similar results. There was no effect modification by age or sex. Mediation analysis confirmed the greater fall in BP in the actively treated group was associated with a greater reduction in dementia risk.

Conclusion The first single-stage individual patient data meta-analysis from randomized double-blind placebo-controlled clinical trials provides evidence to support benefits of antihypertensive treatment in late-mid and later life to lower the risk of dementia. Questions remain as to the potential for additional BP lowering in those with already well-controlled hypertension and of antihypertensive treatment commenced earlier in the life-course to reduce the long-term risk of dementia.

Classification of evidence Class I evidence in favour of antihypertensive treatment reducing risk of incident dementia compared with placebo.

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Structured Graphical Abstract

Key Question

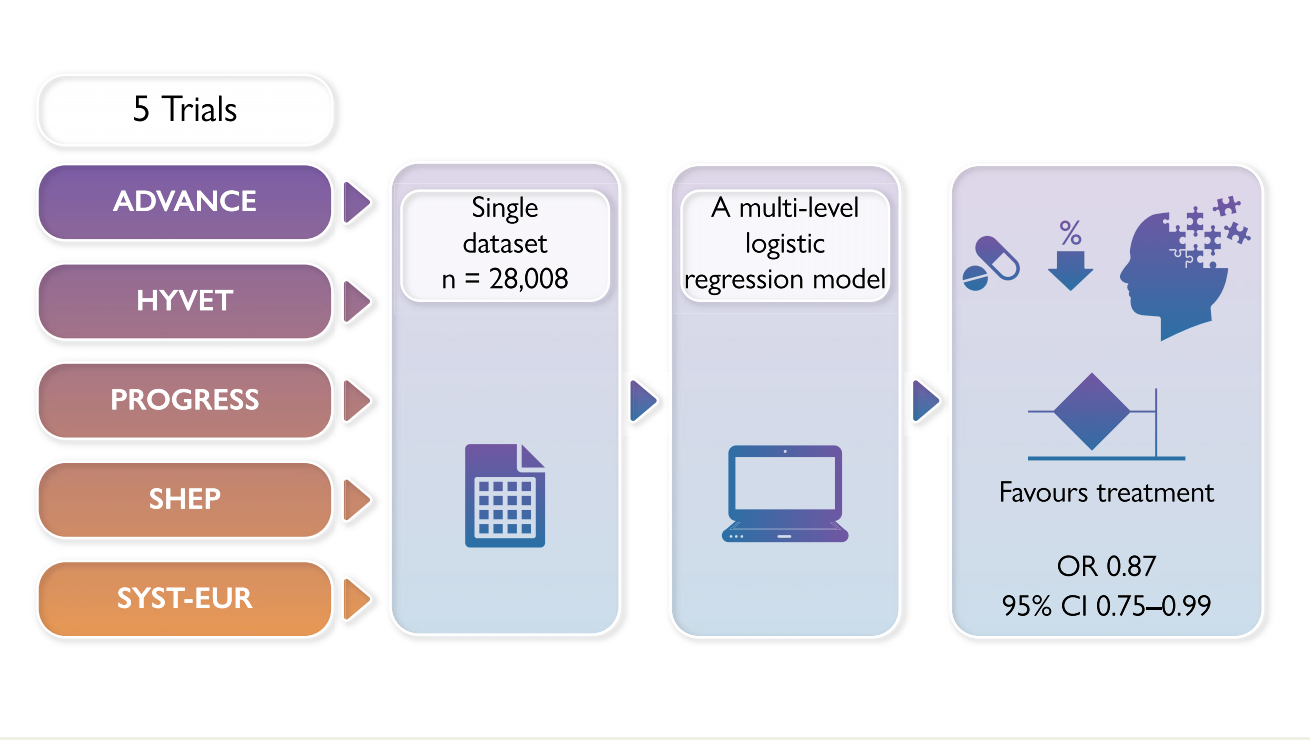
Prior study level meta-analyses of antihypertensive trials and dementia were at risk of bias in their estimates. This limitation can be overcome by a patient-level meta-analysis.

Key Finding

This patient level meta-analysis combining raw data from five large double-blind placebo-controlled trials found that blood pressure reduction was associated with a reduction of incident dementia compared to placebo.

Take Home Message

Blood pressure lowering reduces dementia risk.



- Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE).
- Hypertension in the Very Elderly Trial (HYVET).
- Perindopril Protection Against Recurrent Stroke Study (PROGRESS).
- Systolic Hypertension in the Elderly Program (SHEP).
- SYSTolic Hypertension in EURope Trial (SYST-EUR).

Keywords Hypertension • Blood pressure • Cognition • Dementia • Meta-analysis • Clinical trials

Introduction

Observational studies have shown strong associations between elevated blood pressure (BP), particularly in midlife (age 40–65 years), and increased risks of dementia and cognitive decline that support plausible mechanisms of interaction between the cardiovascular tree and cerebral function.[1] However, this evidence is not universal. A recent comprehensive meta-analysis of seven population-based cohorts involving 17 286 older adults (mean age 75 years) showed that the lowest risk of dementia occurred in those with a mean systolic BP of 185 mmHg [95% confidence interval (CI): 161–230 mmHg] over a mean of 8 years of follow-up but a U-shaped relationship between BP and dementia in the oldest old (age >80 years).[2] This echoed earlier work raising concerns over BP lowering in older age groups.[1,3–5] Although randomized controlled trials can overcome the issues of residual confounding and reverse causality inherent to such observational analysis, they are in themselves challenging and have produced mixed reports on the effects of BP lowering for the prevention of dementia.[6]

Clarity over the effects of BP lowering on the risk of dementia remains a high priority in guiding public health strategies as well as clinical guidelines, where there may be a requirement to tailor thresholds and intensity of BP lowering in older age. Only a handful of BP-lowering trials have included a dementia endpoint, still fewer have been placebo-controlled and, because cardiovascular events occur earlier than incident dementia, most have been stopped early upon achieving the estimated primary cardiovascular endpoint. The impact of BP lowering on cardiovascular events meant that each one of these trials changed cardiovascular guidelines in favour of treatment. Consequently, it is no longer ethical to recruit to a trial comparing antihypertensive treatment to a placebo group who are receiving no other BP-lowering treatment. This also means that although a new placebo-controlled trial specifically designed for the prevention of dementia is desirable, it will require a very large sample size of participants who are also able to have their risk of cardiovascular disease managed within guidelines.[7] Numerous meta-analyses have sought to fill the void,[8–21] but their conclusions are hampered by their inability to standardize analysis and data handling and, in some cases by the combining of observational and clinical trial data. The gold standard for providing precision in synthesizing data from clinical trials is individual participant data (IPD) meta-analysis, where the data from sufficiently similar studies are combined and analysed as a single dataset. Herein, we present the results of a single-stage IPD meta-analysis of the five double-blind placebo-controlled randomized trials of BP lowering that collected dementia endpoints and were designed solely to compare a BP lowering to a no treatment, placebo only arm and that remained double-blind and placebo-controlled throughout. This approach allows a better analysis of causal inferences, and potential interactions and modifications of the effects of treatment on the prevention of dementia. Ethically these trials cannot be replicated and combining their data into a single database provides the strongest opportunity to establish the impact of BP lowering on incident dementia.

Methods

Trial data

We carried out a single-stage IPD meta-analysis using data from a consortium of multisite randomized double-blind placebo-controlled trials of BP lowering with antihypertensives where the outcome of incident dementia was assessed. To minimize the potential bias in the assessment of BP or in the collection of cognition and dementia data, we selected only randomized double-blind placebo-controlled trials (see Supplementary material online, *Supplementary table 1*, *Supplementary text 1*), developed an *a priori* statistical analysis plan agreed by the individual trial teams, and gained ethical approval from the University of New South Wales Human Research Ethics Advisory Panel–C HREAP 3208 prior to any analysis was undertaken. The consortium includes the Hypertension in the Very Elderly Trial (HYVET),[9,22] SYSTolic Hypertension in EURope trial (SYST-EUR),[23,24] Perindopril Protection Against Recurrent Stroke Study (PROGRESS),[25,26] Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE),[27–29] and Systolic Hypertension in the Elderly Program (SHEP).[30] All five trials were large (>2000 participants) and centrally co-ordinated multisite trials that randomized adults to receive double-blind antihypertensive treatment or matching placebo(s). All collected standardized BP measures at baseline and regular intervals. Four of the trials had minimum age criteria for recruitment,[22,24,28,30] however all recruited in late-midlife or later life populations. All five trials remained double-blind and achieved a BP difference between their randomized arms, three trials required elevated BP at trial entry, and had a goal BP for treatment.[22,24,30] The Supplementary material online, *Supplementary table 1* contains further details of the individual trials. All trials were designed to assess BP, and thus had carried out standardized assessments of resting sitting systolic and diastolic BP (in mmHg) at baseline and at approximately annual intervals from randomization until the end of follow-up.

Each trial assessed participants prospectively for incident dementia in addition to collecting data on deaths and stroke. Trial data were obtained *via* direct communication with the trial lead investigators who are part of the study team, except for the SHEP trial where data were obtained by application to the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center. Trials provided data on baseline characteristics of participants, including height and weight for the calculation of body mass index (BMI), history of previous stroke and Type 2 diabetes mellitus, current smoking, and level of education (subsequently categorized as <8, 8–12, 13–20, and >20 year duration). All trials except SHEP also undertook regular assessment of cognitive function using the Mini-Mental State Examination (MMSE) at 12- or 24-month intervals, post-randomization. As is usual for clinical trial analysis, annual time epoch windows relative to the date of randomization were used to standardize annual follow-up visits where multiple visits occurred within a time window; the date of the first was selected for inclusion in the merged database. For those trials with an open-label follow-on phase (SYST-EUR,[31] HYVET,[32] ADVANCE-ON[29]), only initial double-blind phase data were used.

Dementia diagnosis

All trials included diagnostic procedures for the clinical diagnosis of incident dementia using the Diagnostic Statistical Manual of Mental Disorders versions III-R[23,30,31] or IV.[9,25,27] All trials excluded patients with pre-existing dementia or serious cognitive loss at baseline. All trials also used an expert adjudication committee to validate key reported endpoints that included dementia, stroke, and cause-specific mortality, blind to treatment allocation. Stroke and mortality endpoints were verified against regulatory documents (e.g. medical reports, death certificates). Because of the likely overlap in the underlying pathology of dementia,[1,33] and as the trial populations lacked detailed imaging, all-cause dementia was taken as the primary outcome for these analyses.

Cognitive decline

Cognitive data were available for a cognitive screening tool, the MMSE. Three trials (HYVET, PROGRESS, SYST-EUR) collected annual MMSE assessments and one trial (ADVANCE) collected biannual MMSE assessments after baseline. The SHEP trial did not collect the MMSE. The availability of sequential MMSE scores also allowed an additional analysis of change in MMSE score over time. We further calculated a binary variable for incident cognitive decline using an approach that is similar to that originally undertaken by the trial investigators themselves, and similar to the approach used to define cognitive decline in the Systolic Blood Pressure Intervention Trial—Memory and Cognition IN Decreased Hypertension (SPRINT-MIND) but with a different screening tool.[34] Specifically, we defined participants who had a fall in their MMSE score to ≤24 for at least two consecutive annual (HYVET, PROGRESS, SYST-EUR) or biannual (ADVANCE) visits after baseline as cognitive decline.

Statistical analysis

A single-stage IPD pooling of all five trials was undertaken to produce a single data set, where the characteristics of the merged trial sample and individual trials were first examined using descriptive statistics. Mean between-group differences in systolic and diastolic BP were calculated for each year of follow-up.

Dementia

The effect of BP lowering on incident dementia was examined in several ways. First, multilevel logistic regression with study as a random effect (to account of

Table 1 **Baseline characteristics of the trial populations**

	HYVET	Syst-Eur	PROGRESS	ADVANCE	SHEP	Combined group
Total number	3337	2822	6105	11 008	4736	28 008
Placebo group	49.6% (1655)	49.3% (1391)	50.0% (3054)	49.9% (5497)	50.1% (2371)	49.9% (13 968)
Age	83.5 (3.1)	69.4 (6.2)	63.9 (9.6)	65.8 (6.4)	73.3 (6.9)	69.1 (9.3)
Female sex	60.4% (2016)	66.2% (1869)	30.3% (1852)	42.4% (4670)	56.8% (2689)	46.8% (13 096)
Education level						
<8 years	29.2% (969)	2.0% (55)	0.2% (10)	2.4% (260)	9.7 (460)	6.3% (1754)
8–12 years	11.7% (388)	9.6% (270)	8.8% (517)	5.4% (592)	59.5 (2810)	16.5% (4577)
13–20 years	45.6% (1516)	71.5% (2006)	72.3% (4259)	66.3% (7293)	30.4 (1434)	59.5% (16 508)
>20 years	13.6% (451)	16.9% (475)	18.7% (1104)	25.9% (2853)	0.4 (18)	17.7% (4901)
History of stroke	6.5% (216)	1.3% (36)	32.7% (1999)	9.1% (1002)	1.4% (66)	11.9% (3319)
BMI	24.7 (3.6)	27.0 (4.0)	25.7 (3.8)	28.3 (5.0)	27.5 (4.9)	27.0 (4.7)
Current smoker	6.1% (204)	6.8% (191)	20.0% (1220)	14.0% (1538)	12.7% (602)	13.4% (3755)
MMSE	26 (23–28) 25.3 (3.8)	29 (27–30) 28.2 (1.9)	29 (27–30) 28.0 (2.9)	29 (28–30) 28.5 (1.8)		29 (27–30) 27.9 (2.7)
Diabetes mellitus	9.9% (331)	9.0% (253)	12.5% (761)	100% (11 008)	10.3% (478)	46.0% (12 831)
Systolic BP, mmHg	173.0 (8.5)	173.1 (9.8)	147.0 (19.0)	145.0 (21.5)	169.8 (11.7)	155.8 (21.5)
Diastolic BP, mmHg	90.8 (8.5)	86.0 (5.7)	85.7 (10.8)	80.7 (10.9)	77.3 (8.7)	82.9 (10.7)
Systolic/diastolic BP difference between randomized groups at 1 year, mmHg	12.0 (16.8)/4.7 (10.0)	10.1 (14.5)/4.1 (7.4)	9.4 (19.0)/4.2 (10.8)	6.7 (20.1)/2.9 (10.6)	13.8 (17.4)/3.9 (9.7)	9.5 (19.6)/3.7 (10.3)
Case of incident dementia	7.9% (263)	1.1% (32)	6.7% (410)	0.6% (71)	1.8% (85)	3.1% (861)

Data are mean (SD) or % (*n*), unless otherwise specified.
BMI, body mass index; BP, blood pressure; MMSE, Mini-Mental State Examination.

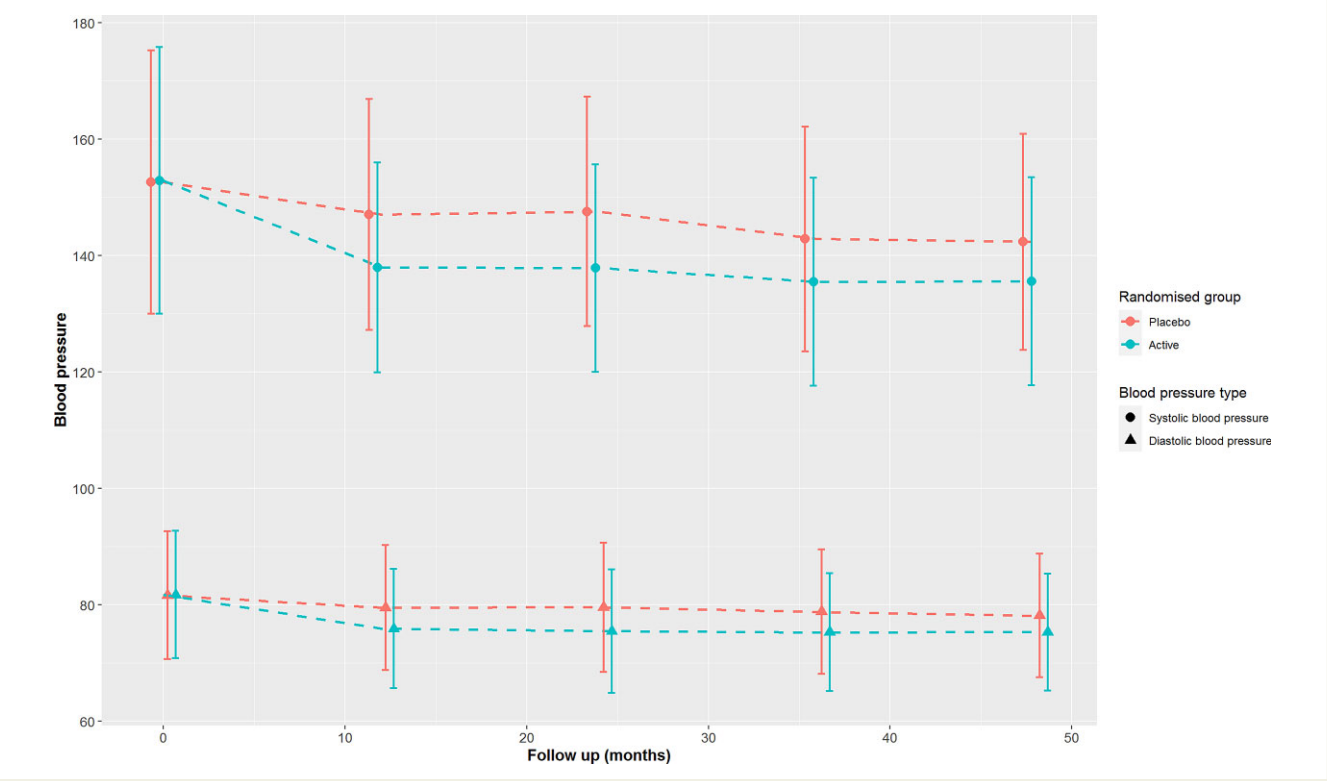


Figure 1 Systolic and diastolic blood pressure over follow-up per treatment group.

clustering within trials) was used to determine the effect of randomized treatment (active vs. placebo medication), unadjusted and subsequently adjusted for age, sex, and prior stroke, and then additionally for BMI, diabetes mellitus, and education. Continuous covariates of BMI and age were modelled, with and without quadratic terms, but as this showed no substantive non-linear effects, quadratic terms were not included in the final models. Multilevel logistic regression was selected as the most conservative option for several reasons: date of dementia diagnosis was not available for all data sets; time to event analysis in dementia has been criticized since dementia is insidious in its onset and in-depth diagnoses are often made after the clinical diagnostic assessment rather than the occurrence of an event. This means that the date of diagnosis can be dependent on the logistics of assessment, for example when a specialist appointment is arranged rather than when there has been a clear change in cognition or function. Furthermore, multilevel regression allowed account of the impact of within study similarities.

Further analysis used multilevel multinominal logistic regression (a generalized version of logistic regression which allows for more than two unstructured outcomes) to account for the competing risk of death: participants were classified as having experienced neither outcome (death or dementia), death (where they had no diagnosis of dementia), or dementia (regardless of subsequent death). Class of antihypertensive agent was not considered in analysis as recent research has shown no heterogeneity of antihypertensive class on incident dementia.[11,13]

Additional analysis using multilevel linear and logistic regression were similarly used to separately model the outcome of cognitive change between baseline and month 24, and binary cognitive decline, respectively.

Subgroup analysis and effect modification

To examine subgroups, additional analysis was carried out by running the same analysis using clinically relevant categorical variables for baseline age (<61, 61–70, 71–80, >80 years), sex, prior stroke, and by tertiles and quintiles of baseline systolic BP.

Additional analysis also examined effect modification by participant age, sex, baseline systolic BP, prior stroke, or baseline MMSE. The main effect of treatment plus the three-way interaction between treatment, age, and baseline systolic BP, was plotted by baseline age and systolic BP. Given the potential attenuation of the association of systolic BP and increasing age, variance inflation factors were checked prior to combining both in the same model.

To evaluate the impact of achieved BP, the relationship between achieved systolic and diastolic BP at 1 year and incident dementia was explored graphically. Achieved BP at 1 year was selected as representing a pragmatic stage in follow-up which maximized the number of participants and maximum achieved BP separation between randomized groups.[22,24,35] Mediation analysis was used to quantify the contribution of trial medication and change in systolic and diastolic BP to incident dementia (see Supplementary material online, *Supplementary text 2*). As confounders were evenly balanced between randomized groups, these were not included in this analysis.

All analyses were carried out according to the intention-to-treat principle, unless otherwise specified, using R and SAS v9.4. For mediation analysis, the framework of Pearl[36] was used with models estimated using generalized additive mixed model software in the R package mgcv.[37]

The study was approved by the University of New South Wales Human Research Ethics Advisory Panel–C HREAP 3208.

Results

The total sample included 28 008 individuals [mean age 69.1 (Standard Deviation (SD): 9.3) years; female 46.8%] from 20 countries with a median 4.3 (InterQuartile Range (IQR): 3.5–4.5) years of follow-up (*Table 1*) with baseline BP of 155.8 (SD: 21.5) mmHg systolic and 82.9 (SD: 10.7) mmHg diastolic. All trials showed a balance of baseline variables across their randomized (antihypertensive and placebo) groups that included age, sex, BMI, diabetes mellitus, previous stroke,

Table 2 Odds ratios for dementia, antihypertensive intervention vs. placebo, by subgroup and overall

Incident all-cause dementia			OR (95% CI)
Subgroups	Sex	Male (cases $n = 415$)	0.87 (0.71, 1.06)
		Female (cases $n = 446$)	0.86 (0.70, 1.05)
	Prior stroke	Present (cases $n = 220$)	0.94 (0.71, 1.24)
		Absent (cases $n = 641$)	0.84 (0.72, 0.99)
	Baseline systolic BP (tertiles)	<147 mmHg ($n = 9287$, cases $n = 219$)	0.77 (0.58, 1.03)
		147–167 mmHg ($n = 9555$, cases $n = 291$)	0.82 (0.64, 1.05)
		>167 mmHg ($n = 9127$, cases $n = 350$)	0.93 (0.75, 1.16)
	Baseline age	≤60 years ($n = 4718$, cases $n = 79$)	0.75 (0.47, 1.18)
		61–70 years ($n = 11473$, cases $n = 190$)	0.74 (0.55, 0.99)
		71–80 years ($n = 7081$, cases $n = 227$)	0.89 (0.68, 1.17)
		>80 years ($n = 4689$, cases $n = 365$)	0.96 (0.77, 1.19)
Overall ($n = 27\,999$[a])			0.87 (0.75, 0.99)

[a]Analysis adjusted for age, sex, and prior stroke, except where these variables define the subgroup.

and prior treatment with antihypertensive agents (see Supplementary material online, *Supplementary table 2* show the main trial inclusion criteria and antihypertensive classes).

The mean differences in BP between the placebo and antihypertensive treatment groups at 12 months were 9.6 (SD 20.3) mmHg systolic and 3.7 (SD 10.4) mmHg diastolic (*Figure 1*). The equivalent values were 10.8 (SD 21.1) and 5.2 (SD 24.4), respectively, at 2 years. Overall, there were 9171 active and 8744 placebo participants with at least 2 years of follow-up [equivalent to 65.4 and 62.7% of active (antihypertensive) and placebo groups, respectively, at baseline]. Incident dementia occurred in 403 (2.9%) and 458 (3.3%) of those in active and placebo groups, respectively.

The trial designs were similar and there were no issues in combining the data for an IPD analysis.

Effect of antihypertensive treatment on incident dementia

Multilevel logistic regression showed an unadjusted odds ratio (OR) of 0.868 (95% CI: 0.756, 0.996) in favour of BP-lowering treatment lowering the risk of incident dementia. After adjustment for age, sex and history of stroke, the OR was 0.865 (95% CI: 0.752, 0.994) (*Table 2*, *Figure 2*, $n = 27\,999$), and 0.860 (95% CI: 0.748, 0.989, $n = 27\,768$) with additional adjustment for BMI and diabetes mellitus. Further adjustment for educational level resulted in an OR of 0.857 (95% CI: 0.743, 0.988). The results were similar with multilevel multinomial regression in a model adjusted for age and sex where, compared with placebo, active treatment reduced risks of combined dementia (OR: 0.853, 95% CI: 0.742, 0.980) and death (OR: 0.876, 95% CI: 0.805, 0.954) compared with achieving neither outcome.

Subgroups and effect modification (*Figures 1* and *2*, *Table 2*)

There was no effect modification for treatment by baseline systolic BP as a continuous variable [$P = 0.18$ estimate 0.006, standard error (SE): 0.004]. Further examination of dementia outcomes by tertiles or quintiles of baseline systolic BP similarly showed no clear pattern (*Table 2*, *Figure 2*). Results are presented for tertiles as these quantiles are the most similar to traditional clinically relevant treatment thresholds: <147 mmHg [OR: 0.77 (95% CI: 0.58, 1.03)], 147–167 mmHg [OR: 0.82 (95% CI: 0.64, 1.05)] and >167 mmHg [OR: 0.93 (95% CI: 0.75, 1.16)]. A similar pattern was observed for quintiles.

There was also no effect modification by participant age ($P = 0.80$ estimate −0.002 SE 0.009), by sex ($P = 0.72$ estimate −0.060; SE: 0.163) or prior stroke ($P = 0.22$ estimate −0.219; SE: 0.180). Additional analysis in those without prior stroke showed this group to be older, with higher baseline BP [153.5 (SD: 23.0)/83.9 (SD: 11.2) mmHg], compared with [147.3 (SD: 20.6)/81.4 (SD: 10.9) mmHg] and more likely to be female, compared with those with a history of stroke. Finally, there was also no effect modification by baseline MMSE score ($P = 0.18$ estimate −0.025; SE: 0.019) in combined data using only HYVET, PROGRESS, ADVANCE, and SYST-EUR trial data. *Figure 3* shows the effect of treatment plus treatment × age × systolic BP interaction to provide a continuous graphical representation by age and systolic BP.

Effect of antihypertensive treatment on incident cognitive decline

Mean MMSE scores at baseline were similar in the active and placebo groups: 27.9 (SD: 2.7) and 27.9 (SD: 2.8) in the active and placebo groups. In 17 581 participants with both baseline and 2-year MMSE scores, the mean change in the active group was a rise of 0.006 (SD: 2.18) of an MMSE point and a median change of 0; in the placebo group, the mean change was a decline of 0.05 (SD: 2.18) of an MMSE point and a median change of 0. In multilevel linear regression which accounted for study and adjustment for age and sex, there was no significant difference between the two groups ($P = 0.15$). For overall cognitive decline, defined categorically using a sustained fall in MMSE, there was similarly no respective effect of treatment (OR: 0.905, 95% CI: 0.695, 1.179) compared with placebo.

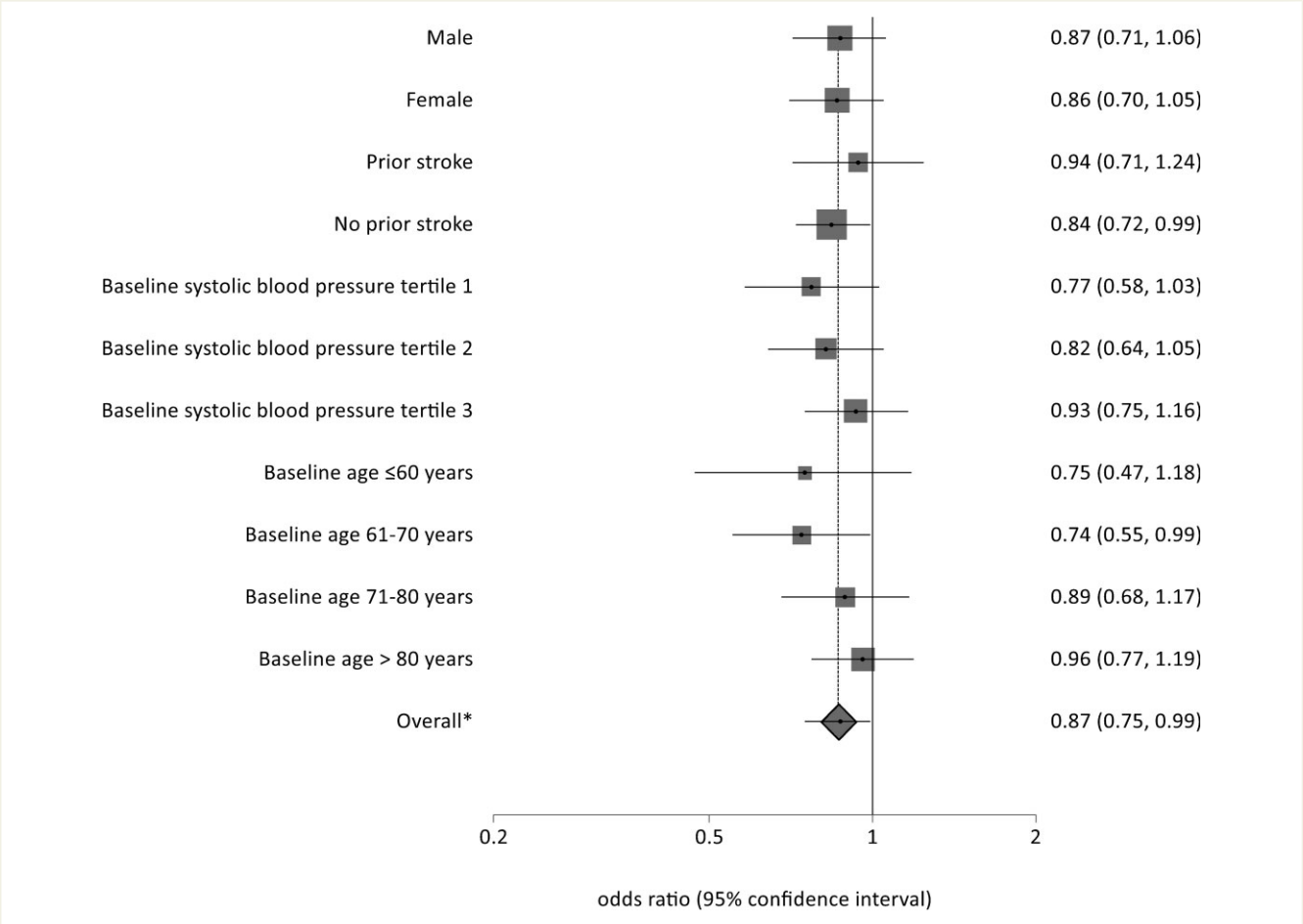


Figure 2 Forest plot showing odds ratios for dementia, antihypertensive intervention vs. placebo, by subgroup.

Mediation analysis

Mediation analysis confirmed a reduction in the risk of dementia by treatment was attributable to fall in BP. The controlled direct effect, a measure of any BP independent effects of the treatment on dementia risk, was a risk difference of −0.178% (95% CI: −0.560%, 0.214%). Conversely, the controlled indirect effect, a measure of the mediating effect of lower BP in the treatment arm, showed a risk difference of −0.218% (95% CI: −0.311%, −0.109%). This is equivalent to attributing 53% (95% CI: 27%, 76%) of the difference in dementia seen between the treatment and control groups to the effect of on systolic BP rather than any other aspects of trial participation or pleotropic antihypertensive drug effects.

Plotting achieved BP at 1 year for both active and placebo groups showed a linear relationship between lower risk of dementia and lower BP, down to at least 100 mmHg systolic and 70 mmHg diastolic (*Figure 4*).

Classification of evidence

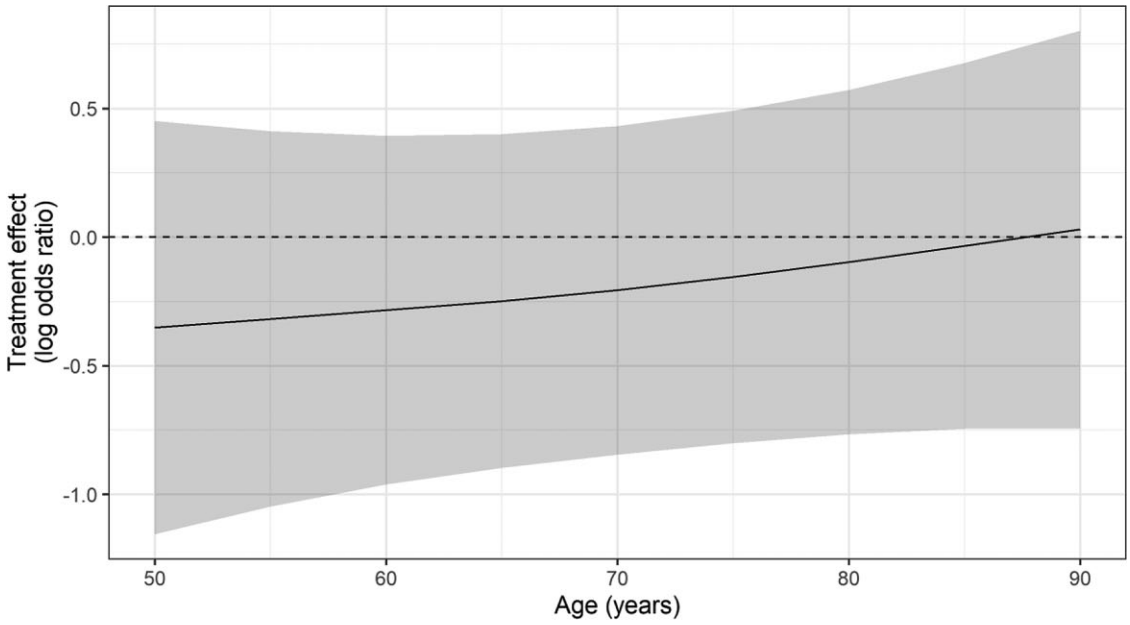
These analyses provide Class I evidence in favour of antihypertensive treatment in late-mid and later life reducing risk of incident dementia compared with placebo.[38]

Discussion

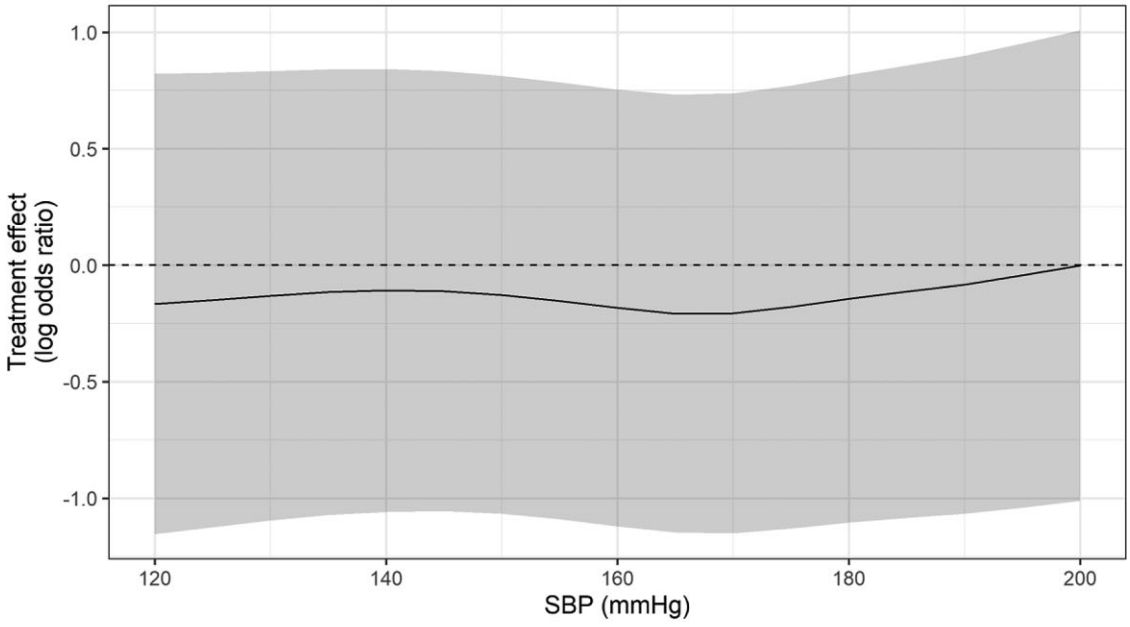
In this pooled analysis of IPD from clinical trials of different BP-lowering agents, there was a significant effect of treatment in lowering the odds of dementia (adjusted OR: 0.87, 95% CI: 0.75, 0.99) associated with a sustained reduction in BP (mean difference, ∼10/4 mmHg) in an older population (mean age 69.1 years) with a history of hypertension (*Structured Graphical Abstract*). There was no evidence of a U-shaped relation of the effect at any age, nor any increase in risk of dementia with treatment in the oldest age. The results were consistent across analyses that accounted for the competing risk of mortality, and there were no interactions by age, baseline BP, or history of stroke.

Our findings support a benefit of BP-lowering treatment for the prevention of dementia and extend prior meta-analyses[8–21] by standardizing analytical approaches across trials and in showing consistency of the effect across late-life and older age. Moreover, our results imply a broadly linear relation of BP reduction and lower risk of dementia. Although the overall effect was apparent with a mean BP fall of 9.6/3.7 mmHg at 12 months, the size of the benefits on the incidence of dementia expected would be consistent at population and individual levels.[39] Overall, in agreement with the recent guideline recommended targets, we found greater benefits from larger reductions in BP but no evidence of increased risks or harms from alterations in cerebral perfusion in older people.

In comparison to the SPRINT-MIND trial,[34] we found no effect of treatment on cognitive decline. We acknowledge that the MMSE is insensitive for detecting mild cognitive impairment, but note there was no difference in overall neuropsychological scores between randomized



[a]*Adjusted for baseline systolic blood pressure (SBP)*



[b]*Adjusted for baseline age*

Figure 3 Relative log odds ratios showing how the effect of antihypertensive treatment on risk of dementia changes with baseline systolic blood pressure[b] and age[a]. [a]Adjusted for baseline systolic blood pressure. [b]Adjusted for baseline age.

groups in SPRINT-MIND.[40] Moreover, intermittent cognitive testing is heavily influenced by participant health or attention, and more sensitive measures are required to detect subtle changes.[41]

Combining double-blind placebo-controlled trials with blinded adjudication of dementia endpoints provides the highest grade of evidence for antihypertensive use to reduce dementia risk. Importantly, our results show a decrease, and certainly no increase, in risk of dementia with BP lowering. The U-shaped patterns and reduced risk at higher BP in population studies may reflect a complex interplay of survival, co-morbidities, and BP change with ageing. Furthermore, our findings are not in opposition, but bring data on treatment impact to complement cohort studies which report on longer term relationships between BP and cognition.

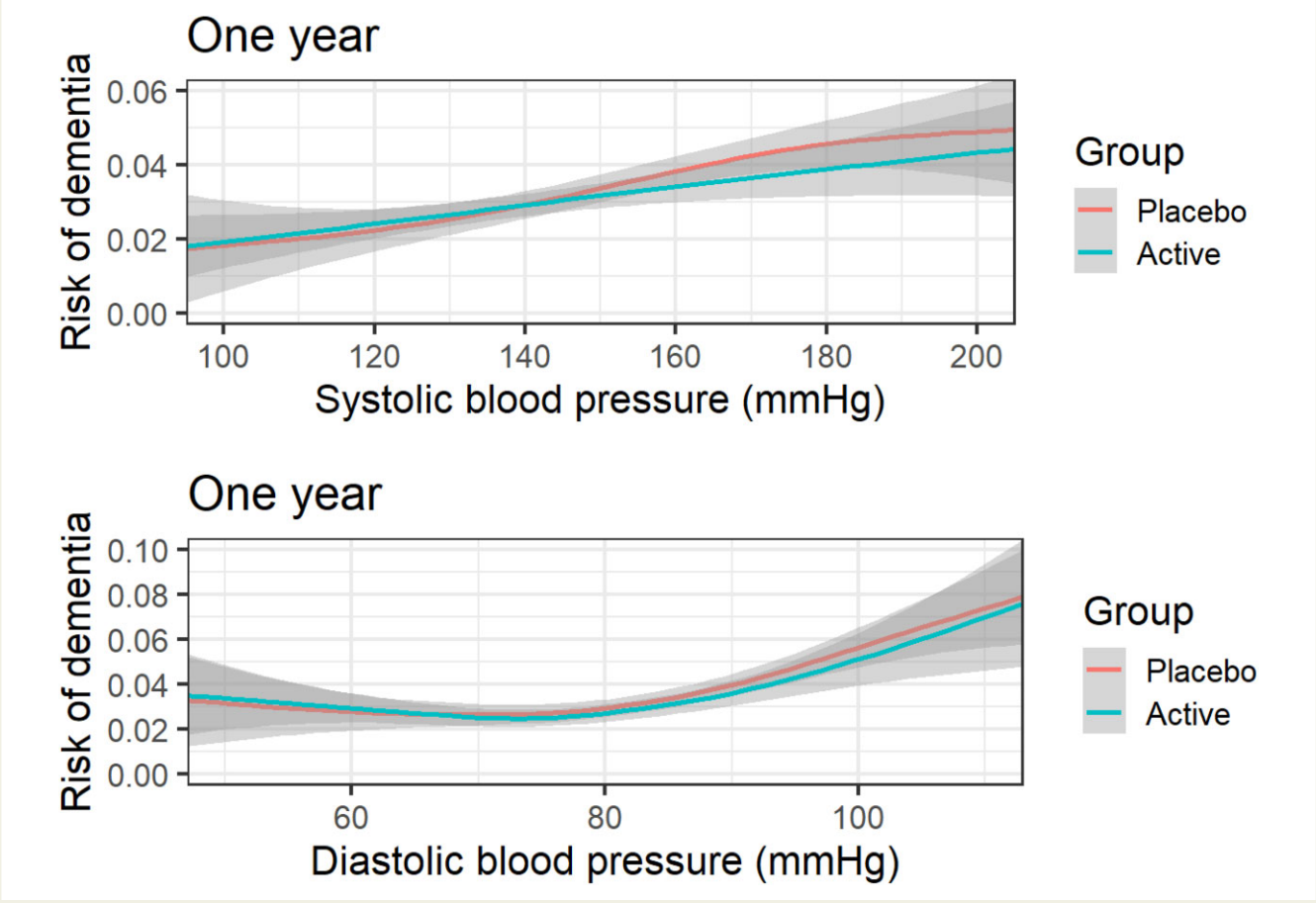


Figure 4 Risk of dementia by achieved blood pressure at 1 year.

There are inevitable limitations to our results. Examining outcomes by subgroup is predicated on balanced randomization, however only HYVET and PROGRESS explicitly stratified randomization by age and sex, and SYST-EUR by sex, but all trials showed balanced randomization at baseline. Despite balanced randomization, however, it is possible that differential attrition, and mortality or stroke rates in the different arms of the trials and combined with early stopping due to cardiovascular benefits, may have reduced the potential to identify incident dementia cases and to follow participants for a longer period, as recommended for the accrual of incident dementia.[42] Nonetheless, this is likely to have driven an under- rather than an over-estimate, of benefit with higher cardiovascular event rates in the placebo arms.[43] The risk of reverse causality also needs to be considered, given the median follow-up of 4.3 years and evidence showing declines in BP are common in the several years prior to the diagnosis of dementia. Whilst it is possible that participants entering the trials may have already been experiencing the effects of their forthcoming dementia, it may also have been the case that dementia was diagnosed at an earlier stage than in usual practice, given the regular trial visits, contact with healthcare professionals, and regular cognitive testing. Moreover, these results are in the context of double-blind placebo-controlled trials, which makes it hard to see how reverse causality could have influenced the treatment group effect. Further issues to consider are the lack of data on dementia subtype and a lack of clear dates associated with dementia diagnosis. Whilst some of the trials sought to allocate dementia types to their incident dementia cases, these were not routinely confirmed by pathology or imaging, and given that vascular risk was required to enter each trial, it is highly likely that some element of vascular pathology was present in most cases. This is also likely to be the most common scenario in clinical practice which further supports the use of an all-cause dementia approach. Date of event is also contentious to a disorder like dementia with an insidious onset, and whilst dates would have allowed us to carry out survival and further competing endpoint analysis, they were not available for all trials and were allocated differently in the different data sets. Furthermore, we were limited in the availability of rigorous and repeated cognitive assessment as the MMSE was designed as a screening tool and was not used across all trials. Consequently, we selected the most conservative option of using logistic regression for analysis and taking study into account. Finally, combining existing data has its limitations, including insufficient power to fully evaluate the impact of population characteristics on the treatment effect for an outcome with incidence rates as low as dementia. However, using raw data from double-blind placebo-controlled trials still provides a unique and high-quality data set to examine this research question. Looking ahead, there may be potential to expand these understandings of the relationships between BP, antihypertensive treatment and dementia with the addition of IPD from non-blinded trials and those without placebo-controlled comparisons groups alongside complementary work with observational data sets using causal inference and Mendelian randomization.[44–46] Currently, we provide the highest grade of available

evidence to show that antihypertensive treatment over several years reduces the risk of dementia. Given population ageing and substantial costs of dementia, currently estimated at $20 000 to $40 000 USD/per person with dementia per year,[47,48] even a small reduction would have considerable global impact. Our work provides a further reason, beyond cardiovascular risk reduction, for controlling high BP in those at risk.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

Data sharing is available on request to the individual trial teams (ADVANCE, HYVET, PROGRESS, SYST-EUR) and on application to the BioLINNC data repository (SHEP).

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