Perspectives on treating hypertension in old age : the burden of polypharmacy, risks of treatment and GPs' treatment probability

Streit, S.R.

Universiteit Leiden

http://hdl.handle.net/###

Association of low systolic blood pressure under antihypertensive treatment and cognition in old age

Sven Streit, Rosalinde KE Poortvliet, Wendy PJ den Elzen, Jeanet W Blom, Jacobijn Gussekloo

Submitted

ABSTRACT

Background/Objectives

Determine if systolic blood pressure (SBP) and antihypertensive treatment are associated with one-year changes in cognitive/daily functioning or quality of life (QoL) in older participants with/without complex health problems.

Design

Population-based prospective cohort with one-year follow-up.

Setting

Participants in the Integrated Systematic Care for Older Persons (ISCOPE) trial.

Participants

Primary care patients, eligible when ≥75 years and SBP recorded in electronic medical records one-year before baseline.

Measurements

Grouped participants into SBP categories (<130mmHg/130-150mmHg/>150mmHg) and antihypertensive treatment (yes/no). Used mixed-effects linear regression models to evaluate change from baseline to one-year follow-up in outcome measures (Mini Mental State Examination (MMSE), Groningen Activities Restriction Scale (GARS), and EQ-5D-3L). Adjusted models for age, sex, baseline values of MMSE/GARS/EQ-5D-3L and stratified for complex health problems.

Results

Participant (n=1,266) age averaged 82.4 (5.1) years; 874 were women (69.2%). In participants under antihypertensive therapy (1,057, 83.5%) with SBP<130mmHg, cognitive decline was 0.90 points in MMSE while in those with an SBP >150mmHg it was 0.14 (i.e. 0.76 less decline). In the multivariable model, cognitive decline was 1.01 (95%CI 0.47-1.55, P<0.001) when SBP was >150mmHg (P-for-trend<0.001). Complex health problems modified the association of SBP with cognitive function: the association was mainly seen in those with complex health problems (P-for-trend<0.001) and not in those without (P-for-trend=0.13). Daily functioning or QoL did not differ across strata of SBP and antihypertensive treatment.

Conclusions

Participants aged ≥75years under antihypertensive treatment with a SBP ≥130mmHg compared to <130 showed a significantly and clinically relevant benefit in cognition after one year, without loss of daily functioning or QoL. This effect was strongest in participants with complex health problems. For those, future trials should investigate if deprescribing is beneficial.

INTRODUCTION

In Western countries, hypertension is present in up to 30% of the population [1] and is a leading disability risk [2]. Its prevalence sharply increases with age [3], but for many years many physicians believed hypertension in old age was a healthy adaptation to arteriosclerotic rigidity [4] and did not treat patients >60 for hypertension [5]. In the 1990s, trials began to show that antihypertensive treatment reduced stroke and myocardial infarction in patients >60 [6-8], and physicians changed their practice. However, as populations "grey", definitions of "old" are shifting. Life expectancy has increased worldwide: people ≥75 years are now the fastest-growing age group; this population will triple within 35 years [9]. Some older individuals are very healthy, but others are frail and have two or more chronic conditions (multimorbidity) or other complex health problems [10].

Though updated guidelines recommend lowering blood pressure targets in older patients, cohort studies have raised concern that lowering SBP too much might harm them, by, for example accelerating cognitive decline [11-21]. A recent network meta-analysis of 17 hypertension trials proved the effectiveness and safety of lowering SBP to <130 mmHg in patients with hypertension [22], spurring the American College of Cardiology/American Heart Association Task Force (ACC/AHA) to update their guidelines. ACC/AHA recommends a target SBP of <130mmHg for non-institutionalized older patients [23]. Hypertension trials often exclude older, frail patients and those with complex health problems [24], so some have questioned the generalizability and applicability of the results of these studies of the general population, especially to older patients [25, 26]. An observational study of 172 patients (mean age 79 years) by Mosello *et al.* found low SBP and cognitive decline were associated in patients with dementia or mild cognitive impairment (MCI) under antihypertensive treatment, but not in untreated patients [27]. This study concluded that optimal SBP in those patients was between 130 and 145 mmHg, since lowering target values might further impair cognitive function, and was the only study that analysed patients under antihypertensive treatment separately from patients without treatment.

We set out to determine if low SBP and cognitive decline were similarly associated in a larger cohort of Dutch community-dwelling older participants under antihypertensive treatment and without. We also tested for an association between SBP and daily functioning and quality of life (QoL). We hypothesized these associations would be strongest in older participants with complex health problems.

METHODS

Design

This is a prospective cohort study based on data from the Integrated Systematic Care for Older Persons (ISCOPE) study, a cluster-randomized trial.

ISCOPE trial

The ISCOPE study included participants from 2009 to 2010 in Leiden, the Netherlands [28]. 560 general practitioners (GPs) were invited, and, of these, 104 (19%) invited their patients to participate. In the Netherlands, every person is registered at a GP practice. Inclusion criteria were age ≥75 years; terminal illness or life expectancy of <3 months were the only exclusion criteria. Participants were randomized to either an integrated care plan with a functional geriatric approach or usual care [28]. Of 11,476 patients in the target population, 7,285 (63.4%) answered a screening questionnaire. We selected a random sample of 1,921 to follow up for one year. Of these, 106 (5.5%) participants died; mortality risk was the same in intervention and control groups (P=0.48).

Study population and eligibility criteria

We needed electronic medical records (EMR) data in order to extract SBP measurements and identify antihypertensive drugs from their Anatomical Therapeutic Chemical (ATC) codes. We thus selected participants based on four criteria: 1) they consented to allow us to analyse their EMR data; 2) we could link their EMR data to link the ISCOPE dataset; 3) they were selected for one year of follow-up in ISCOPE; and 4) their SBP measurements were recorded for the year before they were included in ISCOPE (Study flow chart in Figure 1).

Ethical approval

Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The Ethics Committee of the Leiden University Medical Center, the Netherlands (P09.096) approved the ISCOPE study, registered in the Netherlands Trial Register (NTR1946).

Exposures

We averaged SBP values from EMR of up to five of the most recent measurements taken the year before baseline. We grouped participants, based on mean SBP, into 3 categories (<130 mmHg, 130-150 mmHg, and >150 mmHg). Those with SBP <130mmHg were the reference group. We used EMR data at baseline to determine if participants were under antihypertensive treatment or not.

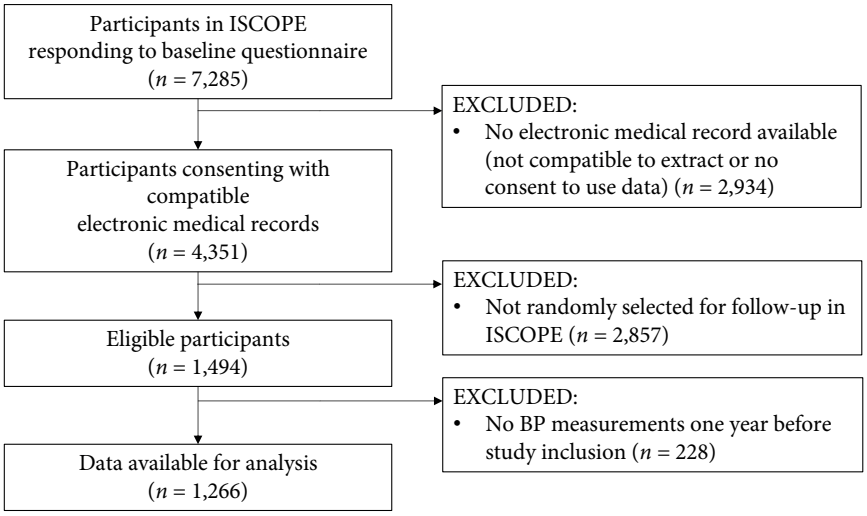

Figure 1. Study flow chart

Outcome measurements

In ISCOPE, research nurses made home visits at baseline and at one-year follow-up [28]. The MMSE measures cognitive function on a scale of 0-30 points (higher scores indicate better function) [29]. The GARS questionnaire measures basic and instrumental activities of daily living. The combined score ranges from 18-72 points (higher score indicates greater disability [30]). QoL was assessed with EQ-5D-3L index values: participants rated their health status in 5 dimensions (mobility; self-care; usual activities; pain and discomfort; anxiety and depression), and at three levels (no, some, or extreme problems) [31], and we converted them to a weighted index, based on the EuroQoL Group (full health has a value of 1, death, a value of 0) [32].

Confounders

We, *a priori,* chose age, sex, and either MMSE, GARS, or EQ-5D-3L at baseline, depending on the outcome as confounders. We took a causal modelling approach to identifying potential confounders of the association between SBP/treatment and our outcomes. We assessed the strength of confounding by examining change between our crude and adjusted models for each of the following covariates: living situation; income; education; diabetes; cardiovascular disease (CVD) (myocardial infarction, angina pectoris, intermittent claudication, other ischemic heart disease, stroke, TIA, or heart failure); and non-cardiovascular co-morbidities (cancer, diabetes, and depression). The final model included all variables a) considered to be confounders (change of +/-10% from crude model) or b) prespecified.

To identify participants with complex health problems, we used scores from a questionnaire that participants received at baseline. The questionnaire covered four domains (functional, somatic, mental, and social) [28], which each contained 4-9 questions. If participants reported problems in ≥2 questions in a domain, their score was 1 for that domain; if they reported no problems, it was 0. Participants that scored 1 in three or all domains, were classed as having complex problems.

Statistical analysis

In descriptive analysis, we compared baseline characteristics of participants with/without SBP measurements in the EMR to determine selection bias, then we compared participants with and without antihypertensive treatment. We used the Chi2-test for categorical data, t-test for normally distributed data, and Wilcoxon ranksum test for not-normally distributed continuous data.

In a primary analysis, we assessed associations between SBP category (<130mmHg, 130-150mmHg, >150mmHg) stratified by antihypertensive therapy (yes or no) and change in function in old age (MMSE, GARS, EQ-5D-3L) from baseline to one-year follow-up. We estimated the change in function and 95% confidence intervals (CI) in a crude mixed-effects regression model that only accounted for the correlated nature of data of participants under antihypertensive treatment or not by the same GP. We calculated P for trend to test a linear trend across categories of SBP within both strata (antihypertensive therapy yes and no). We then adjusted the mixed-effects regression models for sex, age and baseline values of MMSE, GARS, or EQ-5D-3L, depending on the outcome, and estimated the change in function related to SBP <130mmHg (reference category). Linear assumptions were tested and valid for all outcomes.

We performed two sensitivity analyses for the primary analysis: 1) we restricted our analysis to participants with no history of CVD at baseline; and, 2) we included the ISCOPE trial arm as confounder, although the original ISCOPE trial did not show that the integrated care plan increased QoL or daily function or changed health care use.

In a secondary analysis, we took the same approach, but we stratified for participants with and without complex health problems.

A two-sided P-value of 0.05 was statistically significant. We used STATA 15.1 (StataCorp, College Station, TX, USA) for all analyses.

RESULTS

Of 7,285 participants who responded to the screening questionnaire in ISCOPE, we excluded 2,934 (40.3%) because they did not consent to providing a link to their EMR data or their EMR data could not be linked with ISCOPE data. Of the 4,351 who remained, 1,494 (34.3%) were followed-up for one year in ISCOPE. Of those, we excluded 228 (15.3%) because they had no SBP measurements recorded in EMR (flow chart in Figure 1). Those we excluded for lack of SBP measurements were healthier overall than the study participants; they had less CVD (21% vs. 40%, P<0.001), less antihypertensive therapy (49% vs. 84%, P<0.001), less diabetes (15% vs. 22%, P=0.030), lower GARS score (27 vs. 31, P<0.001), higher EQ-5D 0.81 vs 0.77, P<0.001), higher MMSE-score [28 (26-29) vs. 28 (27-29), P=0.019], and less complex health problems (39% vs. 53%, P>0.001) (Appendix table 1).

The final dataset comprised 1,266 participants. Most of them (83.5%) were under antihypertensive treatment for hypertension (Table 1). At baseline, the sociodemographic characteristics of participants under or not under antihypertensive treatment were similar, but participants under antihypertensive treatment more often had an SBP >150 mmHg (35 % vs. 23%; P=0.004), more CVD (48% vs. 4%; P<0.001), more diabetes (23% vs. 15%; P=0.013), higher GARS score (31 vs. 28, P=0.003) and lower QoL (EQ-5D 0.77 vs. 0.78, P=0.045).

Crude one-year changes in cognitive function, daily function and quality of life

Figure 2 displays the crude estimates of changes from baseline to one-year follow-up in cognitive function (Panel A), daily functioning (Panel B), and QoL (Panel C). In participants under antihypertensive treatment, we found a clear trend across categories of SBP: with lower SBP, cognitive decline worsened (measured by MMSE) after one-year follow-up (P for trend 0.013). In participants under antihypertensive treatment and SBP <130mmHg, cognitive decline in one year averaged 0.90 points (95%CI 0.43-1.36) in MMSE, while it was 0.14 (95%CI 0.21-0.49) in those with SBP >150mmHg (0.76 points less decline in MMSE in participants with an SBP >150mmHg than in those with SBP <130mmHg). In participants without antihypertensive treatment, we observed a similar trend but it was not statistically significant (1.75 points, 95%CI 0.80-2.70 if SBP<130mmHg vs. 0.54 points, 95%CI 0.43-1.41 if SBP>150mmHg; P for trend 0.08).

We found no association between SBP and daily functioning or QoL in participants under or not under antihypertensive therapy.

Multivariable models for cognitive function, daily functioning and QoL

Table 2 displays the changes in function among the reference group (<130mmHg) stratified by antihypertensive treatment for each outcome, separately (MMSE, GARS, EQ-5D-3L).

Table 1. Baseline characteristics of participants overall and grouped by antihypertensive treatment (n=1,266)

	Overall (n=1,266)	Antihypertensive treatment		P-value[a]
		Yes (n=1,057)	No (n=209)	
Sociodemographic data				
Female, n (%)	874 (69)	728 (69)	146 (70)	0.72
Age, years (SD)	82.4 (5)	82.5 (5)	82.3 (5)	0.59
Primary school only, n (%)	656 (52)	541 (52)	115 (55)	0.33
Low income[b], n (%)	197 (16)	166 (16)	31 (15)	0.72
Residential home, n (%)	101 (8)	83 (8)	18 (9)	0.72
Systolic blood pressure, n (%)				
<130 mmHg	237 (19)	197 (19)	40 (19)	
130-150 mmHg	613 (48)	493 (47)	120 (57)	0.004
>150 mmHg	416 (33)	367 (35)	49 (23)	
Comorbidities, n (%)				
Cardiovascular disease (CVD)[c]	511 (40)	503 (48)	8 (4)	<0.001
Diabetes mellitus	274 (22)	242 (23)	32 (15)	0.013
Depression	182 (15)	148 (14)	34 (16)	0.42
Cancer	159 (13)	134 (13)	25 (12)	0.75
Baseline function, median (IQR[d])				
MMSE[e] score	28 (26-29)	28 (26-29)	28 (26-29)	0.99
GARS[f] score	31 (24-39)	31 (24-40)	28 (22-36)	0.003
EQ-5D-3L[g] index values	0.77 (0.57-0.84)	0.77 (0.51-0.84)	0.78 (0.65-0.89)	0.045
Complex health problems[h]	674 (53)	571 (54)	103 (50)	0.23

[a] P-value from chi-square test for categorical data; t-test for normally-distributed continuous data, Wilcoxon ranksum test for not normally-distributed continuous data

[b] defined as state pension only (about EUR 750 monthly)

[c] CVD included myocardial infarction, angina pectoris, intermittent claudication, other ischemic heart disease, stroke, TIA, and heart failure

[d] IQR = inter quartile range

[e] Mini-Mental State Examination (MMSE) on a scale of 0-30 points (higher scores indicate better cognitive function)

[f] Groningen Activities Restriction Scale (GARS); the score ranges from 18 to 72 (higher scores indicate greater disability)

[g] Quality of life (EQ-5D-3L index values; full health has a value of 1, dead a value of 0)

[h] Defined as patients having problems in three or more of four domains (functional, somatic, mental, and social)

Compared to the reference group, participants under antihypertensive therapy showed less cognitive decline after one year by 0.71 points in MMSE (95%CI 0.20-1.22, P=0.007) when SBP was 130-150mmHg and by 1.01 points in MMSE (95%CI 0.47-1.55, P<0.001) when SBP was >150mmHg (P for trend <0.001). In participants not under antihypertensive therapy, the trend was in the same direction but not significant (P for trend 0.07).

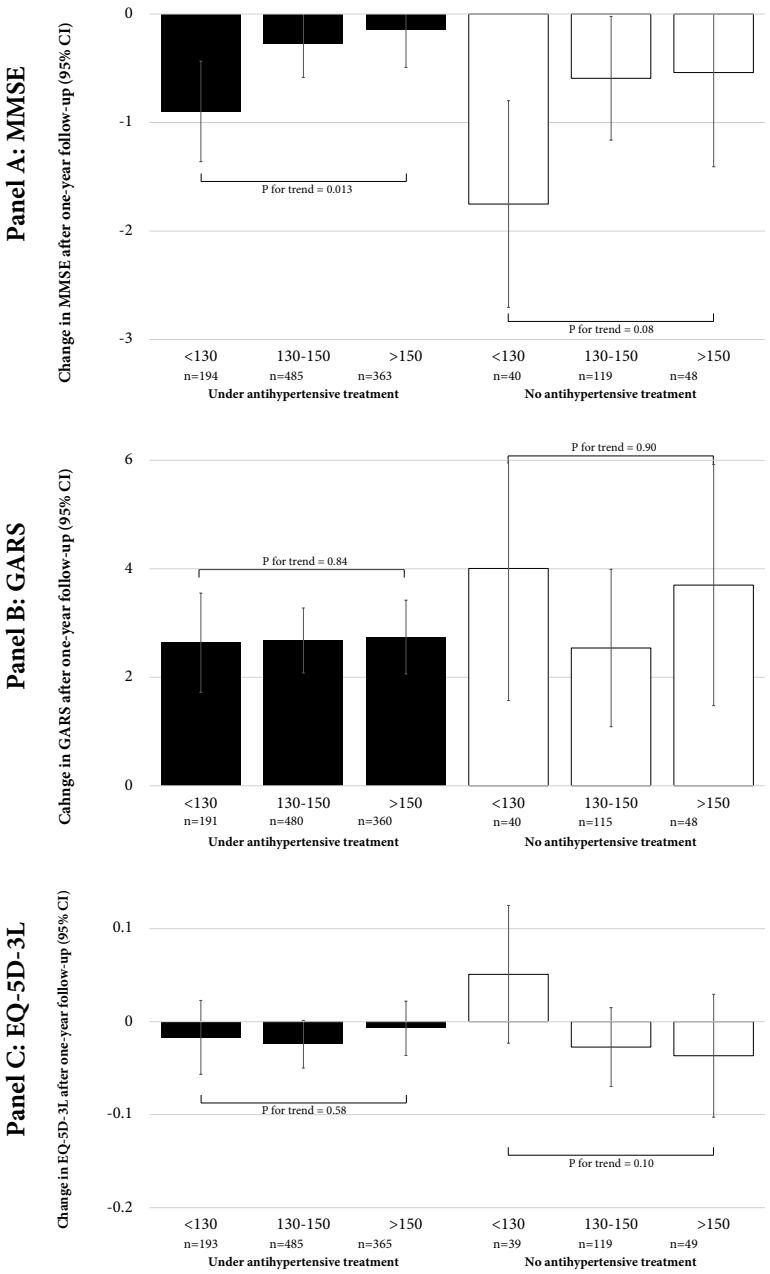

Figure 2. Associations of systolic blood pressure, antihypertensive treatment, and change in function after a one-year follow-up. Estimates, 95% CI and p-for trend from crude mixed-effects linear regression accounting for clustering within general practitioners. Panel A: cognitive function measured by Mini Mental State Examination (MMSE), (less points = cognitive decline); Panel B: daily functioning measured by Groningen Activities Restriction Scale (GARS), (more points = more disability); Panel C: Quality of life measured by EQ-5D-3L, (less points = lower quality of life).

Table 2. Associations of baseline systolic blood pressure (SBP) and antihypertensive treatment with change in cognitive/daily function and quality of life after one-year follow-up (n=1,266). Multivariable mixed-effects regression model adjusted for age, sex, baseline MMSE/GARS/EQ-5D-3L and accounting for clustering within general practitioners.

	Antihypertensive treatment							
	Yes (n=1,057)				No (n=209)			
	n	Change (95% CI)	P-value	P-trend	n	Change (95% CI)	P-value	P-trend
Cognitive function								
<130 mmHg	194	*Ref.*	-	<0.001	40	*Ref.*	-	0.07
130-150 mmHg	485	0.71 (0.20, 1.22)	0.007	-	118	1.04 (-0.04, 2.12)	0.06	-
>150 mmHg	362	1.01 (0.47, 1.55)	<0.001	-	48	1.22 (-0.03, 2.47)	0.06	-
Daily function								
<130 mmHg	191	*Ref.*	-	0.47	40	*Ref.*	-	0.70
130-150 mmHg	480	-0.08 (-1.11, 0.96)	0.88	-	114	-1.73 (-4.54, 1.10)	0.42	-
>150 mmHg	359	-0.37 (-1.47, 0.74)	0.51	-	48	-0.75 (-4.02, 2.52)	0.65	-
Quality of life								
<130 mmHg	193	*Ref.*	-	0.17	39	*Ref.*	-	0.14
130-150 mmHg	484	0.00 (-0.04, 0.04)	0.98	-	118	-0.06 (-0.14, 0.02)	0.13	-
>150 mmHg	364	0.03 (-0.02, 0.07)	0.24	-	49	-0.07 (-0.16, 0.02)	0.12	-

Reading example: Patients under antihypertensive treatment and a baseline SBP of >150mmHg had 1.01 (95% CI 0.47 to 1.55) less cognitive decline compared to patients under antihypertensive therapy with a baseline SBP of <130mmHg.

For the outcomes of daily functioning and QoL, there was no association between SBP category and change in GARS or EQ-5D-3L in either strata (antihypertensive therapy yes/no).

Sensitivity analyses

The findings remained robust when we restricted the sample to participants with no history of CVD at baseline (Appendix table 2). When we added the ISCOPE trial arm to which participants were allocated our estimates remained the same (data not shown).

Secondary analysis for complex health problems

In participants with complex health problems (n=674, 53%, Table 3), we found the same association. Compared to the reference group (SBP<130mmHg), participants showed less cognitive decline after one year by 0.99 points in MMSE (95%CI 0.32-1.66, P=0.004) when SBP was 130-150mmHg and by 1.39 points in MMSE (95%CI 0.68-2.11, P<0.001) when SBP was >150mmHg (P for trend <0.001). This association was not found in participants without complex health problems (P for trend 0.35, Appendix table 3). Complex health problems did not modify the effect on daily functioning or QoL.

Table 3. Subgroup analysis restricted to patients with complex health problems (n=674). Associations of baseline systolic blood pressure (SBP) and antihypertensive treatment with change in cognitive/daily function and quality of life after one-year follow-up (n=1,266). Multivariable mixed-effects regression model adjusted for sex, age, baseline MMSE/GARS/EQ-5D-3L and accounting for clustering within general practitioners.

	Antihypertensive treatment							
	Yes (n=571)				No (n=103)			
	n	Change (95% CI)	P-value	P-trend	n	Change (95% CI)	P-value	P-trend
Cognitive function								
<130 mmHg	117	*Ref.*	-	<0.001	20	*Ref.*	-	0.13
130-150 mmHg	258	0.99 (0.32, 1.66)	0.004	-	60	1.90 (0.05, 3.75)	0.044	-
>150 mmHg	189	1.39 (0.68, 2.11)	<0.001	-	22	1.78 (-0.42, 3.98)	0.11	-
Daily function								
<130 mmHg	115	*Ref.*	-	0.59	20	*Ref.*	-	0.65
130-150 mmHg	254	-0.18 (-1.57, 1.20)	0.79	-	57	-2.02 (-6.14, 2.10)	0.34	-
>150 mmHg	188	-0.40 (-1.88, 1.09)	0.60	-	22	-1.20 (-6.11, 3.72)	0.63	-
Quality of life								
<130 mmHg	117	*Ref.*	-	0.61	19	*Ref.*	-	0.19
130-150 mmHg	257	-0.03 (-0.08, 0.03)	0.21	-	60	-0.11 (-0.23, 0.01)	0.08	-
>150 mmHg	190	0.01 (-0.05, 0.07)	0.99	-	22	-0.10 (-0.24, 0.04)	0.16	-

Reading example: Patients under antihypertensive treatment and a baseline SBP of >150mmHg had 1.39 (95% CI 0.68 to 2.11) less cognitive decline compared to patients under antihypertensive therapy with a baseline SBP of <130mmHg.

DISCUSSION

In this large Dutch primary care cohort of older persons with a follow-up of one year, those under antihypertensive treatment had less cognitive decline if their SBP in the year before baseline was ≥130 mmHg. The association between higher SBP and less cognitive decline in participants under antihypertensive treatment was strongest seen in those with complex health problems. Daily functioning and QoL were the same across strata of SBP and antihypertensive treatment. Sensitivity analyses that excluded participants with CVD or that included the trial arm of the ISCOPE trial in the model supported these findings.

Interpretation and scientific context

Our study builds on Mosello *et al.* [27], but is much larger (1,266 vs. 172 participants), and was conducted in a different setting (general practice vs outpatient memory clinics). Mosello *et al.* included only patients with dementia or mild cognitive impairment. Our study included participants often excluded from trials because they are sicker and have complex health problems. We found the same associations, but also demonstrated that complex health problems

changed the association. This finding lines up with other studies that found associations changed with frailty [33, 34]. Studies of older patients that did not stratify on antihypertensive treatment, found either no association [35] or an association between higher SBP, better cognition, and lower risk of dementia [36]. Our study helps explain this difference by showing that, in participants without complex health problems, low SBP is not as clearly associated with cognitive decline [37] as in those with complex health problems.

Less cognitive decline by 1.39 points in MMSE (95%CI 0.68-2.11) than the reference group (SBP<130 mmHg) is a clinically meaningful difference: this difference of 1.39 MMSE points is greater than the average annual decline in MMSE in those aged 85 [12].

At the same time, we found no evidence SBP was associated with changes in daily function under antihypertensive therapy, though prior studies identified both positive and negative associations [13, 38, 39]. A cohort study of 35 centenarians in Poland found higher SBP benefitted daily activity after follow-up [13]. The Leiden-85-plus study found higher SBP levels were associated with lower ADL disability over 5 years [38]. In contrast, a US longitudinal cohort study of about 600 75-year-olds found high SBP was associated with declining physical function (measured by gait speed) over 10 years of follow-up [39]. This diametric association might be explained by age: there was evidence that high SBP was associated with physical function at age 75, but that high SBP increased physical function in those >85 and >100. Most studies that assessed the association between SBP and function in old age did not assess QoL. A Polish study of about 11,500 old patients found that those treated for hypertension (especially those on multiple antihypertensive medications) had optimal QoL with higher SBP [40], but our results suggest no association between SBP and one-year change in daily function or QoL.

Strengths and limitations

Strengths of our study are the high number of older participants recruited by a large group of GPs, and the extensive measurements that take into account cognitive function, daily functioning, and QoL. Our study has the following limitations. It was observational, so we cannot exclude residual confounding, but the strength of the associations we identified, consistency with prior studies, dose-response relationship, and temporal relationship of SBP measurements and outcome assessments all point towards a causal interpretation. Although the participants we excluded because they had no SBP measurements recorded in the last year before the start of the study were healthier, they did otherwise not differ from responders. This last limitation can also be considered a strength, since we included sicker, older participants with a high proportion of CVD under antihypertensive treatment, and this ever-increasing group is often excluded from trials.

Implications

If higher blood pressure under treatment is better for cognitive function, then it might benefit patients to increase their blood pressure by deprescribing antihypertensive treatment. Early trials like the Dutch DANTE study asked if deprescribing antihypertensive medication improved cognitive function in older patients with mild cognitive impairment but found no evidence of effect after 16 weeks of follow-up [41]. The long term effects of deprescribing antihypertensives are still uncertain, but a recent Cochrane review found withdrawing from antihypertensive therapy in old age did not increase mortality [42]. We encourage researchers to conduct new randomized trials to test the long-term effectiveness and safety of deprescribing antihypertensive therapy to raise SBP, especially in individuals with complex health problems.

Until the results of these new trials are available, clinicians must daily decide on appropriate treatment for hypertension in older patients with limited evidence, including this study [25, 26]. Antihypertensive treatment is intended to reduce the risk of cardiovascular events and to preserve cognitive/daily function and QoL in older people. But our results show that SBP <130 mmHg under antihypertensive treatment is associated with additional cognitive decline. Our results suggest SBP thresholds for treatment should be redefined, especially for older persons with complex health problems. A more individualized approach might be best right now [43]. Since older patients are more likely to have complex problems and suffer accelerated cognitive decline, clinicians are advised to be cautious about lowering SBP too much.

Conclusions

In our study in the primary care setting, older participants aged ≥75 years under antihypertensive treatment with an SBP ≥130 mmHg showed significant and clinically relevant benefit in cognitive function after one year compared to participants whose SBP was <130mmHg, without loss to either daily functioning or QoL. A similar, but not significant trend was seen in participants not under antihypertensive treatment. This effect was strongest in participants with complex health problems under antihypertensive treatment. A more individualized approach to treat hypertension in older patients with complex health problems might be best right now until deprescribing trials could test if deprescribing antihypertensive treatment is beneficial or not.

REFERENCES

1. Egan, B.M., Y. Zhao, and R.N. Axon, *US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008.* Jama, 2010;303(20):2043-50.
2. Collaborators, G.B.D.R.F., *Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015.* Lancet, 2016;388(10053):1659-1724.
3. Lacruz, M.E., et al., *Prevalence and Incidence of Hypertension in the General Adult Population: Results of the CARLA-Cohort Study*. Medicine (Baltimore), 2015;94(22):e952.
4. Prince, M.J., et al., *Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults.* BMJ, 1996;312(7034):801-5.
5. Beard, K., et al., *Management of elderly patients with sustained hypertension*. BMJ, 1992;304(6824):412-6.
6. Staessen, J.A., et al., *Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators.* Lancet, 1997;350(9080):757-64.
7. Beckett, N.S., et al., *Treatment of hypertension in patients 80 years of age or older.* N Engl J Med, 2008;358(18):1887-98.
8. SHEP Cooperative Research Group, *Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP).* Jama, 1991;265(24):3255-64.
9. The United Nations: *World Population Prospects: The 2012 Revision*. http://esa.un.org/unpd/wpp
10. World Health Organisation (WHO). *Active Ageing: A Policy Framework, 2002.* http://apps.who.int/iris/bitstream/10665/67215/1/WHO_NMH_NPH_02.8.pdf
11. Yeung, S.E. and W.L. Thornton, *Age-related effects of blood pressure on everyday cognitive function in community-dwelling women*. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 2011;18(6):733-55.
12. van Vliet, P., et al., *NT-proBNP, blood pressure, and cognitive decline in the oldest old: The Leiden 85-plus Study*. Neurology, 2014;83(13):1192-9.
13. Szewieczek, J., et al., *Better cognitive and physical performance is associated with higher blood pressure in centenarians*. J Nutr Health Aging, 2011;15(8):618-22.
14. Pieraccioli, M.C., et al., *Low ambulatory blood pressure as predictor of cognitive decline in older subjects with dementia or mild cognitive impairment*. European Geriatric Medicine, 2012;3:S141.
15. Oveisgharan, S., et al., *Blood pressure, memory, and executive function changes in late-life.* Alzheimer's and Dementia, 2012;1:P88.
16. Nilsson, S.E., et al., *Low systolic blood pressure is associated with impaired cognitive function in the oldest old: longitudinal observations in a population-based sample 80 years and older.* Aging Clin Exp Res, 2007;19(1):41-7.
17. Mossello, E., et al., *Effects of low blood pressure in cognitively impaired elderly patients treated with antihypertensive drugs.* Jama Intern Med, 2015;175(4):578-85.
18. Molander, L., et al., *Lower systolic blood pressure is associated with greater mortality in people aged 85 and older.* J Am Geriatr Soc, 2008;56(10):1853-9.
19. Lv, Y.B., et al., A *U-shaped Association Between Blood Pressure and Cognitive Impairment in Chinese Elderly*. J Am Med Dir Assoc, 2017;18(2):193.e7-193.e13.
20. Corrada, M.M., et al., *Age of onset of hypertension and risk of dementia in the oldest-old: The 90+ Study*. Alzheimers Dement, 2017;13(2):103-110.

21. Duarte, P.O., et al., *Cardiovascular risk factors and inflammatory activity among centenarians with and without dementia*. Aging Clin Exp Res, 2017;29(3):411-7.
22. Bangalore, S., et al., *Optimal Systolic Blood Pressure Target After SPRINT: Insights from a Network Meta-Analysis of Randomized Trials*. Am J Med, 2017;130(6):707-719 e8.
23. Whelton, P.K., et al., *2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* J Am Coll Cardiol, 2018;71(19):2176-2198.
24. Messerli, F.H., J. Sulicka, and B. Gryglewska, *Treatment of hypertension in the elderly.* N Engl J Med, 2008;359(9):972-3; author reply 973-4.
25. Lonn, E.M. and S. Yusuf, *Should Patients With Cardiovascular Risk Factors Receive Intensive Treatment of Hypertension to <120/80 mm Hg Target? An Antagonist View From the HOPE-3 Trial (Heart Outcomes Evaluation-3).* Circulation, 2016;134(18):1311-1313.
26. Oparil, S. and C.E. Lewis, *Should Patients With Cardiovascular Risk Factors Receive Intensive Treatment of Hypertension to <120/80 mm Hg Target? A Protagonist View From the SPRINT Trial (Systolic Blood Pressure Intervention Trial).* Circulation, 2016;134(18):1308-1310.
27. Mossello, E. and D. Simoni, *High blood pressure in older subjects with cognitive impairment.* Monaldi Arch Chest Dis, 2016;84(1-2):730.
28. Blom, J., et al., *Effectiveness and cost-effectiveness of a proactive, goal-oriented, integrated care model in general practice for older people. A cluster randomised controlled trial: Integrated Systematic Care for older People-the ISCOPE study*. Age Ageing, 2016;45(1):30-41.
29. Folstein, M.F., S.E. Folstein, and P.R. McHugh, *"Mini-mental state". A practical method for grading the cognitive state of patients for the clinician*. J Psychiatr Res, 1975;12(3):189-98.
30. Kempen, G.I., et al., *The assessment of disability with the Groningen Activity Restriction Scale. Conceptual framework and psychometric properties*. Soc Sci Med, 1996;43(11):1601-10.
31. EuroQol, G., *EuroQol-a new facility for the measurement of health-related quality of life*. Health Policy, 1990;16(3):199-208.
32. EuroQoL Group. https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-3L_UserGuide_2015.pdf
33. Odden, M.C., et al., *Blood Pressure Trajectory, Gait Speed, and Outcomes: The Health, Aging, and Body Composition Study*. J Gerontol A Biol Sci Med Sci, 2016;71(12):1688-1694.
34. Odden, M.C., et al., *Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty*. Arch Intern Med, 2012;172(15):1162-8.
35. Johnson, K.C., et al., *A prospective study of the effect of hypertension and baseline blood pressure on cognitive decline and dementia in postmenopausal women: the Women's Health Initiative Memory Study*. J Am Geriatr Soc, 2008;56(8):1449-58.
36. Kivipelto, M., et al., *Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study*. BMJ, 2001;322(7300):1447-51.
37. Williamson, J.D., et al., *Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >/=75 Years: A Randomized Clinical Trial.* Jama, 2016;315(24):2673-82.
38. Sabayan, B., et al., *High blood pressure and resilience to physical and cognitive decline in the oldest old: the Leiden 85-plus Study*. J Am Geriatr Soc, 2012;60(11):2014-9.
39. Rosano, C., et al., *High blood pressure accelerates gait slowing in well-functioning older adults over 18-years of follow-up.* J Am Geriatr Soc, 2011;59(3):390-7.
40. Zygmuntowicz, M., et al., *Blood pressure for optimal health-related quality of life in hypertensive patients. J Hypertens*, 2013;31(4):830-9.

41. Moonen, J.E., et al., *Effect of Discontinuation of Antihypertensive Treatment in Elderly People on Cognitive Functioning-the DANTE Study Leiden: A Randomized Clinical Trial.* Jama Intern Med, 2015;175(10):1622-30.
42. Jongstra, S., et al., *Antihypertensive withdrawal for the prevention of cognitive decline*. Cochrane Database Syst Rev, 2016;11:CD011971.
43. Benetos, A., et al., *Polypharmacy in the Aging Patient: Management of Hypertension in Octogenarians.* Jama, 2015;314(2):170-80.

Appendix table 1. Baseline characteristics of participants with and without blood pressure measurements 1 year prior to study inclusion (*n*=1,494).

Domains	Overall (n = 1,494)	Blood pressure measurements 1 year before study inclusion		P-value[a]
		Yes (n = 1,266)	No (n = 228)	
Sociodemographic data				
Female, n (%)	1,018 (68)	874 (69)	144 (63)	0.074
Age, years (SD)	82.3 (5)	82.4 (5)	81.4 (5)	0.006
Primary school only, n (%)	768 (52)	656 (52)	112 (49)	0.43
Low income[b], n (%)	225 (15)	197 (16)	28 (12)	0.20
Residential home, n (%)	124 (8)	101 (8)	23 (10)	0.29
Comorbidities, n (%)				
Cardiovascular disease (CVD)[c]	554 (37)	506 (40)	48 (21)	<0.001
Under antihypertensive therapy	1,168 (78)	1,057 (84)	111 (49)	<0.001
Diabetes mellitus	309 (20)	274 (22)	35 (15)	0.030
Depression	209 (14)	182 (15)	27 (12)	0.30
Cancer	186 (13)	159 (13)	27 (12)	0.76
Baseline function, median (IQR[d])				
MMSE[e] score	28 (26-29)	28 (26-29)	28 (27-29)	0.019
GARS[f] score	30 (24-39)	31 (24-39)	27 (21-34)	<0.001
EQ-5D-3L[g] index values	0.78 (0.60-0.84)	0.77 (0.57-0.84)	0.81 (0.67-0.89)	<0.001
Complex health problems[h]	764 (51)	674 (53)	90 (39)	<0.001

[a] P-value from chi-square test for categorical data; t-test for normally-distributed continuous data, Wilcoxon ranksum test for not normally-distributed continuous data

[b] defined as state pension only (about EUR 750 monthly)

[c] CVD included myocardial infarction, angina pectoris, intermittent claudication, other ischemic heart disease, stroke, TIA, and heart failure

[d] IQR = inter quartile range

[e] Mini-Mental State Examination (MMSE) on a scale of 0-30 points (higher scores indicate better cognitive function)

[f] Groningen Activities Restriction Scale (GARS); the score ranges from 18 to 72 (higher scores indicate greater disability)

[g] Quality of life (EQ-5D-3L index values; full health has a value of 1, dead a value of 0)

[h] Defined as patients having problems in three or more of four domains (functional, somatic, mental, and social)

Appendix table 2. Subgroup analysis restricted to patients without history of cardiovascular disease (n=755). Associations of baseline systolic blood pressure (SBP) and antihypertensive treatment with change in cognitive/daily function and quality of life after one-year follow-up. Multivariable mixed-effects regression model adjusted for age, sex, baseline MMSE/GARS/EQ-5D-3L and accounting for clustering within general practitioners.

	Antihypertensive treatment							
	Yes (n=554)				No (n=201)			
	n	Change (95% CI)	P-value	P-trend	n	Change (95% CI)	P-value	P-trend
Cognitive function								
<130 mmHg	83	*Ref.*	-	0.031	39	*Ref.*	-	0.07
130-150 mmHg	249	0.79 (0.15, 1.57)	0.046	-	113	1.07 (-0.03, 2.17)	0.06	-
>150 mmHg	214	0.98 (0.18, 1.77)	0.017	-	47	1.22 (-0.03, 2.52)	0.06	-
Daily function								
<130 mmHg	81	*Ref.*	-	0.76	39	*Ref.*	-	0.72
130-150 mmHg	248	-0.27 (-1.79, 1.25)	0.73	-	108	-1.69 (-4.61, 1.22)	0.26	-
>150 mmHg	214	-0.29 (-1.86, 1.28)	0.72	-	47	-0.73 (-4.08, 2.62)	0.67	-
Quality of life								
<130 mmHg	82	*Ref.*	-	0.08	38	*Ref.*	-	0.14
130-150 mmHg	250	0.02 (-0.04, 0.08)	0.49	-	112	-0.07 (-0.15, 0.01)	0.09	-
>150 mmHg	216	0.05 (-0.01, 0.11)	0.11	-	48	-0.08 (-0.17, 0.02)	0.11	-

Reading example: Patients under antihypertensive treatment and a baseline SBP of >150mmHg had 0.98 (95% CI 0.18 to 1.77) less cognitive decline compared to patients under antihypertensive therapy with a baseline SBP of <130mmHg.

Appendix table 3. Subgroup analysis restricted to patients without complex health problems (n=591). Associations of baseline systolic blood pressure (SBP) and antihypertensive treatment with change in cognitive/daily function and quality of life after one-year follow-up (n=1,266). Multivariable mixed-effects regression model adjusted for sex, age, baseline MMSE/GARS/EQ-5D-3L and accounting for clustering within general practitioners.

	Antihypertensive treatment							
	Yes (n=486)				No (n=105)			
	n	Change (95% CI)	P-value	P-trend	n	Change (95% CI)	P-value	P-trend
Cognitive function								
<130 mmHg	77	*Ref.*	-	0.35	19	*Ref.*	-	0.15
130-150 mmHg	227	0.20 (-0.59, 0.99)	0.63	-	58	0.23 (-0.80, 1.25)	0.67	-
>150 mmHg	173	0.38 (-0.44, 1.20)	0.37	-	26	0.80 (-0.35, 1.96)	0.17	-
Daily function								
<130 mmHg	76	*Ref.*	-	0.56	19	*Ref.*	-	0.84
130-150 mmHg	226	-0.03 (-1.54, 1.60)	0.97	-	57	-2.07 (-5.92, 1.78)	0.29	-
>150 mmHg	171	-0.38 (-2.02, 1.25)	0.65	-	26	-0.77 (-5.06, 3.51)	0.72	-
Quality of life								
<130 mmHg	76	*Ref.*	-	0.35	19	*Ref.*	-	0.44
130-150 mmHg	227	0.03 (-0.03, 0.08)	0.36	-	58	0.02 (-0.08, 0.12)	0.7868	-
>150 mmHg	174	0.03 (-0.03, 0.09)	0.29	-	27	-0.04 (-0.15, 0.08)	0.52	-

Reading example: Patients under antihypertensive treatment and a baseline SBP of >150mmHg had 0.38 (95% CI -0.44 to 1.20) less cognitive decline compared to patients under antihypertensive therapy with a baseline SBP of <130mmHg.