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Blood pressure and neuropsychiatric symptoms in old age

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Chapter 5

Effect of Discontinuation of ANtihypertensive Treatment in Elderly people on cognitive functioning. The DANTE Study Leiden a randomized clinical trial



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Abstract

Background

Observational studies indicate that lower blood pressure (BP) increases risk for cognitive decline in elderly individuals. Older persons are at risk for impaired cerebral autoregulation; lowering their BP may compromise cerebral blood flow and cognitive function. We assessed whether discontinuation of antihypertensive treatment in older persons with mild cognitive deficits improves cognitive, psychological, and general daily functioning.

Methods

A community-based randomized clinical trial with a blinded outcome assessment at the 16-week follow-up was performed at 128 general practices in the Netherlands. A total of 385 participants 75 years or older with mild cognitive deficits (Mini-Mental State Examination score, 21-27) without serious cardiovascular disease who received antihypertensive treatment were enrolled in the Discontinuation of Antihypertensive Treatment in Elderly People (DANTE) Study Leiden from June 26, 2011, through August 23, 2013 (follow-up, December 16, 2013). Intention-to-treat analyses were performed from January 20 through April 11, 2014. Participants were randomized to discontinuation ($n = 199$) versus continuation ($n = 186$) of antihypertensive treatment (allocation ratio, 1:1). The primary outcome measure was change in the overall cognition compound score. Secondary outcomes included changes in scores on cognitive domains, the Geriatric Depression Scale-15, Apathy Scale, Groningen Activity Restriction Scale (functional status), and Cantril Ladder (quality of life).

Results

Compared with 176 participants undergoing analysis in the control (continuation) group, 180 in the intervention (discontinuation) group had a greater increase (95% CI) in systolic BP (difference, 7.36 [3.02 to 11.69] mm Hg; $P = .001$) and diastolic BP (difference, 2.63 [0.34 to 4.93] mm Hg; $P = .03$). The intervention group did not differ from the control group in change (95% CI) in overall cognition compound score (0.01 [-0.14 to 0.16] vs -0.01 [-0.16 to 0.14]; difference, 0.02 [-0.19 to 0.23]; $P = .84$). The intervention and control groups did not differ significantly in secondary outcomes, including differences (95% CIs) in change in compound scores of the 3 cognitive domains (executive function, -0.07 [-0.29 to 0.15; $P = .52$], memory, 0.08 [-0.12 to 0.29; $P = .43$], and psychomotor speed, -0.85 [-1.72 to 0.02; $P = .06$]),

symptoms of apathy (0.17 [-0.65 to 0.99; P = .68]) and depression (0.14 [-0.20 to 0.48; P = .41]), functional status (-0.72 [-1.52 to 0.09; P = .08]), and quality-of-life score (-0.09 [-0.34 to 0.16; P = .46]). Adverse events were equally distributed.

Conclusion

In older persons with mild cognitive deficits, discontinuation of antihypertensive treatment did not improve cognitive, psychological, or general daily functioning at the 16-week follow-up.

Trial registration

trialregister.nl Identifier: NTR2829

Introduction

Midlife high blood pressure (BP) is a well-known risk factor for cerebrovascular disease¹ and, consequently, cognitive decline in old age.² However, the effect of late-life BP on cognition is less clear. Systematic reviews of observational studies^{3,4} indicate that in old age a lower rather than a higher BP increases the risk for cognitive decline. Whether older persons benefit from lowering of BP for the preservation of cognitive functioning is debatable. In the Hypertension in the Very Elderly Trial (HYVET), antihypertensive treatment did not reduce the incidence of dementia in persons 80 years or older.⁵ Meta-analyses, including the HYVET and other placebo-controlled, double-blinded trials in elderly individuals suggest that antihypertensive treatment does not reduce the risk for dementia^{6,7} or does so only marginally.⁵ The age at which the association between BP and cognitive functioning is supposed to change is approximately 75 years.⁸

In late life, a higher BP may be needed to ensure sufficient cerebral blood flow (CBF). Older persons with established cerebrovascular disease are at risk for impaired cerebral autoregulation,⁹ which normally keeps CBF constant despite variations in BP. Extensive BP lowering in persons with impaired cerebral autoregulation may compromise CBF and result in hypoperfusion,¹⁰ which can contribute to cognitive decline.^{11,12} In addition, a lower BP in older individuals has been associated with psychological¹³ and general daily dysfunction,¹⁴ possibly mediated by a lower CBF.^{15,16}

In the Discontinuation of Antihypertensive Treatment in Elderly People (DANTE) Study Leiden, a community-based randomized clinical trial with a blinded outcome assessment, we evaluated whether temporary discontinuation of antihypertensive treatment improves cognitive, psychological, and general daily functioning in persons 75 years or older with mild cognitive deficits who use antihypertensive treatment. Magnetic resonance imaging (MRI) and magnetic resonance angiography were performed at baseline to assess the presence of cerebrovascular disease and CBF. We hypothesized that increasing BP by discontinuation of antihypertensive treatment would improve cognitive, psychological, and general daily functioning.

Methods

Trial design and participants

From June 26, 2011, through August 23, 2013, we performed a randomized clinical trial in 128 general practices in and around Leiden, the Netherlands. Patients were eligible for inclusion if they were 75 years or older, used antihypertensive treatment, had a systolic BP (SBP) of 160 mm Hg or less, and had a Mini-Mental State Examination (MMSE) score of 21

to 27.¹⁷ Exclusion criteria were a clinical diagnosis of dementia, use of antihypertensives for reasons other than hypertension, current angina pectoris, cardiac arrhythmia, heart failure, myocardial infarction or a coronary reperfusion procedure less than 3 years ago, a history of stroke or transient ischemic attack, or a limited life expectancy. Furthermore, persons with a history of peripheral arterial disease, myocardial infarction, or a coronary reperfusion procedure or persons with diabetes mellitus could participate if their SBP was 140 mm Hg or less.

Our study was approved by the medical ethical committee of the Leiden University Medical Center. All participants provided written informed consent after complete written and verbal description of the study was given in the presence of a close relative serving as a proxy decision maker.¹⁸ Serious adverse events defined as death, myocardial infarction, stroke, transient ischemic attack, or any hospitalization between randomization and the end of follow-up were closely monitored by a data safety monitoring board. No interim analyses for efficacy or futility were performed.

Randomization and masking

Concealment of treatment allocation was ensured by a central computerized randomization procedure. Participants were randomly assigned, in a 1:1 ratio, to parallel discontinuation (intervention group) or continuation (control group) of antihypertensive treatment (Figure 1). Stratified block randomization was used (with block sizes of 4 per general practice) to ensure that intervention and control participants were equally distributed within general practices. Participants and the physicians conducting the intervention were not masked to the allocated intervention. Study outcomes and MRIs were assessed in a standardized manner by research personnel (including J.E.F.M., J.C.F.-D., and A.S.B.) masked to the allocated intervention.

Discontinuation of antihypertensive treatment

During a 6-week period after randomization, the discontinuation of antihypertensive treatment was performed by the participant's physician according to an algorithm composed by the investigators (in Supplementary material). All physicians were instructed to withdraw antihypertensive treatment until a maximum increase of 20 mm Hg in SBP was reached. During this phase, the physician monitored BP every week until no further changes in antihypertensive treatment were made.

Study procedures

Demographic characteristics were assessed at baseline using standardized interviews. At baseline and at the follow-up 16 weeks after randomization, BP was measured and

cognitive, psychological, and general daily functioning were assessed by trained blinded research personnel during home visits. The time of follow-up was set at 16 weeks because we expected to detect short-term benefits of the increase in BP on cerebral perfusion and cerebral functioning after the discontinuation of antihypertensive treatment. In addition, this short follow-up was ethically motivated because discontinuation of antihypertensive treatment for a longer period may increase the risk for cardiovascular disease. Structured questionnaires were used to obtain information on medical history and the use of medication from the physicians. Furthermore, at 6 and 10 weeks after randomization, research personnel performed BP measurements in all participants. Blood pressure was measured twice in a sitting position using a digital sphygmomanometer on the right arm. The mean of the 2 measurements was used for the analyses. During the 6 to 16-week period after randomization, the physician was instructed to restart antihypertensive treatment for safety reasons when measurements of BP at the home visit showed a diastolic BP (DBP) of 120 mm Hg or greater, an SBP of 200 mm Hg or greater (180 mm Hg for participants with diabetes mellitus or those who had had a cardiovascular event >3 years ago), or an increase in SBP of 60 mm Hg or greater relative to baseline. All BP measurements reported come from the home visits. The date of last follow-up was December 16, 2013.

Outcomes

At inclusion and follow-up, global cognitive functioning was assessed with the MMSE (range, 0-30, with lower scores indicating worse functioning).¹⁷ In addition, a battery of cognitive tests was administered, from which we calculated 3 cognitive domain scores and an overall compound cognitive score. Executive function was assessed with the difference (Δ) between the time to complete the Trail Making Test parts A and B¹⁹ and the Interference score of the abbreviated Stroop Color-Word Test (lower scores on both tests indicate better executive function).²⁰ The Immediate (3 trials) (range, 0-45 words) and Delayed Recall (range, 0-15 words) performance on the 15 Word Verbal Learning Test (lower scores indicate worse memory function) and the Visual Association Test (range, 0-12; lower scores indicate worse memory function)²¹ were used to measure memory function. Psychomotor speed was evaluated with the Letter Digit Substitution Test²² using the number of correctly digits coded after 90 seconds for analyses (lower scores indicate worse psychomotor speed). All of the 6 aforementioned tests were combined in the overall cognition compound score. Compound scores were computed by converting the raw scores of each test to standardized z scores [(test score – mean)/SD] and calculating the mean z score across the tests in each compound. The primary outcome measure was the change in overall cognition compound score between baseline and follow-up. Changes in the different cognitive domains and separate cognitive tests were secondary outcome measures.

Further secondary outcome measures were changes in psychological and general daily functioning. The Apathy Scale was used to measure symptoms of apathy (range, 0-42 points, with higher scores indicating more symptoms of apathy),²³ and the Geriatric Depression Scale-15 was used to measure symptoms of depression (range, 0-15 points, with higher scores indicating more symptoms of depression).²⁴ General daily functioning was assessed with the Groningen Activity Restriction Scale (range, 18-72 points, with higher scores indicating lower functioning)²⁵ and quality of life was assessed with the Cantril Ladder (range, 1-10 points, with higher scores indicating better quality of life).²⁶

Interrater reliability was determined by having research personnel score these outcome measures for 7 participants using anonymous video registrations. For all tests and questionnaires, the interrater reliability (Cronbach α) ranged from 0.86 to 1.00.

MRI sub-study

In a nested 3T MRI sub-study, MRI and magnetic resonance angiography at baseline were performed to assess the presence and severity of cerebrovascular disease and CBF, respectively. This sub-study is of particular interest because the presence of cerebrovascular disease may require a higher BP to overcome the increased resistance of narrowed cerebral arterioles and to guarantee adequate CBF. The sub-study was approved by the medical ethical committee of the Leiden University Medical Center. Additional exclusion criteria for this sub-study were MRI contraindications. A total of 236 participants gave additional written informed consent for the MRI sub-study, which was performed before randomization. Subsequently, 16 of these participants were excluded from the DANTE Study Leiden owing to incidental MRI findings, and 15 were excluded who had no follow-up assessment of cognitive, psychological, or general daily functioning; these exclusions left 205 participants for further analysis (Figure 1). The Supplementary material provides a detailed description of MRI and magnetic resonance angiography acquisition and image analyses.

Statistical analysis

Data analysis was performed from January 20 through April 11, 2014. Assuming a dropout rate of 10% in each arm, we estimated that 200 participants in each group were needed to detect a minimum standardized mean (SD) difference of 0.3 (1.0) in overall cognition compound score between the intervention and control groups, with a power of 80% at a 5% level of statistical significance. Baseline characteristics of the 2 groups are reported as mean (SD), median (interquartile range), or number (percentage) where appropriate. Changes in the primary and secondary outcome measures were calculated by subtracting the baseline score from the follow-up score and were compared between the 2 groups using linear mixed models with physicians as the random factor, according

to the intention-to-treat principle. We performed a per-protocol analysis that included the participants in the intervention group who completely (n=90) or partially (n=45) discontinued antihypertensive treatment and discarded those whose treatment had not been changed, who had missing data, or who restarted or were prescribed additional antihypertensive treatment. Reasons for not receiving the intervention included having a BP that exceeded safety limits (n=24), dizziness (n=1), dyspnea (n=1), angina pectoris (n=2), atrial fibrillation (n=3), not showing up for the intervention (n=4), refusal of the physician to discontinue medication therapy (n=1), or unknown reasons (n=9). We also assessed the dose-effect association of the change in SBP (per 10-mm Hg increase) on the change in outcome measures in the intervention group (n=180).

We further explored the intervention effect by performing stratified analyses by median age (80.5 years), the presence of orthostatic hypotension (defined as a decrease in SBP of ≥ 20 mm Hg and/or a decrease in DBP of ≥ 10 mm Hg within 3 minutes on standing), median Groningen Activity Restriction Scale score (22 points), and median MMSE score (26 points). Similarly, stratified analyses were conducted by median volume of white matter hyperintensities (21.7 mL), the presence of microbleeds or lacunar infarcts, and median CBF (51.9 mL per 100 g per minute) in those with a baseline MRI (n=205).

Missing values were not imputed. $P \leq .05$ was considered statistically significant. All analyses were performed with SPSS software (version 20.0; IBM Corp).

Results

Figure 1 presents the study flowchart. A total of 199 participants were randomized to discontinuation of antihypertensive treatment (i.e., the intervention group) and 186 to continuation of antihypertensive treatment (i.e., the control group). A total of 8 participants were excluded after randomization for not meeting eligibility criteria, including 4 with cardiac arrhythmias, 2 with a history of stroke, 1 with current angina pectoris, and 1 with an SBP exceeding 160 mm Hg at the time of inclusion. Furthermore, 19 participants in the intervention group and 10 in the control group had no follow-up measurement. Baseline characteristics of both groups were well balanced except for a slight imbalance in the use of β -blockers and in Trail Making Test Δ scores (Table 1).

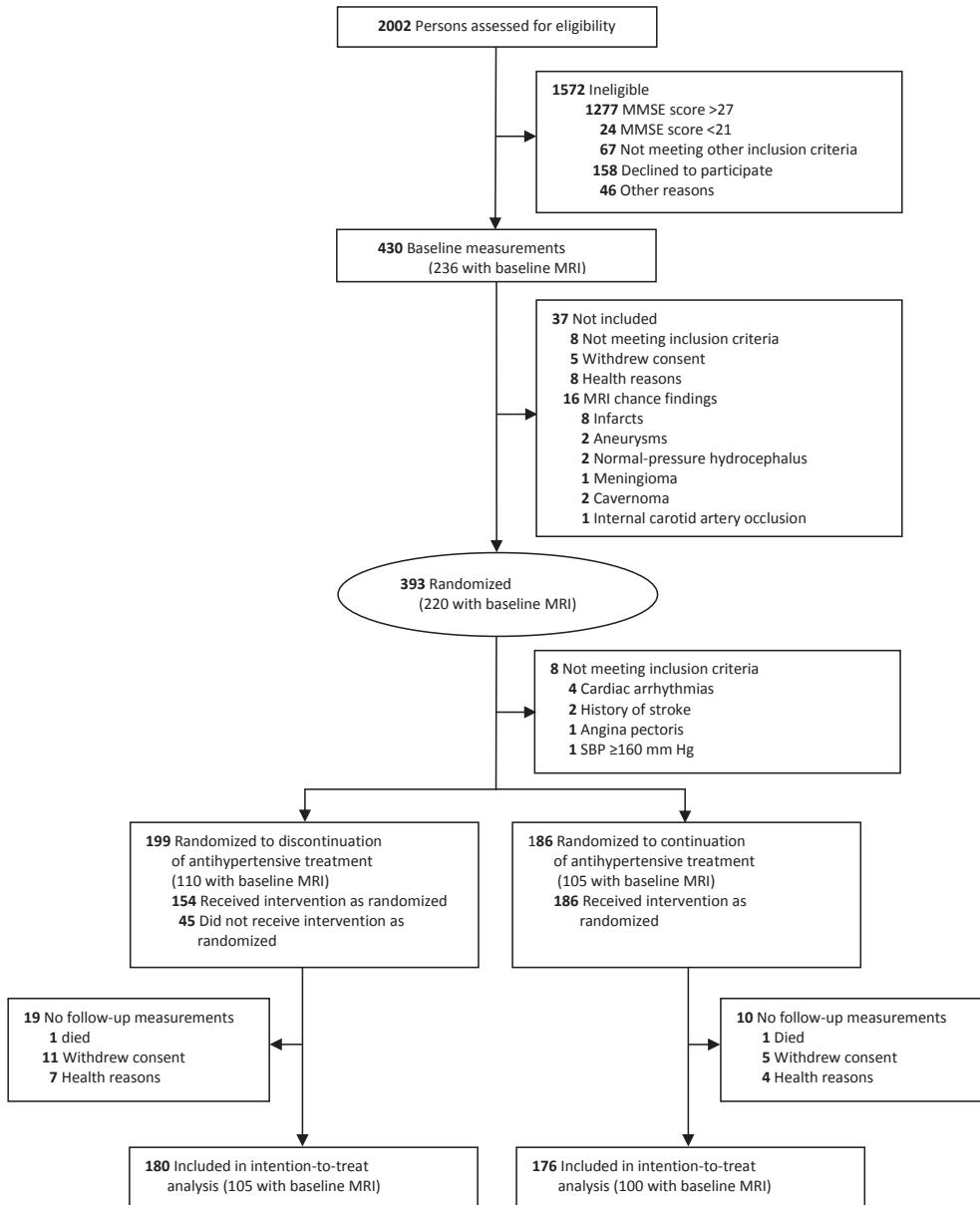


FIGURE 1. CONSORT Flowchart of the Study

MMSE indicates Mini-Mental State Examination; MRI, magnetic resonance imaging.

TABLE 1. Baseline characteristics of all 356 participants^a

Characteristic	Intervention Group (n=180)	Control Group (n=176)
Demographic		
Age, mean (SD), y	81.1 (4.3)	81.5 (4.6)
Male sex	77 (42.8)	70 (39.8)
Educational level, median (IQR), y	9 (6-10)	9 (6-10)
Clinical		
BMI, mean (SD)	27 (4.3)	27 (3.8)
Current smoking	21 (11.7)	13 (7.4)
Alcohol consumption >14 U/wk	20 (11.1)	20 (11.4)
CVD ^b	20 (11.1)	20 (11.4)
Myocardial infarction	11 (6.1)	14 (8.0)
Coronary intervention procedure	5 (2.8)	8 (4.5)
Peripheral arterial disease	7 (3.9)	6 (3.4)
Presence of chronic diseases other than CVD ^c	103 (57.2)	106 (60.2)
Diabetes mellitus	36 (20.0)	39 (22.2)
Psychotropic medication ^d	31 (17.2)	31 (17.6)
Antihypertensive medication		
B-Blocker	64 (35.6)	75 (42.6)
Diuretic	99 (55.0)	92 (52.3)
Angiotensin-converting enzyme-inhibitor	60 (33.3)	61 (34.7)
Angiotensin receptor blocker	60 (33.3)	63 (35.8)
Calcium channel blocker	40 (22.2)	40 (22.7)
≥2 Agents	109 (60.6)	110 (62.5)
SBP, mean (SD), mm Hg	148.8 (21.1)	147.0 (22.3)
DBP, mean (SD), mm Hg	82.3 (10.8)	80.0 (10.7)
Orthostatic hypotension ^e	86 (47.8)	77 (43.8)
Global Cognitive Function		
MMSE global cognitive functioning score, median (IQR) ^f	26 (25-27)	26 (25-27)
Executive Function		
TMT Δ in time to complete, median (IQR), s ^{g,h}	136 (84-201)	115 (73-190)
Stroop Interference time to complete, median (IQR), s ^g	32 (22-50)	31 (21-49)
Memory function		
15-WVLT Immediate Recall score, median (IQR) ⁱ	17 (12-20)	16 (12-19)
15-WVLT Delayed Recall score, median (IQR) ⁱ	4 (2-6)	4 (2-6)
VAT score, median (IQR) ^j	12 (11-12)	12 (10-12)
Psychomotor speed		
LDST psychomotor speed score, mean (SD), s ^k	31 (9.0)	31 (10.0)
Psychological functioning		
Apathy Scale score, mean (SD) ^l	11 (4.6)	11 (4.7)
GDS-15 score, mean (SD) ^m	1 (0-3)	1 (0-3)
General daily functioning		
GARS functional status score, median (IQR) ⁿ	23 (18-28)	22 (19-29)
Cantril Ladder quality-of-life score, mean (SD) ^o	8 (1.2)	8 (1.1)

TABLE 1. Baseline Characteristics of All 356 Participants (continued)

Characteristic	Intervention Group (n=180)	Control Group (n=176)
MRI sub-study (n=205) ^p		
White matter hyperintensity volume, median (IQR), mL	20 (7.9-56.3)	24 (9.1-55.8)
Microbleeds	27 (25.7)	25 (25.0)
Lacunar infarcts	22 (21.0)	31 (31.0)
CBF, mean (SD), mL/100g per min	52.9 (14.3)	50.8 (13.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CBF, cerebral blood flow; CVD, cardiovascular disease; DBP, diastolic blood pressure; GARS; Groningen Activity Restriction Scale; GDS-15, Geriatric Depression Scale-15; IQR, interquartile range; LDST, Letter Digit Substitution Test; MMSE, Mini-Mental State Examination; s, seconds; SBP, systolic blood pressure; TMT, Trail Making Test; VAT, Visual Association Test; 15-WVLT, 15-Word Verbal Learning Test. a Unless otherwise indicated, data are expressed as number (percentage) of participants.

b Includes myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft more than 3 years ago, or peripheral arterial disease.

c Includes diabetes mellitus, Parkinson disease, chronic obstructive pulmonary disease, malignant neoplasms, and osteoarthritis.

d Includes antipsychotics, antidepressants, or benzodiazepines.

e Defined as an SBP decrease of 20 mm Hg or more and/or a DBP decrease of 10 mm Hg or more within 3 minutes on standing.

f Scores range from 0 to 30, with lower scores indicating worse functioning.

g Lower scores indicate better functioning.

h Δ indicates the difference between TMT parts A and B.

i Scores range from 0 to 45 for the 15-WVLT Immediate Recall and from 0 to 15 for the 15-WVLT Delayed Recall, with lower scores indicating worse functioning.

j Scores range from 0 to 12 pictures remembered, with lower scores indicating worse functioning.

k Lower scores indicate worse functioning.

l Scores range from 0 to 42, with higher scores indicating more symptoms of apathy.

m Scores range from 0 to 15, with higher scores indicating more symptoms of depression.

n Scores range from 18 to 72, with higher scores indicating lower functioning.

o Scores range from 1 to 10, with higher scores indicating better quality of life.

p The 205-participant substudy includes 105 in the intervention group and 100 in the control group.

Figure 2 shows that SBP and DBP at 6, 10, and 16 weeks after randomization were significantly higher in the intervention group than in the control group ($P < .001$ for all). At 16 weeks, the mean (SE) SBP had increased by 5.4 (1.6) mm Hg and the DBP by 1.3 (0.9) mm Hg in the intervention group compared with a decrease of 2.0 (1.5) mm Hg (difference, 7.36 [95% CI, 3.02-11.69]; $P = .001$) and of 1.3 (0.8) mm Hg (difference, 2.63 [95% CI, 0.34-4.93]; $P = .03$), respectively, in the control group. In Table S1 in Supplementary material, more detail is provided on proportions of participants with various BP changes.

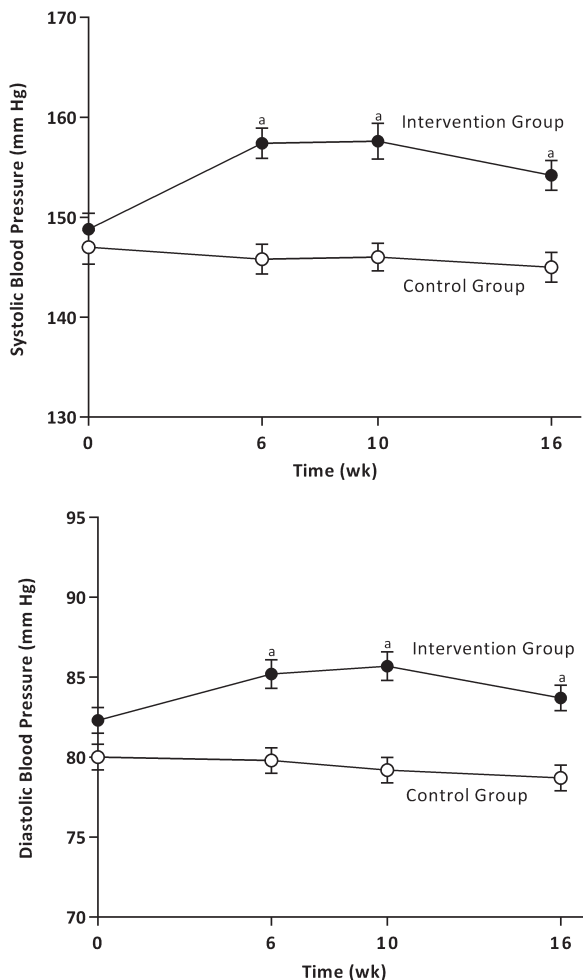


FIGURE 2. Systolic and diastolic blood pressure over time

Bars represent the means and standard errors.

^a indicates a significant difference ($P < 0.001$) for comparison between the intervention and control groups at 6, 10 and 16 weeks. P values were calculated using an independent sample t -test.

The effect of discontinuation of antihypertensive treatment after 16 weeks on the overall cognition compound score was a change (95% CI) of 0.01 (−0.14 to 0.16) in the intervention group vs −0.01 (−0.16 to 0.14) in the control group (difference, 0.02 [−0.19 to 0.23]; $P = .84$) (Table 2). The intervention and control groups did not differ significantly in secondary outcomes, including differences (95% CIs) in change in compound scores of the 3 cognitive domains (executive function, −0.07 [−0.29 to 0.15; $P = .52$], memory, 0.08 [−0.12 to 0.29; $P = .43$], and psychomotor speed, −0.85 [−1.72 to 0.02; $P = .06$]), symptoms of apathy (0.17 [−0.65 to 0.99; $P = .68$]) and depression (0.14 [−0.20 to 0.48; $P = .41$]), functional status (−0.72 [−1.52 to 0.09; $P = .08$]), and quality-of-life score (−0.09 [−0.34 to 0.16; $P = .46$]).

In the intervention group, as defined for the per-protocol analysis (n=135), at 16 weeks the mean (SE) increase in SBP was 11.1 (1.9) mm Hg and the increase in DBP was 4.3 (1.0) mm Hg. In accordance with the intention-to-treat analysis, the per protocol analysis showed that the change in the overall cognition compound score did not differ between the intervention and control groups (difference, 0.01 [95% CI, -0.22 to 0.24]; $P=0.92$) (Table S2 in Supplementary material). Furthermore, in the intervention group, the dose-effect association of the increase in SBP showed no effect on any of the outcome measures (Table S3 in Supplementary material).

TABLE 2. Change in outcome measures in the intervention vs control groups^a

Outcome	Mean Difference in Score (95% CI)		P value
	Intervention Group (n=180)	Control Group (n=176)	
Primary outcome			
Overall cognition, compound score ^b	0.01 (-0.14 to 0.16)	-0.01 (-0.16 to 0.14)	0.84
Secondary outcomes			
Domains			
Executive function, compound score	-0.04 (-0.19 to 0.12)	0.04 (-0.12 to 0.19)	0.52
Memory function, compound score	0.04 (-0.11 to 0.19)	-0.04 (-0.20 to 0.11)	0.43
LDST, psychomotor speed	-0.25 (-0.90 to 0.40)	0.60 (-0.06 to 1.26)	0.06
Cognitive tests			
MMSE Global Cognitive Functioning score	1.15 (0.85 to 1.45)	0.81 (0.51 to 1.12)	0.12
Stroop Interference score, s	-4.05 (-9.33 to 1.24)	-1.83 (-7.09 to 3.43)	0.53
TMT Δ, s	9.07 (0.43 to 17.71)	-0.99 (-9.81 to 7.82)	0.11
15-WVLT Immediate Recall score	1.17 (0.54 to 1.81)	0.93 (0.28 to 1.57)	0.58
15-WVLT Delayed Recall score	0.47 (0.15 to 0.78)	0.31 (-0.01 to 0.64)	0.50
VAT score	0.10 (-0.12 to 0.31)	-0.04 (-0.26 to 0.18)	0.38
Psychological and general daily functioning			
Apathy Scale score	-0.33 (-0.92 to 0.27)	-0.50 (-1.10 to 0.10)	0.68
GDS-15 score score	-0.05 (-0.29 to 0.19)	-0.19 (-0.43 to 0.05)	0.41
GARS functional status score	-0.77 (-1.33 to -0.20)	-0.05 (-0.62 to 0.52)	0.08
Cantril's Ladder quality-of-life score	-0.14 (-0.31 to 0.04)	-0.04 (-0.22 to 0.14)	0.46

Abbreviations: GARS, Groningen Activity Restriction Scale; GDS-15, Geriatric Depression Scale-15; LDST, Letter Digit Substitution Test; MMSE, Mini-Mental State Examination; TMTΔ, Trail Making Test difference; VAT, Visual Association Test; 15-WVLT, 15-Word Verbal Learning Test.

a Includes 356 participants. Test scores are described in Table 1. P values were calculated using linear mixed models with physicians as the random factor.

b Computed if 5 of the following 6 tests were available: Stroop Interference, TMTΔ, 15-WVLT Immediate Recall, 15-WVLT Delayed Recall, VAT, and LDST. Data were missing for 3 participants in the intervention group and 2 in the control group.

Figure 3 presents a forest plot of the results of exploratory subgroup analyses according to age, presence of orthostatic hypotension, Groningen Activity Restriction Scale score, and MMSE score among all participants and according to the volume of white matter hyperintensities, presence of microbleeds, presence of lacunar infarcts, and CBF in participants in the MRI sub-study. In these subgroups, the change in the overall cognition compound score was not significantly different when comparing the intervention with the control group.

The number of serious adverse events did not differ between the 2 groups. In the intervention and control groups, 1 death, 1 myocardial infarction, and 1 transient ischemic attack occurred during the 16-week follow-up, whereas only 1 stroke occurred in the intervention group. The number of hospitalizations (excluding those related to aforementioned vascular events and deaths) was 9 in the intervention group and 10 in the control group (Table S4 in Supplementary material).

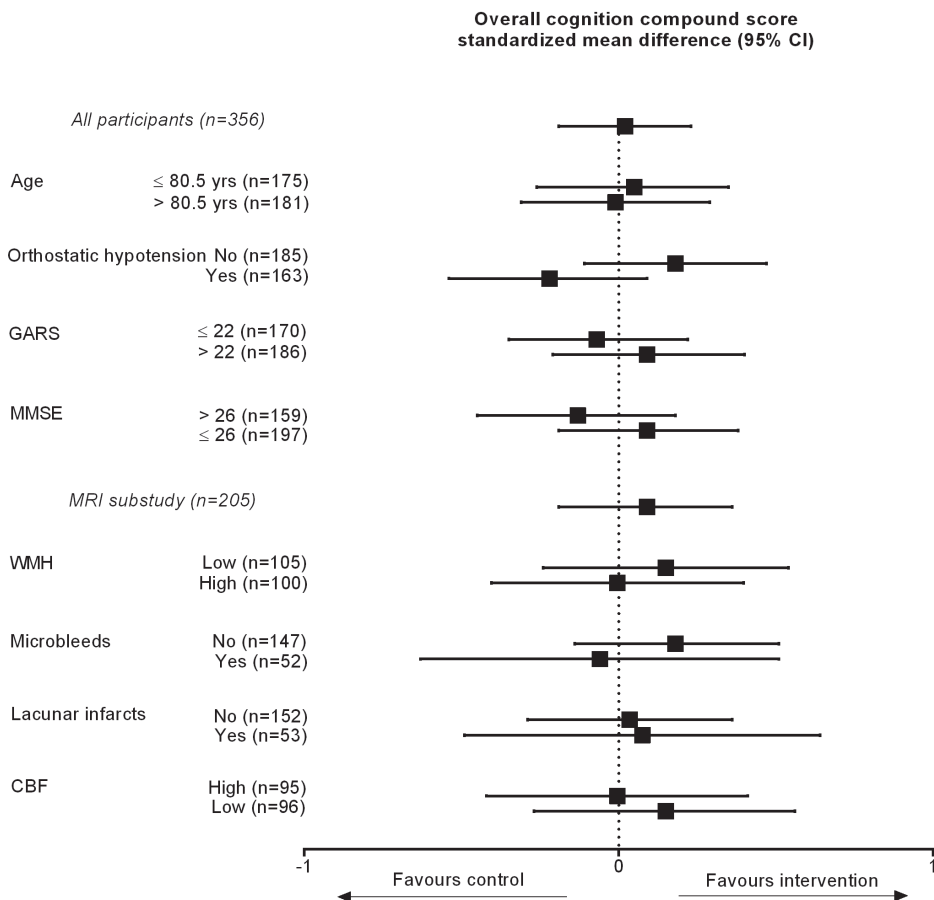


FIGURE 3. Change in overall cognition compound score in subgroups of participants

Data markers represent standardized mean difference of the overall cognition compound score; error bars, 95% CI. Groningen Activity Restriction Scale (GARS) scores and Mini-Mental State Examination (MMSE) scores are described in the Outcomes subsection of the Methods section. Magnetic resonance imaging (MRI) microbleeds data were missing for 6 participants; cerebral blood flow (CBF) data, for 14 participants. WMH indicates white matter hyperintensities.

Discussion

In this community-based randomized clinical trial with blinded outcome assessment, discontinuation of antihypertensive treatment in persons 75 years or older with mild cognitive deficits did not improve their cognitive, psychological, or daily functioning at the 16-week follow-up compared with continuation of antihypertensive treatment. Exploratory analyses in subgroups of older persons, those with orthostatic hypotension, worse cognitive or general daily functioning, lower CBF, or more white matter hyperintensities, microbleeds, and/or lacunar infarcts also showed no benefit from discontinuation of antihypertensive treatment.

This trial is, to our knowledge, the first to assess the effect of discontinuation of antihypertensive treatment on cognitive functioning in older persons. The premise of our trial was based on observational evidence in which a lower BP increased the risk for cognitive decline in older persons.^{3,4}

Several factors may explain the lack of effect of the intervention. We may have failed to observe any effect by unintentionally selecting a population with a relatively intact cerebral autoregulation who were therefore unable to increase cerebral perfusion. For safety reasons, we selected older persons without serious cardiovascular disease, whereas cerebral autoregulation is more likely to be impaired in those with cardiovascular disease.²⁷ Furthermore, the recruitment of those older persons who were willing and able to participate in this trial resulted in a population with an overall high level of cognitive, psychological, and general daily functioning at baseline. However, stratified analyses in subgroups of older persons who are possibly most prone to impaired cerebral autoregulation also showed no benefit from the discontinuation of antihypertensive treatment. Furthermore, the study may have been underpowered. The difference in change in BP between the groups may have been too small to be able to detect the intended 0.3 standardized mean difference in overall cognition compound scores (an equivalent of a 0.4-point difference in MMSE score) between groups within the current sample size. Finally, among elderly persons, no true relation may exist between a short-term increase in BP and cognitive function. The relation between a lower BP and cognitive dysfunction may not be causal but rather attributable to common causes, such as subtle neurodegenerative cerebral lesions in BP regulation centers²⁸ or cardiac dysfunction.²⁹

Our study has several strengths. Cognitive functioning was assessed extensively using various well-validated tests for executive function, memory function, and psychomotor speed, which showed an interrater reliability reflecting high internal consistency. Furthermore, as intended, a significant increase in BP was attained in the intervention group. Also, the dropout rate was low, and the degree of data capture was high. Finally, by performing neuroimaging in a subset of participants we were able to assess the effect of

discontinuation of antihypertensive treatment in those persons with more cerebrovascular disease and/or lower cerebral blood flow at baseline.

Some limitations need to be considered. The participants and physicians conducting the intervention were not blinded to the allocated treatment because no placebo was used. Nevertheless, study outcomes and MRIs were assessed in a standardized manner by blinded research personnel to prevent information bias. Finally, the DANTE trial investigated the effect of complete or partial discontinuation of different classes of antihypertensive treatment to achieve an increase in blood pressure. Thus, conclusions regarding the effect of discontinuation of an individual class of antihypertensives are impeded by confounding by indication.

We addressed a narrowly defined research question. Therefore, we can only conclude that discontinuation of antihypertensive treatment in older persons with mild cognitive deficits and without serious cardiovascular disease has no short-term cognitive benefit. We cannot exclude that a sustained increase in BP during a longer period may prevent long-term structural damage, such as lacunar infarcts or white matter lesions, and thereby may prevent cognitive deterioration. Moreover, this trial did not investigate the potential benefits of discontinuation of antihypertensive treatment in older persons in terms of orthostatic hypotension, dizziness, falls, or CBF. Finally, although the incidence of serious adverse events, such as cardiovascular events and deaths, was similar between the groups during the 16 weeks of follow-up, this trial was not designed to assess long-term risks of discontinuation of antihypertensive treatment.

Current evidence states that antihypertensive treatment in very old persons reduces the risk for cardiovascular morbidity and mortality,³⁰ with no effect on total mortality.³¹ For the present, trials in older persons indicate no increased or decreased risk for cognitive decline of antihypertensive treatment.⁵⁻⁷ Nevertheless, observational evidence showed that in lower-functioning older persons, a lower BP was associated with an increased risk for cognitive decline¹⁴ and total mortality.³² The newest recommendations from the Eighth Joint National Committee allow BP to be as high as 150/90 mm Hg for persons 60 years or older.³³ Moreover, a recent Canadian guideline that was specifically developed for lower functioning (i.e., frail) older persons, although based on limited evidence, recommended starting antihypertensive treatment only if the SBP exceeds 160 mm Hg and, in general, not to prescribe more than 2 antihypertensive medications.³⁴

Future randomized clinical trials with longer follow-up should determine whether older persons with impaired cerebral autoregulation might benefit from less stringent BP targets. Nursing home residents would form a study population of interest because they often have more serious cerebrovascular disease and are thus prone to have an impaired cerebral autoregulation. In persons 75 years or older who were using antihypertensive treatment and who had mild cognitive deficits, discontinuation of antihypertensive treatment did not improve their cognitive, psychological, or general daily functioning after 16 weeks.

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Supplementary Material

Algorithm for discontinuation of antihypertensive treatment

Monotherapy with a calcium channel blocker, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or diuretic was discontinued promptly, while a beta blocker was first halved and then stopped the next week. In the case of combination therapy of 2 drugs, first 1 drug was discontinued promptly and the other drug was halved, followed by complete discontinuation the next week. In the case of combination therapy of 3 drugs, first 2 drugs were discontinued promptly and the third was fully continued. In the consecutive 2 weeks this remaining third drug was first halved and then completely discontinued.

MRI and MRA acquisition and image analyses

MRI acquisition

All imaging was performed on a whole-body MR system operating at a field strength of 3-Tesla (Philips Medical Systems, Best, The Netherlands). Three-dimensional (3-D) T1-weighted images were acquired with repetition time (TR)=9.7 ms, echo time (TE)=4.6 ms, flip angle (FA)=8°, and 224×177×168 mm field of view (FOV), resulting in a nominal voxel size of 1.17×1.17×1.4 mm. T2-weighted images were acquired with TR=4200 ms, TE=80 ms, FA=90°, FOV=224×180×144 mm, matrix size 448×320, 40 slices, 3.6 mm thick. Fluid attenuated inversion recovery (FLAIR) images were acquired with TR=11 000 ms, TE=125 ms, FA=90°, FOV=220×176×137 mm, matrix size=320×240, 25 transverse slices, 5 mm thick. T2*-weighted images were acquired with TE=45 ms, TE=31 ms, FA=13°, FOV=250×175×112 mm. Based on a localizer angiographic slab in the sagittal plane, a 2D phase contrast section was positioned at the level of the pons through the basilar artery and both internal arteries to measure the flow volume these arteries. The MRA 2D phase-contrast images were acquired with TR=13 ms, TE=8.6 ms, FA=10°, slice thickness=5.0 mm, FOV=150×103 mm; matrix size=256×256, number of signal averages=20 and velocity=200 cm/s.

White matter hyperintensities

For the automated measurement of white matter hyperintensity volume images were analyzed using tools of FMRIB Software Version 5.0.1. Library.^{1,2} 3D-T1-weighted images were skull stripped,³ and FLAIR and 3D-T1 image were co-registered.^{4,5} Thereafter the brain extracted and the FLAIR image was affine-registered to MNI152 standard space using the FMRIB's Linear Image Registration Tool. A MNI152 standard space white matter mask was used to extract the white matter from the FLAIR image. Subsequently a threshold was set to identify which white matter voxels were hyperintense, followed by manually checking and editing for quality control.

Cerebral microbleeds and cerebral lacunar infarcts

MRI scans were visualized using the freely available software Philips DICOM viewer R3.0-SP03. Cerebral microbleeds defined as focal areas of signal void (on T2-weighted images), which increased in size on T2*-weighted images (blooming effect).⁶ In this way, cerebral microbleeds were distinguished from vascular flow voids. Symmetric hypointensities in the basal ganglia, likely to represent calcifications or non-haemorrhagic iron deposits, were disregarded. Cerebral lacunar infarcts were assessed on FLAIR, T2-weighted and 3D-T1-weighted images. A cerebral infarct was defined as a parenchymal defect (with signal intensity identical to cerebrospinal fluid on all sequences) of at least 3 mm in diameter,⁷ surrounded by a zone of parenchyma with increased signal intensity on T2-weighted and FLAIR images.

Cerebral blood flow

Flow measurements were performed on MRA, 2D phase-contrast images with the internally developed software package MASS[®] (Division of Image Processing, Department of Radiology, Leiden University Medical Center). With this software, after automatic delineation of the vessel, the blood vessel is identified manually. The region of interest was manually drawn around the vessel in the phase images and checked on the anatomical image. Total cerebral blood flow (mL/min) was defined as the sum of the flow in the basilar artery and both internal carotid arteries. Because cerebral blood flow is strongly dependent on brain volume we expressed cerebral blood flow in mL/100g/min brain volume.

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TABLE S1. Change in blood pressure in the intervention and control group, intention-to-treat (n=356)

	Intervention Group (n=180)	Control Group (n=176)
SBP change, n (%)		
<10 mm Hg	108 (60.0)	127 (72.2)
10-20 mm Hg	29 (16.1)	31 (17.6)
>20 mm Hg	43 (23.9)	18 (10.2)
DBP change, n (%)		
<5 mm Hg	117 (65.0)	134 (76.1)
5-10 mm Hg	24 (13.3)	20 (11.4)
>10 mm Hg	39 (21.7)	22 (12.5)

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure
BP change = BP at follow-up minus BP at baseline

TABLE S2. Change in outcome measures in the intervention versus control group assessed by per-protocol analyses^a

Outcome	Mean Difference in Score (95% CI)		P value
	Intervention Group (n=135)	Control Group (n=176)	
Primary outcome			
Overall cognition, compound score ^b	0.01 (-0.16 to 0.18)	-0.01 (-0.16 to 0.15)	0.92
Secondary outcomes			
Domains			
Executive function, compound score	-0.09 (-0.26 to 0.09)	0.06 (-0.09 to 0.22)	0.21
Memory function, compound score	0.07 (-0.10 to 0.25)	-0.06 (-0.21 to 0.10)	0.26
LDST, psychomotor speed	-0.43 (-1.17 to 0.32)	0.58 (-0.08 to 1.25)	0.04
Cognitive tests			
MMSE Global Cognitive Functioning score	1.14 (0.78 to 1.49)	0.81 (0.49 to 1.13)	0.17
Stroop Interference score, s ^c	-2.01 (-7.73 to 3.71)	-1.76 (-6.73 to 3.21)	0.95
TMT Δ, s ^c	10.25 (0.17 to 20.33)	-1.00 (-9.91 to 7.92)	0.10
15-WVLT Immediate Recall score	1.32 (0.59 to 2.05)	0.93 (0.28 to 1.58)	0.42
15-WVLT Delayed Recall score	0.58 (0.21 to 0.94)	0.31 (-0.01 to 0.63)	0.27
MMSE Global Cognitive Functioning score	0.06 (-0.20 to 0.32)	-0.04 (-0.27 to 0.19)	0.55
Psychological and general daily functioning			
Apathy Scale score ^c	-0.13 (-0.81 to 0.56)	-0.51 (-1.12 to 0.10)	0.39
GDS-15 score score ^c	-0.11 (-0.39 to 0.17)	-0.19 (-0.44 to 0.05)	0.67
GARS functional status score ^c	-0.69 (-1.32 to -0.06)	-0.05 (-0.60 to 0.50)	0.14
Cantril's Ladder quality-of-life score	-0.11 (-0.32 to 0.10)	-0.04 (-0.23 to 0.14)	0.63

Data are presented as the mean difference in score (score follow-up minus score baseline) with 95% CI.

Abbreviations: LDST, letter digit substitution test; MMSE, Mini-Mental State Examination; TMT, trail making test; VAT, visual association test; 15-WVLT, 15 word verbal learning test; GDS-15, Geriatric Depression Scale-15; GARS, Groningen Activity Restriction Scale.

^a Includes 311 participants. P values were calculated using linear mixed models with physicians as the random factor.

^b cognition compound score of: Stroop interference, TMT delta, 15-WVLT immediate, 15-WVLT delayed, VAT, LDST was computed if 5 out of 6 tests were available

^c higher scores indicate worse functioning

TABLE S3. Change in primary and secondary outcome measures in the intervention group per 10 mm Hg increase in systolic blood pressure (n=180)

Outcome	B (95% CI)	P value
Primary outcome		
Overall cognition, compound score ^a	-0.02 (-0.09 to 0.05)	0.57
Secondary outcomes		
Domains		
Executive function, compound score	-0.04 (-0.11 to 0.03)	0.24
Memory function, compound score	<-0.01 (-0.07 to 0.07)	0.93
LDST, psychomotor speed, digits coded	-0.08 (-0.38 to 0.22)	0.61
Cognitive tests		
MMSE Global Cognitive Functioning score	-0.03 (-0.16 to 0.10)	0.65
Stroop Interference score, s ^b	0.19 (-2.13 to 2.51)	0.87
TMT Δ, s ^b	3.78 (-0.34 to 7.89)	0.07
15-WVLT Immediate Recall score, words remembered	0.06 (-0.22 to 0.34)	0.67
15-WVLT Delayed Recall score, words remembered	-0.05 (-0.20 to 0.10)	0.48
VAT score, pictures remembered	0.02 (-0.07 to 0.12)	0.60
Psychological and general daily functioning		
Apathy Scale score ^b	-0.02 (-0.29 to 0.25)	0.86
GDS-15 score score ^b	0.08 (-0.03 to 0.18)	0.15
GARS functional status score ^b	-0.21 (-0.49 to 0.06)	0.12
Cantril's Ladder quality-of-life score	<0.01 (-0.09 to 0.09)	0.95

Data are presented as unstandardized Beta with 95% CI. Linear mixed models was used to examine the effect of 10 mm Hg change in systolic blood pressure (systolic blood pressure at follow-up minus systolic blood pressure at baseline) as independent variable on outcome measures (score at follow-up minus score at baseline) as dependent variable.

Abbreviations: LDST, letter digit substitution test; MMSE, Mini-Mental State Examination; TMT, trail making test; VAT, visual association test; 15-WVLT, 15 word verbal learning test; GDS-15, Geriatric Depression Scale-15; GARS, Groningen Activity Restriction Scale; s, seconds.

^a cognition compound score of: Stroop interference, TMT delta, 15-WVLT immediate, 15-WVLT delayed, VAT, LDST was computed if 5 out of 6 tests were available.

^b higher scores indicate worse functioning

TABLE S4. Adverse events

	Intervention Group (n=199)	Control Group (n=186)
Deaths	1 ^a	1 ^b
Myocardial infarction	1	1
Stroke	1	0
Transient Ischemic Attack	1	1
Hospitalizations ^c	9	10
Elective	3	5
Not elective	6 ^d	5 ^e

^a Cause of death: heart- and respiratory failure. Symptoms developed before start of intervention.

^b Cause of death: myocardial infarction.

^c Excluding vascular events and deaths.

^d including hospitalizations for: hip surgery (n=2), spondylodiscitis (n=1), atrial fibrillation (n=1), analysis back pain; M. Kahler (n=1), diverticular bleeding (n=1).

^e including hospitalizations for: collapse due to atrial fibrillation de novo (n=1), collapse and head trauma (n=1), pneumonia (n=1), cholelithiasis (n=1), post-traumatic intracranial hematoma during use of anticoagulants (n=1).

