ARTICLE CLASS OF EVIDENCE

Effects of blood pressure and lipid lowering on cognition

Results from the HOPE-3 study

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Abstract

Objective

To assess whether long-term treatment with candesartan/hydrochlorothiazide, rosuvastatin, or their combination can slow cognitive decline in older people at intermediate cardiovascular risk.

Methods

The Heart Outcomes Prevention Evaluation-3 (HOPE-3) study was a double-blind, randomized, placebo-controlled clinical trial using a 2 × 2 factorial design. Participants without known cardiovascular disease or need for treatment were randomized to candesartan (16 mg) plus hydrochlorothiazide (12.5 mg) or placebo and to rosuvastatin (10 mg) or placebo. Participants who were ≥70 years of age completed the Digit Symbol Substitution Test (DSST), the modified Montreal Cognitive Assessment, and the Trail Making Test Part B at baseline and study end.

Results

Cognitive assessments were completed by 2,361 participants from 228 centers in 21 countries. Compared with placebo, candesartan/hydrochlorothiazide reduced systolic blood pressure by 6.0 mm Hg, and rosuvastatin reduced low-density lipoprotein cholesterol by 24.8 mg/dL. Participants were followed up for 5.7 years (median), and 1,626 completed both baseline and study-end assessments. Mean participant age was 74 years (SD ±3.5 years); 59% were women; 45% had hypertension; and 24% had ≥12 years of education. The mean difference in change in DSST scores was −0.91 (95% confidence interval [CI] −2.25 to 0.42) for candesartan/hydrochlorothiazide compared with placebo, −0.54 (95% CI −1.88 to 0.80) for rosuvastatin compared with placebo, and −1.43 (95% CI −3.37 to 0.50) for combination therapy vs double placebo. No significant differences were found for other measures.

Conclusions

Long-term blood pressure lowering with candesartan plus hydrochlorothiazide, rosuvastatin, or their combination did not significantly affect cognitive decline in older people.

ClinicalTrials.gov identifier

NCT00468923.

Classification of evidence

This study provides Class II evidence that for older people, candesartan plus hydrochlorothiazide, rosuvastatin, or their combination does not significantly affect cognitive decline.

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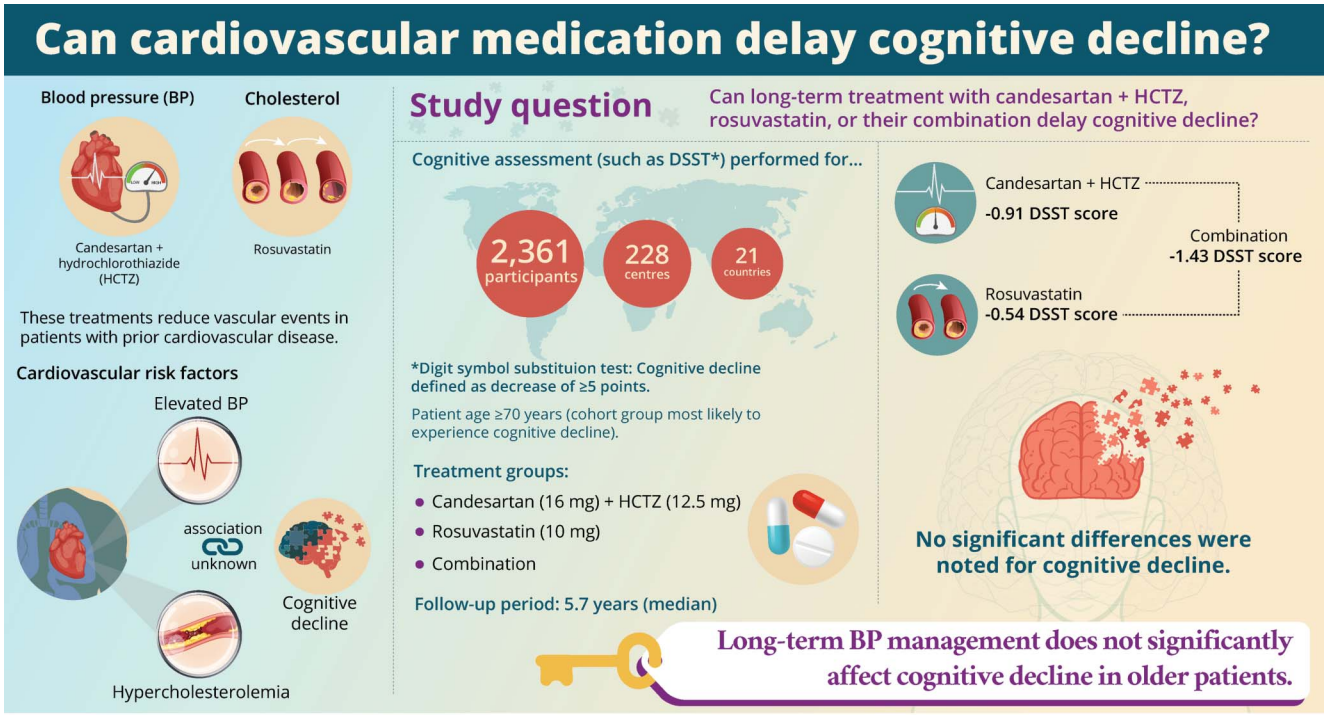
Coinvestigators are listed at links.lww.com/WNL/A01.

Glossary

ADL = activities of daily living; **ANCOVA** = analysis of covariance; **BP** = blood pressure; **CI** = confidence interval; **CVD** = cardiovascular disease; **DSST** = Digit Symbol Substitution Test; **EQ-5D** = EuroQol 5D; **HOPE-3** = Heart Outcomes Prevention Evaluation-3; **LDL** = low-density lipoprotein; **LDL-C** = low-density lipoprotein cholesterol; **MIND** = Memory and Cognition in Decreased Hypertension; **mMoCA** = modified 12-item Montreal Cognitive Assessment; **OR** = odds ratio; **PRoFESS** = Prevention Regimen for Effectively Avoiding Second Strokes; **SAGE** = Standard Assessment of Global Activities in the Elderly; **SBP** = systolic blood pressure; **SPRINT** = Systolic Blood Pressure Intervention Trial; **SPS3** = Secondary Prevention of Small Subcortical Strokes Trial; **TMT-B** = Trail Making Test Part B.



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Cognitive impairment and dementia are major contributors to disability, affecting 35.6 million people worldwide and ≈10% of the population >60 years of age. The number of affected individuals is expected to triple by 2050.[1,2] Both vascular risk factors and cognitive decline are associated with functional decline.[3,4] Although vascular risk factors are associated with cognitive impairment,[5] to date, there is no convincing evidence that modification of vascular risk factors prevents cognitive decline or dementia,[6] although it has been speculated that better vascular risk factor control may have contributed to the decline in the prevalence of dementia in these populations.[3,4,7]

Elevated blood pressure (BP) in midlife is associated with later-life development of cognitive impairment, but it is not known whether lowering BP can prevent cognitive decline.[8–11] Hypercholesterolemia is also linked to cognitive impairment, but some observational studies have suggested that use of statins may accelerate cognitive decline.[12] In 2012, the US Food and Drug Administration issued a warning about the potential adverse effects of statin use on cognition.[13] In contrast to the observational studies, meta-analyses of randomized trials have not demonstrated an adverse effect of statins on cognition.[14–17]

We have previously reported the results of the Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial, which examined the effects of BP lowering with candesartan plus hydrochlorothiazide and cholesterol lowering with rosuvastatin compared to placebo on major vascular events in patients at intermediate cardiovascular risk with no prior cardiovascular disease (CVD). This group represents a large proportion of middle-aged and older persons. There was no effect of BP-lowering treatment on vascular events overall, but there was a 24% reduction in events in

those with the highest baseline BP levels; rosuvastatin reduced vascular events by 25% in all participants. Here, we report the effects of BP lowering with candesartan plus hydrochlorothiazide, cholesterol lowering with rosuvastatin, and their combination on cognition and function in HOPE-3 participants ≥70 years of age.

Methods

Primary research questions

1. Does the use of candesartan plus hydrochlorothiazide in those at intermediate risk of CVD prevent cognitive decline compared to placebo (Class II evidence)?
2. Does the use of rosuvastatin in those at intermediate risk of CVD prevent cognitive decline compared to placebo (Class II evidence)?
3. Does the use of candesartan plus hydrochlorothiazide and rosuvastatin in those at intermediate risk of CVD prevent cognitive decline compared to placebo (Class II evidence)?

Study design

Details of the HOPE-3 study design and the main outcomes have been published.[18–20] HOPE-3 was a multicenter, international, double-blind, randomized, placebo-controlled trial that used a 2 × 2 factorial design to evaluate the effects of BP lowering with candesartan plus hydrochlorothiazide, cholesterol lowering with rosuvastatin, and their combination compared to placebo on the prevention of major cardiovascular events in participants at intermediate cardiovascular risk.

Participants

HOPE-3 included men ≥55 years of age and women ≥65 years of age with at least 1 additional clinical cardiovascular risk factor or women ≥60 years of age with 2 additional risk factors. Participants were excluded if they had an established, guideline-based indication for either study drug. The cognition and function substudy restricted eligibility to participants who were at least 70 years old because these participants are at highest risk of cognitive decline.[21]

Procedures

Participants completed a single-blind, 4-week run-in period on active drug (1 tablet each of candesartan/hydrochlorothiazide 16/12.5 mg and rosuvastatin 10 mg). Those who tolerated the medication and wanted to continue were randomized by a blinded central randomization system to receive daily 1 tablet each of candesartan/hydrochlorothiazide 16/12.5 mg or placebo and rosuvastatin 10 mg or placebo. Participants were seen at 6 weeks, 6 months, and then every 6 months thereafter until a common study end date of October 31, 2015. Median follow-up was 5.7 years.

Cognitive and functional outcomes

Cognitive testing was completed at randomization and study end. Three validated measures were used to assess cognition: the Digit Symbol Substitution Test (DSST) (primary outcome measure), the modified 12-item Montreal Cognitive Assessment (mMoCA), and the Trail Making Test Part B (TMT-B). The DSST, which has been widely used in randomized trials and community-based studies,[22–24] evaluates psychomotor speed, attention, and executive function[25] by requiring participants to match symbols to numbers using a key. The score indicates the number of correct matches completed in 120 seconds to a maximum of 133.[25] A decrease in score of ≥5 points is considered meaningful cognitive decline on the basis of the difference in score observed between those who are 70 and 75 years old in the Cardiovascular Health Study.[22,26] In those without known cognitive dysfunction such as those enrolled in HOPE-3, the DSST is more sensitive to change in cognition than other measures such as the Mini-Mental State Examination.[27] The mMoCA includes assessment of delayed recall, orientation, and verbal fluency and is scored out of 13 (1 point is added if the participant had ≤12 years of education).[28] The TMT-B measures attention and psychomotor speed by measuring the time (in seconds) to connect numbers and letters randomly placed on a page in an alphanumeric sequence.[29] Times between 78 and 128 seconds are considered average for this age group.[30]

Functional status was evaluated at baseline and study end in all those ≥70 years of age with the activities of daily living (ADL) subset of the 3-level version of the EuroQol 5D (EQ-5D), which measures 3 domains (mobility, self-care, and usual activities); higher scores indicate greater impairment in ADL.[31] At study end, a more detailed evaluation of the ability to perform ADL was performed with the 15-item Standard Assessment of Global Activities in the Elderly (SAGE), which assesses the ability to independently carry out daily activities required for independent functioning. Points are awarded when some, moderate, or complete help is required to carry out a task, with a maximum score of 45 indicating total dependence. Institutionalization was collected at each visit, and dementia was collected as a reason for hospitalization or study drug discontinuation.

Standard protocol approvals, registrations, and patient consents

All aspects of study conduct, including the consent process and collection of the assessments used in this analysis, were approved by institutional ethics review boards for each site (ClinicalTrials.gov NCT00468923).

Statistical analysis

The primary cognitive outcome measure was change in DSST score, calculated as the difference between randomization and study end scores, such that positive scores would indicate an improvement in score and negative scores would indicate a decline. The effect of each treatment was analyzed with analysis of covariance (ANCOVA) and adjusted for the baseline score. The mean difference and 95% confidence interval (CI) are reported. In a secondary analysis, the number of participants with a decline in DSST score of ≥5 points was analyzed for each group using logistic regression with the odds ratios (ORs) and 95% CIs reported.

The analyses for the secondary outcomes included the effect of treatment on mean change in mMoCA and TMT-B scores, using ANCOVA and adjusting for baseline scores. In addition, a composite outcome of decline in score on any cognitive measure, defined as a decrease of ≥5 points for the DSST, ≥2 points for the mMoCA, and ≥10% for the TMT-B, was analyzed with a χ^2 test to explore the treatment effect.

Sensitivity analyses were performed with 2 different imputations techniques to determine the effect of missing end-of-study cognitive scores on study outcomes. Assuming that missingness was random,[32] the first method imputed the missing study-end score by matching on age, sex, baseline cognitive score, and other available study-end cognitive scores; the second method imputed the study-end score with a multiple imputation procedure.

For functional outcomes using EQ-5D, we examined whether the proportion of participants who reported new functional impairments differed by treatment groups using a χ^2 test. Participants' study-end SAGE scores were categorized as follows: no impairment (score of 0), mild impairment (score of 1–3), or moderate or greater impairment (score of ≥4). Scores were compared between treatment groups with the use of a χ^2 test.

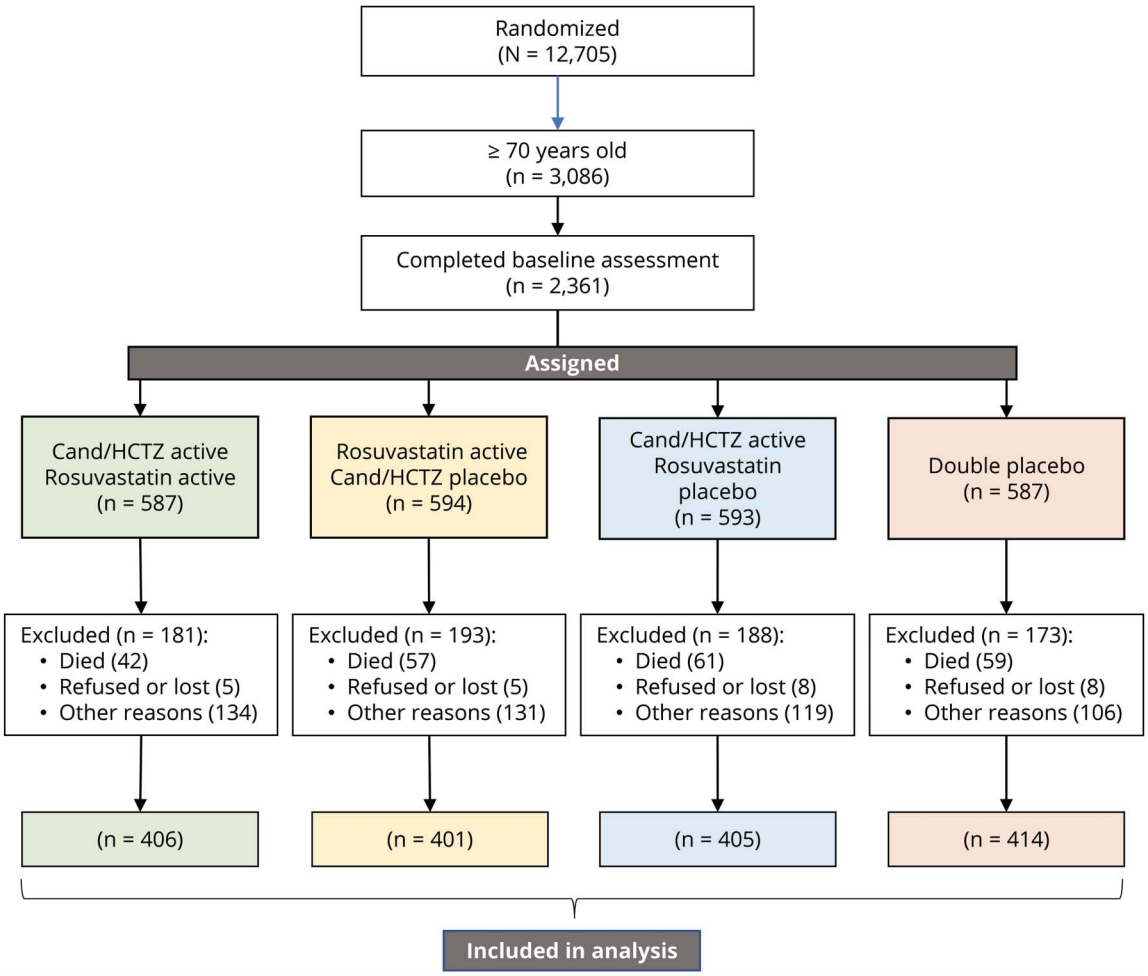
All analyses were performed with SAS software, version 9.2 (SAS Institute Inc, Cary, NC).

With a sample size of 1,626, the study had 80% power to detect a 2.6-point difference in mean change in cognitive function (measured by the DSST) for any of the comparisons.

Data availability

Data will be disclosed only on request and on approval of the proposed use of the data by the study review committee. Deidentified individual participant data will be made available, as will data dictionaries, the study protocol, and the statistical analysis plan for the primary results. Data are available for 4.5 years after the main study publication (2016).

Figure 1 CONSORT diagram



Baseline and study-end assessments were completed for 1,626 participants. Cand/HCTZ = candesartan/hydrochlorothiazide; CONSORT = Consolidated Standards of Reporting Trials.

Table 1 Baseline characteristics overall and by BP, lipid lowering, and combination comparisons[a]

		BP lowering		Lipid lowering		BP and lipid lowering	
	Completed baseline and study end	Candesartan-hydrochlorothiazide	Placebo	Rosuvastatin	Placebo	Candesartan-hydrochlorothiazide + rosuvastatin	Placebo plus placebo
Randomized, n	1,626	811	815	807	819	406	414
Age, y	74.1 ± 3.5	74.2 ± 3.5	74.1 ± 3.5	74.2 ± 3.6	74.1 ± 3.3	74.1 ± 3.6	73.9 ± 3.3
Female, n (%)	963 (59.2)	485 (59.8)	478 (58.7)	468 (58.0)	495 (60.4)	237 (58.4)	247 (59.7)
Medical history, n (%)							
Hypertension	728 (44.8)	369 (45.5)	359 (44.0)	352 (43.6)	376 (45.9)	187 (46.1)	194 (46.9)
Diabetes mellitus	94 (5.8)	44 (5.4)	50 (6.1)	45 (5.6)	49 (6.0)	18 (4.4)	23 (5.6)
Falls	77 (4.7)	40 (4.9)	37 (4.5)	40 (5.0)	37 (4.5)	18 (4.4)	15 (3.6)
Fractures	162 (10.0)	76 (9.4)	86 (10.6)	82 (10.2)	80 (9.8)	42 (10.3)	46 (11.1)
Rheumatoid arthritis	24 (1.5)	13 (1.6)	11 (1.4)	10 (1.2)	14 (1.7)	5 (1.2)	6 (1.5)
Cataracts	165 (10.1)	72 (8.9)	93 (11.4)	79 (9.8)	86 (10.5)	37 (9.1)	51 (12.3)
Cancer	45 (2.8)	25 (3.1)	20 (2.5)	24 (3.0)	21 (2.6)	11 (2.7)	7 (1.7)
Cholesterol, mg/dL							
Total	205.6 ± 38.5	204.9 ± 38.8	206.4 ± 38.3	206.2 ± 38.7	205.0 ± 38.4	206.1 ± 38.5	206.4 ± 37.7
LDL-C	127.0 ± 34.5	125.8 ± 33.7	128.2 ± 35.2	127.5 ± 34.6	126.5 ± 34.4	127.0 ± 33.9	128.5 ± 35.2
HDL-C	52.2 ± 14.3	52.5 ± 14.2	51.8 ± 14.4	52.1 ± 14.9	52.3 ± 13.6	52.3 ± 15.0	51.7 ± 13.9
BP, mm Hg							
Systolic (Omron)	139.7 ± 15.0	139.6 ± 14.4	139.7 ± 15.6	140.2 ± 15.0	139.1 ± 15.0	140.2 ± 14.5	139.1 ± 15.5
Diastolic (Omron)	79.4 ± 9.6	79.6 ± 9.8	79.3 ± 9.4	79.8 ± 9.7	79.1 ± 9.5	80.0 ± 9.7	79.0 ± 9.2
Ankle-arm BP	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2
Heart rate, bpm	71.6 ± 10.1	72.2 ± 10.1	70.9 ± 10.1	71.6 ± 10.1	71.6 ± 10.2	71.9 ± 9.9	70.7 ± 10.1
High-sensitivity C-reactive protein, median (IQR), mg/L	2.0 (1.0–4.0)	2.1 (1.0–4.1)	1.9 (1.0–3.8)	1.9 (1.0–4.0)	2.1 (1.0–4.0)	1.9 (1.0–3.9)	1.9 (1.0–3.7)
Weight, kg	69.9 ± 14.5	69.6 ± 14.3	70.2 ± 14.7	69.5 ± 14.0	70.3 ± 15.0	69.6 ± 13.8	71.1 ± 15.1
Body mass index, kg/m^2[b]	26.9 ± 4.7	26.8 ± 4.5	27.0 ± 4.9	26.8 ± 4.6	27.0 ± 4.8	26.7 ± 4.4	27.2 ± 5.0
Waist-to-hip ratio, men	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1

Continued

Table 1 Baseline characteristics overall and by BP, lipid lowering, and combination comparisons[a] *(continued)*

	Completed baseline and study end	BP lowering		Lipid lowering		BP and lipid lowering	
		Candesartan-hydrochlorothiazide	Placebo	Rosuvastatin	Placebo	Candesartan-hydrochlorothiazide + rosuvastatin	Placebo plus placebo
Waist-to-hip ratio, women	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
Medications, n (%)							
Aspirin	246 (15.1)	123 (15.2)	123 (15.1)	113 (14.0)	133 (16.2)	54 (13.3)	64 (15.5)
β-Blocker	211 (13.0)	104 (12.8)	107 (13.1)	99 (12.3)	112 (13.7)	53 (13.1)	61 (14.7)
Calcium channel blocker	294 (18.1)	148 (18.2)	146 (17.9)	146 (18.1)	148 (18.1)	74 (18.2)	74 (17.9)
Oral hypoglycemic agent	36 (2.2)	15 (1.8)	21 (2.6)	15 (1.9)	21 (2.6)	4 (1.0)	10 (2.4)

Abbreviations: BP = blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
There are no statistically significant differences in baseline characteristics between those in the candesartan + hydrochlorothiazide and placebo groups, the rosuvastatin and placebo groups, and the candesartan/hydrochlorothiazide plus rosuvastatin and placebo plus placebo groups.
[a] Plus-minus values are mean ± SD.
[b] Body mass index is weight in kilograms divided by the square of height in meters.

Results

In the main study, the 12,705 HOPE-3 participants were randomized from 221 centers in 21 countries. Of the 3,086 who were ≥70 years of age, 2,361 agreed to participate and completed a baseline DSST, 219 died during the study, and 1,626 (76%) completed a DSST at study end (median follow up 5.7 years) (figure 1). The functional subset of the EQ-5D (mobility, ADL, and usual activities) was completed at baseline and study end by all those ≥70 years of age (n = 2,474), and the SAGE was completed at study end by 1,592 of those who completed baseline and study-end DSST.

Baseline characteristics were similar between randomized treatment groups for the BP-lowering or cholesterol-lowering groups compared to their respective control groups (table 1). The average age of participants who completed a baseline and study-end DSST was 74.1 years (SD 3.5 years); mean BP was 140/79 mm Hg; mean low-density lipoprotein (LDL) cholesterol (LDL-C) was 126.8 mg/dL; 59% were female; and 45% had a history of hypertension. The only significant differences in baseline characteristics between participants who completed both a baseline DSST and a study-end DSST and those who completed only a baseline DSST were postsecondary education (24% of those who completed both tests had postsecondary education compared to 12% of those who completed only a baseline test, $p \leq 0.0001$) and ethnicity, with more Latin Americans compared with others not completing the DSST at both time points (table 2).

The mean difference in systolic BP (SBP) reduction between baseline and study end for those on candesartan/hydrochlorothiazide compared with placebo was 6.0 mm Hg, and the mean reduction in LDL-C for those on rosuvastatin compared with placebo was 24.8 md/dL. The mean reduction in BP and LDL did not differ between those who completed baseline only compared with those who completed baseline and study-end DSSTs, nor was it significantly different from the treatment effects observed in the main trial population.

Cognitive and functional outcomes

Baseline and mean change scores by treatment group are provided in table 3. Overall, there was a mean decline in DSST scores of 5.4 from baseline. There were no significant differences in DSST scores (primary outcome) with an ANCOVA adjusted for baseline DSST between the candesartan plus hydrochlorothiazide and placebo groups (difference in adjusted means −0.91, 95% CI −2.25 to 0.42), between rosuvastatin and placebo groups (difference in adjusted means −0.54, 95% CI −1.88 to 0.80), or between candesartan plus hydrochlorothiazide plus rosuvastatin and double placebo groups (difference in adjusted means −1.43, 95% CI −3.37 to 0.50) (figure 2).

There was no significant difference in the odds of experiencing a decline in DSST scores of ≥5 points between those taking candesartan plus hydrochlorothiazide vs placebo (405 vs 406, OR 1.00, 95% CI, 0.79–1.24, $p = 0.94$), those taking rosuvastatin vs placebo (398 vs 413, OR 1.03, 95% CI 0.82–1.30,

Table 2 Baseline characteristics of participants who completed a baseline and study-end DSST and those who completed only a baseline DSST[a]

	Completed baseline and study end	Completed baseline only
Randomized, n	1,626	735
Age, y	74.1 ± 3.5	75.0 ± 4.1
Women, n (%)	963 (59.2)	432 (58.8)
>12 y education, n (%)	388 (23.9)	98 (13.3)
Medical history, n (%)		
Hypertension	728 (44.8)	319 (43.4)
Diabetes mellitus	94 (5.8)	42 (5.7)
Falls	77 (4.7)	46 (6.3)
Fractures	162 (10.0)	73 (9.9)
Rheumatoid arthritis	24 (1.5)	24 (3.3)
Cancer	45 (2.8)	25 (3.4)
Cholesterol, mg/dL		
Total	205.6 ± 38.5	205.5 ± 38.9
LDL-C	127.0 ± 34.5	127.7 ± 35.9
HDL-C	52.2 ± 14.3	51.4 ± 13.3
BP, mm Hg		
Systolic	139.7 ± 15.0	138.6 ± 15.9
Diastolic	79.4 ± 9.6	79.4 ± 9.4
Heart rate, bpm	71.6 ± 10.1	71.5 ± 10.3
High-sensitivity C-reactive protein, median (IQR), mg/L	2.0 (1.0, 4.0)	2.4 (1.3, 4.7)
Weight, kg	69.9 ± 14.5	69.3 ± 15.1
Body mass index, kg/m^2[b]	26.9 ± 4.7	26.9 ± 5.1
Waist-to-hip ratio, men	1.0 ± 0.1	1.0 ± 0.1
Waist-to-hip ratio, women	0.9 ± 0.1	0.9 ± 0.1
Medication, n (%)		
Aspirin	246 (15.1)	89 (12.1)
β-Blocker	211 (13.0)	88 (12.0)
Calcium channel blocker	294 (18.1)	168 (22.9)
Oral antihyperglycemic agents	36 (2.2)	17 (2.3)
Ethnicity or race, n (%)		
South Asian	74 (4.6)	34 (4.6)
Chinese	382 (23.5)	71 (9.7)
Other Asian	132 (8.1)	49 (6.7)
Black	32 (2.0)	37 (5.0)
White	392 (24.1)	131 (17.8)
Latin American	587 (36.1)	394 (53.6)
Other	27 (1.7)	19 (2.6)

Abbreviations: BP = blood pressure; DSST = Digit Symbol Substitution Test; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
[a] Plus-minus values are means ± SD.
[b] Body mass index is weight in kilograms divided by the square of height in meters.

$p = 0.80$), or those taking candesartan/hydrochlorothiazide plus rosuvastatin vs double placebo (211 vs 219, OR 1.02, 95% CI 0.74–1.40, $p = 0.90$).

Secondary outcomes

The mean change in scores did not differ between the active and placebo groups for the mMoCA or TMT-B for BP lowering compared with placebo, rosuvastatin compared with placebo, or the combination compared with double placebo (table 3).

For the composite outcome on cognitive decline (defined as decrease of ≥5 points on the DSST, ≥2 points on the mMoCA, and ≥10% on the TMT-B), results were similar in the active vs placebo groups for candesartan/hydrochlorothiazide and placebo (584 vs 612, $p = 0.37$), rosuvastatin and placebo (597 vs 599, $p = 0.76$), and candesartan/hydrochlorothiazide plus rosuvastatin and double placebo (304 vs 319, $p = 0.40$).

Sensitivity analyses using 3 different imputation techniques for study-end scores demonstrated similar results for all comparisons (data not shown).

By study end, ≈20% of participants experienced a new impairment in basic ADL, as measured by EQ-5D, which did not differ by treatment group. Mean SAGE scores demonstrated that two-thirds had some functional impairment (in ADL, activities requiring cognitive and motor skills, or cognitive planning activities), and distributions were similar between treatment groups (table 4).

Only 16 individuals were reported to develop dementia, and 4 were institutionalized by study end, with no differences in occurrence between treatment allocations (12 BP lowering vs 8 placebo; 12 rosuvastatin vs 8 placebo; 6 double active vs 6 BP lowering vs 6 rosuvastatin vs 2 placebo).

Subgroups

There was no statistically significant difference in the effects of either intervention on cognitive decline in subgroups based on age, SBP, use of antihypertensive medication at baseline, or education (figure 3, A and B.).

Table 3 Baseline and mean change score in outcomes by treatment group

BP lowering	Candesartan-hydrochlorothiazide No.	Candesartan-hydrochlorothiazide Mean[a] (SD)	Placebo No.	Placebo Mean[a] (SD)	*p* Value
DSST score					
Baseline	1,180	32.8 (18.3)	1,181	32.6 (18.3)	
Change	811	−5.91 (18.4)	815	−4.94 (18.3)	0.29
mMoCA score					
Baseline	1,353	10.8 (1.7)	1,374	10.7 (1.8)	
Change[a]	998	−0.39 (0.06)	1011	−0.49 (0.06)	0.25
TMT-B score					
Baseline	524	150.6 (90.7)	507	152.8 (87.3)	
Change[a]	243	0.56 (3.8)	229	6.87 (3.89)	0.24

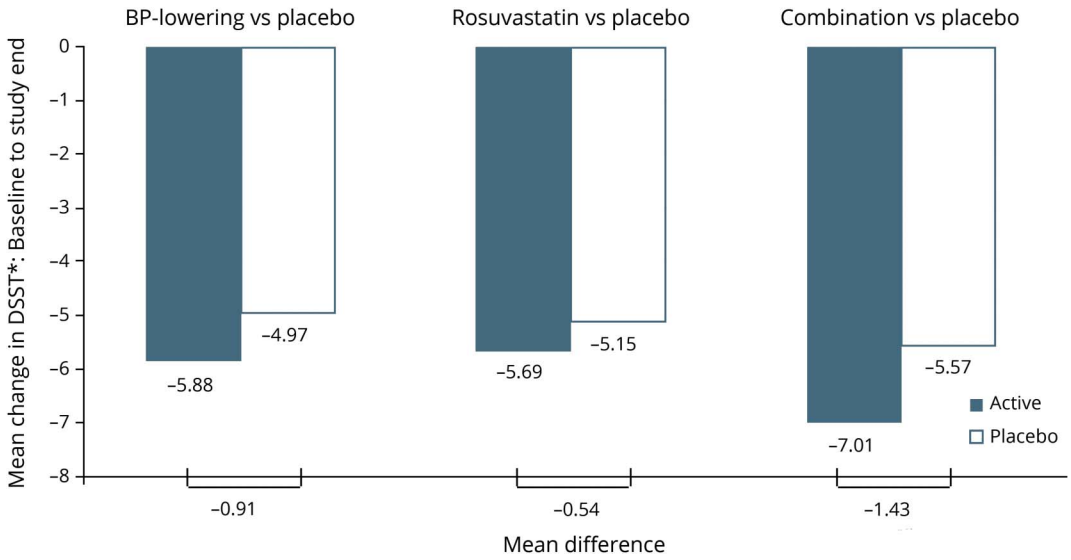
Cholesterol lowering	Rosuvastatin No.	Rosuvastatin Mean[a] (SD)	Placebo No.	Placebo Mean[a] (SD)	*p* Value
DSST score					
Baseline	1,181	32.2 (18.6)	1180	33.1 (18.1)	
Change	807	−5.37 (19.3)	819	−5.47 (17.3)	0.91
mMoCA score					
Baseline	1,371	10.7 (1.8)	1356	10.8 (1.8)	
Change[a]	996	−0.46 (0.06)	1013	−0.41 (0.06)	0.51
TMT-B score					
Baseline	515	150.1 (89.4)	516	153.3 (88.6)	
Change[a]	252	4.46 (3.7)	220	2.71 (4.0)	0.75

Combined BP and cholesterol lowering	Double active No.	Double active Mean[a] (SD)	Double placebo No.	Double placebo Mean[a] (SD)	*p* Value
DSST score					
Baseline	587	32.9 (19.1)	587	33.6 (18.6)	
Change	406	−6.72 (19.7)	414	−5.85 (17.7)	0.50
mMoCA score					
Baseline	676	10.8 (1.7)	679	10.8 (1.9)	
Change[a]	492	−0.42 (0.08)	507	−0.46 (0.08)	0.72
TMT-B score					
Baseline	254	143.9 (86.2)	246	149.3 (81.8)	
Change[a]	128	4.19 (4.9)	105	9.25 (5.4)	0.49

Abbreviations: BP = blood pressure; DSST = Digit Symbol Substitution Test; mMoCA = modified 12-item Montreal Cognitive Assessment; TMT-B = Trail Making Test Part B.
[a] Adjusted for baseline score.

In an exploratory subgroup analysis of participants (n = 181) with the highest tertile of baseline SBP (cutoff SBP >145.0 mm Hg, mean ± SD SBP 156 ± 9.4 mm Hg) and the highest tertile of baseline LDL-C (cutoff LDL >140.0 mg/dL, mean ± SD LDL-C 164.7 ± 20.9 mg/dL) who were treated with the combination of BP lowering and rosuvastatin compared with double placebo, there was a significant reduction in cognitive decline as measured

Figure 2 Mean study-end DSST score by treatment group



A decrease in score of ≥5 points is considered meaningful cognitive decline. BP = blood pressure; DSST = Digit Symbol Substitution Test. *Adjusted for baseline score.

by the DSST (reduction in score 5.84 vs 10.30 points, p for interaction = 0.04).

Discussion

In a population ≥70 years of age at intermediate risk of CVD (defined as an annual risk of major cardiovascular events of ≈1%), we observed that BP lowering with candesartan/hydrochlorothiazide, lipid lowering with rosuvastatin, and the combination did not reduce or increase the rate of cognitive or functional decline over median follow-up of 5.7 years. The results were consistent in different cognitive and functional assessments and in different subgroups. Sensitivity analyses accounting for nonrandom missing data did not alter our findings. However, in an exploratory analysis of study participants who had the highest SBP and LDL-C at baseline (mean SBP 156.3 mm Hg, mean LDL-C 164.7 mg/dL), we found that the combination of BP lowering and rosuvastatin compared with placebo reduced the rate of cognitive decline.

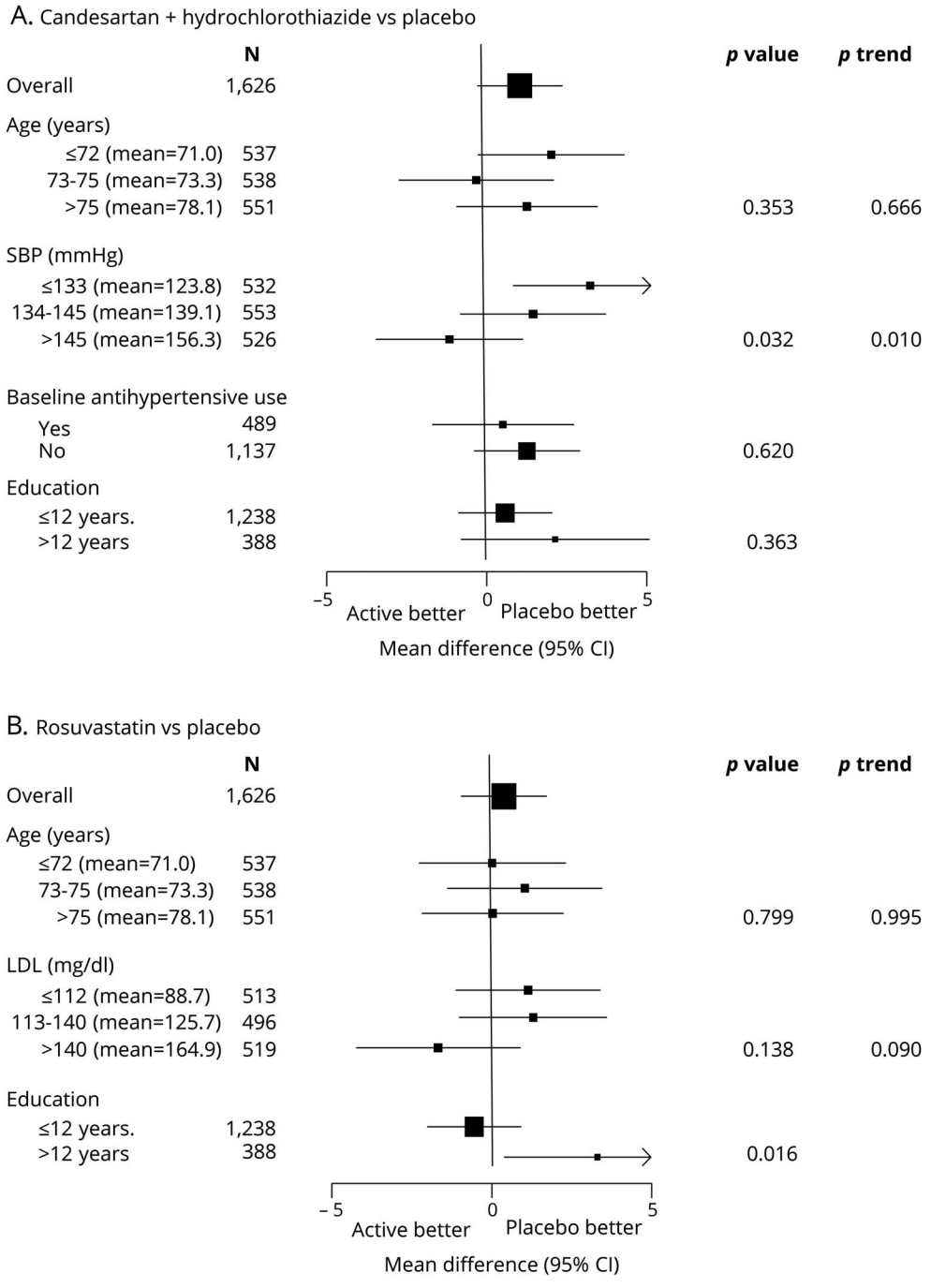
Our finding that lipid lowering with rosuvastatin, a hydrophilic statin, did not worsen cognitive decline is consistent with the results of recent meta-analyses indicating that statins have no adverse effect on cognitive function.[15,17,33] It is likely that the results from observational studies that report a harmful effect of statins on cognition are confounded.

Table 4 Study-end SAGE scores and change in EQ-5D from baseline to study end

	Candesartan-hydrochlorothiazide	Placebo	*p* Value	Rosuvastatin	Placebo	*p* Value	Candesartan-hydrochlorothiazide + rosuvastatin	Double placebo	*p* Value
SAGE score									
0	481 (40.3)	483 (41.1)	0.76	472 (39.3)	492 (42.1)	0.37	240 (39.7)	251 (43.4)	0.44
1–3	341 (28.6)	343 (29.2)		357 (29.8)	327 (28.0)		175 (29.0)	161 (27.8)	
>3	371 (31.1)	349 (29.7)		371 (30.9)	349 (29.9)		189 (31.3)	167 (28.8)	
EQ-5D									
New impairment in basic ADL	269 (21.8)	271 (21.9)	0.96	265 (21.2)	275 (22.5)	0.46	135 (21.5)	141 (22.8)	0.58

Abbreviations: ADL = activities of daily living; EQ-5D = EuroQol 5D; SAGE = Standard Assessment of Global Activities in the Elderly.

Figure 3 Forest plot of primary outcome in subgroups



(A) Candesartan plus hydrochlorothiazide and (B) rosuvastatin vs placebo. CI = confidence interval; LDL = low-density lipoprotein; SBP = systolic blood pressure.

The relationship between BP and cognition is not clear. Midlife hypertension has been associated with later-life cognitive impairment,[11] while later-life hypotension has been associated with an increased risk of cognitive impairment.[8,9] While a relationship between BP and cognition seems evident, BP-lowering studies do not consistently demonstrate less cognitive decline.[34,35] These studies included low-risk participants, were of short duration, and used insensitive tools (such as Mini-Mental State Examination) to measure change in cognition.[36] A meta-analysis examining the effect of antihypertensive treatment in those with hypertension but without a history of cerebrovascular disease demonstrated a small but significant effect on cognitive decline.[37] Several trials that included participants at higher CVD risk or with higher baseline BPs suggested a benefit of BP lowering in preventing cognitive and functional decline, but even in this population, the results are inconsistent.[38,39] There was no effect of antihypertensive treatment on cognitive decline in those with cerebrovascular disease in either the Secondary Prevention of Small Subcortical Strokes Trial (SPS3)[40] or

Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS)[41] trial, and there was no effect of intense BP control on cognition in those with diabetes mellitus.[42] Results of the Systolic Blood Pressure Intervention Trial (SPRINT) and Memory and Cognition in Decreased Hypertension (MIND) study[43] will provide further insights into the effect of intensive BP lowering on cognition. Our results indicating an effect of combined BP and lipid lowering in the prevention of cognitive decline in those with the highest initial BP levels suggest that those at highest cardiovascular risk may benefit. This is consistent with the main study results, demonstrating an effect in those with the highest baseline SBP.

It is possible that a treatment duration of 5.7 years may not be long enough to prevent cognitive decline, especially in a population with normal BP.[11] The slower rate of decline seen in the group with higher baseline BP and lipids and the potential benefit of longer treatment should be evaluated in future studies.

While we demonstrated an overall change in cognition, we were not able to detect a treatment effect, and this may be due to several limitations. First, although efforts were made to obtain all data, we were able to get measures at both time points in only ≈75% of those who were alive at the end of the study. For many, the final visit was completed by telephone, and it is possible that severe cognitive decline prevented these participants from returning, in which case our imputation methods may have overestimated their final score, but the numbers missing between groups are similar and therefore would not affect results. Baseline DSST scores and the magnitude of cognitive decline observed in HOPE-3 participants are similar to those reported in the Long Life Family Study and the Cardiovascular Health Study,[22] suggesting that the participants are representative of the broader population.[26]

We administered the cognitive assessments to an older cohort in this study. It is possible that there was a selection bias at the sites, with only the healthiest older adults at low risk of cognitive decline agreeing to participate in the study. In addition, 27% refused to complete the initial questionnaires, indicating that participants may be self-selecting, perhaps refusing to participate because of awareness of cognitive issues. Therefore, our study may have included a healthier-than-average group of older adults at intermediate risk of CVD. Nevertheless, the study was well powered to detect a treatment difference. With 1,619 who completed both end-of-study and baseline DSST assessments, we had nearly 100% power to detect a 5-point treatment difference in the DSST score. The study had 91% power to detect a 3-point difference.

In the HOPE-3 study, a decline in cognitive function and functional status was observed over 5.7 years in an older population at intermediate risk of CVD. BP lowering, rosuvastatin, or their combination did not affect cognitive or functional decline in the overall study population, but the combination may be of benefit in the subgroup with the highest baseline BP and cholesterol, and longer BP treatment may be necessary.

Author contributions

Study concept and design, acquisition of data, analysis and interpretation of data, study supervision: J. Bosch, E.M. Lonn, S. Yusuf. Study concept and design, acquisition of data, interpretation of data, critical revision of manuscript: M. O'Donnell, G. Dagenais, R. Diaz, K. Khunti, B. Lewis, A. Avezum, C. Held, M. Keltai, C. Reid, W. Toff, A. Dans, L. Leiter, K. Sliwa. Analysis and interpretation of data: B. Swaminathan, S.F. Lee, J. Pogue. Statistical analysis: B. Swaminathan. Interpretation of data and critical revision of manuscript: M. Sharma, R. Hart.

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