ORIGINAL RESEARCH

Effects of Lipid-Lowering and Antihypertensive Treatments in Addition to Healthy Lifestyles in Primary Prevention: An Analysis of the HOPE-3 Trial

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***Background*—**It is not clear whether the effects of lipid-lowering or antihypertensive medications are influenced by adherence to healthy lifestyle factors. We assessed the effects of both drug interventions in subgroups by the number of healthy lifestyle factors in participants in the HOPE-3 (Heart Outcomes Prevention Evaluation) trial.

***Methods and Results*—**In this primary prevention trial, 4 healthy lifestyle factors (nonsmoking status, physical activity, optimal body weight, and healthy diet) were recorded in 12 521 participants who were at intermediate risk of cardiovascular disease (CVD) and were randomized to rosuvastatin, candesartan/hydrochlorothiazide, their combination, or matched placebos. Median follow-up was 5.6 years. The outcome was a composite of CVD events. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox regression models. Participants with ≥2 healthy lifestyle factors had a lower rate of CVD compared with those with fewer factors (HR: 0.85; 95% CI, 0.73–1.00). Rosuvastatin reduced CVD events in participants with ≥2 healthy lifestyle factors (HR: 0.74; 95% CI, 0.62–0.90) and in participants with <2 factors (HR: 0.79; 95% CI, 0.61–1.01). Consistent results were observed with combination therapy (≥2 factors: HR: 0.74; 95% CI, 0.57–0.97; <2 factors: HR: 0.61; 95% CI, 0.43–0.88). Candesartan/hydrochlorothiazide tends to reduce CVD only in participants with <2 healthy lifestyle factors (HR: 0.78; 95% CI, 0.61–1.00).

***Conclusions*—**Healthy lifestyles are associated with lower CVD. Rosuvastatin alone and combined with candesartan/hydrochlorothiazide is beneficial regardless of healthy lifestyle status; however, the benefit of antihypertensive treatment appears to be limited to patients with less healthy lifestyles.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT00239681. **(*J Am Heart Assoc*. 2018;7: e008918. DOI: 10.1161/JAHA.118.008918.)**

Key Words: antihypertensive agent • statin

Observational studies indicate that healthy lifestyles, defined as avoidance of tobacco, moderate or vigorous physical activities, optimal body weight, and healthy diet, are associated with lower mortality and cardiovascular disease (CVD).[1–11] Both statins and blood pressure lowering (in those with elevated blood pressure) reduce the risk of CVD in randomized clinical trials, but no analyses of randomized trial data have evaluated whether the effects of statins or antihypertensive agents compared with placebo vary in patients who adhere or do not adhere to healthy lifestyles. We assessed in post hoc analysis whether the benefits of lipid-lowering or antihypertensive medications or their

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/7/15/e008918/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- In 12 705 HOPE-3 (Heart Outcomes Prevention Evaluation) participants at risk for cardiovascular disease and followed for 5.6 years, those who adhered to ≥2 of 4 healthy lifestyle factors at baseline had a lower cardiovascular disease risk than those with <2 of 4 factors.
- Participants randomized to candesartan/hydrochlorothiazide versus placebo had a trend for benefit limited to participants with <2 of 4 lifestyle factors who were at greater risk than those with healthier factors.
- Rosuvastatin alone or combined with candesartan/hydrochlorothiazide versus placebo was beneficial to participants with both healthier and poorer lifestyles.

What Are the Clinical Implications?

- Healthy lifestyle approaches should be improved and integrated with a pharmacologic strategy for primary prevention of cardiovascular disease.

combination versus placebo were similar or differed depending on the number of healthy lifestyle factors in participants of the HOPE-3 (Heart Outcomes Prevention Evaluation) trial.

Methods

Study Design and Population

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Details of the HOPE-3 trial (ClinicalTrials.gov: NCT00239681) have been reported.[12–15] Briefly, HOPE-3 was an international, double-blind, randomized, placebo-controlled trial with a 2×2 factorial design performed in 12 705 participants without CVD but at intermediate cardiovascular risk.

Participants from 21 countries (in South and North America, Europe, Asia, and Australia) were men aged ≥55 years and women aged ≥65 years with at least 1 additional CVD risk factor or women aged ≥60 years with 2 additional risk factors. The risk factors were family history of premature coronary artery disease, elevated waist/hip ratio, recent or current tobacco use, dysglycemia, concentration of high-density lipoprotein cholesterol <1.0 mmol/L (38.7 mg/dL) for men and <1.3 mmol/L (50 mg/dL) for women, and mild renal dysfunction (microalbuminuria, creatinine >124 but <180 μmol/L [>1.4 but <2.0 mg/dL], or estimated glomerular filtration rate <60 but >45 mL/min per 1.73 m^2). Participants were excluded if they had preexisting CVD; had renal dysfunction (1 value outside the study's eligibility range); were taking an angiotensin modulator, hydrochlorothiazide or a statin; had contraindications to these medications; or had debilitating disease reducing their life expectancy to <5 years. The ethics committee at each center approved the HOPE-3 protocol, and all participants provided written informed consent.

Study Medications and Follow-up

Participants completed a single-blind 4-week run-in period on active medications (1 daily tablet of rosuvastatin 10 mg and 1 daily tablet of candesartan/hydrochlorothiazide 16/12.5 mg) to assess their tolerance and adherence. Participants who tolerated and took ≥80% of medications and wished to continue in the trial were randomized to receive daily 1 tablet each of rosuvastatin 10 mg or matching placebo and candesartan/hydrochlorothiazide 16/12.5 mg or matching placebo. Participants were seen at 6 weeks and 6 months after randomization and every 6 months thereafter until study end on October 31, 2015; the median follow-up was 5.6 years. Lifestyle advice was provided on the basis of individual needs at each study visit. The site nurse or physician had to complete a standardized questionnaire identifying an unhealthy lifestyle and note counseling given for any abnormal factor according to current guidelines.

Data Collection

Baseline characteristics included medical history; medications; blood pressure; blood measurements of glucose, creatinine, C-reactive protein and lipids; resting ECG; and sociodemographic and lifestyle factors. A standardized questionnaire based on the INTERHEART study[3] was used at entry and at the end of the study to document medical history, medications, smoking status, physical activity performance, and diet. We recorded participants' food intake using a qualitative short food frequency questionnaire. Weight, height, and abdominal and hip circumferences were measured with participants in light clothes and without shoes at entry and at the end of the study. The waist/hip ratio was used instead of body mass index due the large number of HOPE-3 Asian participants. Blood pressure was measured at each visit in the first year and annually thereafter (mean of 2 measurements obtained after a 5-minute quiet rest period). Fasting blood samples were obtained at baseline in 91% of all randomized participants, in a sample of 12% at 1 and 3 years, and in 14% at the end of the study for lipid and C-reactive protein levels. All hospitalizations during follow-up were recorded.

Definition of Healthy Lifestyles and Scoring

The 4 healthy related lifestyle factors used in this analyses were (1) nonsmoking (never smokers and those who had quit >1 year earlier) versus current smoking, including those

within 1 year of discontinuation; (2) moderate or vigorous physical activities, either at work (eg, predominantly walking on 1 level and no heavy lifting, mainly walking including climbing stairs or walking up hill or lifting heavy objects, continuous heavy physical labor) or during leisure time (eg, walking, bicycle riding, or gardening ≥3.5 hours/week), versus less activity; (3) optimal waist/hip ratio (≤0.89 for men and ≤0.84 for women) versus a higher ratio; and (4) healthy versus unhealthy diet, assessed using a 9-point Mediterranean diet score, based on an adaptation of the approach described by Trichopoulou et al.[16] Participants were asked, "In the last 12 months, how often did you consume foods from each of the following categories?" and a list of food groups was presented. Recorded frequencies of consumption were converted to daily intake. We included 9 food groups in our scoring system. Mediterranean diet food groups of legumes/nuts, whole grains, fruits, vegetables, and dairy products were classified as healthy; confectionary, sugar, meat, and fried foods were classified as unhealthy. For each healthy food group, participants received a score of 1 if consumption was at or above the median; otherwise, a value of 0 was assigned. For each unhealthy food group, participants received scores of 1 if consumption was below median and 0 otherwise. Scores were summed, and each individual's Mediterranean diet score was calculated. A higher total score indicated more frequent intake of healthy foods and less frequent intake of unhealthy foods and greater degree of adherence to Mediterranean diet. In calculating the results of the 4 health-related lifestyle factors, a value of 1 was assigned if the participant's total Mediterranean diet score was at or above median value; otherwise, a value of 0 was assigned.

Each of the 4 health-related lifestyle factors was allocated a score of 1. Each participant could have a health-related lifestyle score ranging from 0 (least healthy) to 4 (most healthy).

Outcomes

We used the secondary composite outcome as prespecified for HOPE-3: CVD death, nonfatal myocardial infarction, stroke, heart failure, revascularization, resuscitated cardiac arrest, or angina with documented ischemia. This composite outcome is the HOPE-3 co–primary outcome with the addition of angina with ischemia. We use this outcome considering the need for more events, given the subdivision of each pharmacological intervention into those with more and fewer lifestyle factors. All outcomes were predefined and centrally adjudicated by trained physicians unaware of the medication allocation.[14]

Statistical Analysis

All analyses were performed according to the intention-to-treat principle. We determined the effects of the lipid-lowering medication, the antihypertensive medication, or their combination versus their respective placebos in reducing CVD in people with ≥2 versus <2 healthy lifestyle factors. Participant lifestyle scores were categorized into subgroups by the baseline number of healthy lifestyle factors ≥2 versus <2, and then the effects of the randomized treatments were assessed using the t test, Kruskal–Wallis test, or chi-squared test, as appropriate. The Cox proportional hazards regression models were used to estimate the effects of ≥2 versus <2 healthy lifestyle factors on the event rates and the hazard ratios (HRs) and 95% confidence

Table 1. Healthy Lifestyle Factor Distribution and Scores by Treatment Allocation

	Overall, n (%)	Both Treatments, n (%)	Rosuvastatine Alone, n (%)	CH Alone, n (%)	Both Placebos, n (%)
Participants	12 521	3131	3137	3131	3122
Healthy lifestyle factors					
Nonsmokers	9731 (77.72)	2424 (77.42)	2458 (78.36)	2417 (77.20)	2432 (77.90)
Moderate/vigorous physical activities	5498 (43.91)	1386 (44.27)	1368 (43.61)	1383 (44.17)	1361 (43.59)
Optimal body size	1445 (11.54)	356 (11.37)	358 (11.41)	379 (12.10)	352 (11.27)
Healthy eating	6756 (53.96)	1703 (54.39)	1669 (53.20)	1694 (54.10)	1690 (54.13)
Lifestyle score at baseline (0–4)					
0 (no healthy lifestyle factor)	601 (4.80)	146 (4.66)	159 (5.07)	144 (4.60)	152 (4.87)
1 (1 healthy lifestyle factor)	3591 (28.68)	880 (28.11)	887 (28.28)	906 (28.94)	918 (29.40)
2 (2 healthy lifestyle factors)	5379 (42.96)	1382 (44.14)	1366 (43.54)	1329 (42.45)	1302 (41.70)
3 (3 healthy lifestyle factors)	2719 (21.72)	667 (21.30)	666 (21.23)	699 (22.23)	687 (22.01)
4 (4 healthy lifestyle factors)	231 (1.84)	56 (1.79)	59 (1.88)	53 (1.69)	63 (2.02)
Healthy lifestyle (2–4)	8329 (66.52)	2105 (67.23)	2091 (66.66)	2081 (66.46)	2052 (65.73)

CH indicates candesartan/hydrochlorothiazide.

Table 2. Baseline Characteristics by Randomized Medication Groups Subdivided by Number of Healthy Lifestyle Factors

	Both Treatments		Rosuvastatin Alone		CH Alone		Both Placebos	
	Less Healthy (0–1)	Healthy (2–4)	Less Healthy (0–1)	Healthy (2–4)	Less Healthy (0–1)	Healthy (2–4)	Less Healthy (0–1)	Healthy (2–4)
Participants, n	1026	2105	1046	2091	1050	2081	1070	2052
Age, y, mean (SD)	65.50 (6.45)	65.81 (6.24)	65.52 (6.48)	65.94 (6.41)	65.27 (6.45)	65.81 (6.38)	65.49 (6.39)	65.81 (6.18)
Female, n (%)	406 (39.6)	1041 (49.5)	439 (42.0)	1029 (49.2)	436 (41.5)	992 (47.7)	453 (42.3)	1007 (49.1)
European ethnicity, n (%)	145 (14.1)	489 (23.2)	152 (14.5)	469 (22.4)	164 (15.6)	455 (21.9)	155 (14.5)	457 (22.3)
Asian ethnicity, n (%)	542 (52.8)	1012 (48.1)	551 (52.7)	1009 (48.3)	535 (51.0)	1025 (49.3)	527 (49.3)	1028 (50.1)
Education <7 y, n (%)	534 (52.0)	858 (40.8)	553 (52.9)	864 (41.3)	551 (52.5)	881 (42.4)	562 (52.5)	845 (41.2)
Family history of CAD, n (%)	227 (22.1)	602 (28.6)	259 (24.8)	572 (27.4)	252 (24.0)	577 (27.7)	246 (23.0)	571 (27.8)
SBP, mm Hg, mean (SD)	139.60 (14.49)	137.47 (14.83)	139.01 (14.62)	137.35 (15.13)	138.73 (13.79)	137.91 (15.05)	138.47 (14.56)	137.66 (14.55)
DBP, mm Hg, mean (SD)	82.05 (9.48)	81.80 (9.32)	82.13 (9.44)	81.63 (9.25)	82.06 (9.35)	81.89 (9.31)	81.92 (9.44)	81.75 (9.02)
BMI, kg/m^2, mean (SD)	27.06 (4.93)	27.17 (4.72)	27.09 (4.88)	27.17 (4.73)	27.03 (5.08)	27.06 (4.74)	26.91 (4.57)	27.16 (4.77)
WHR, mean (SD)	0.95 (0.08)	0.93 (0.09)	0.95 (0.07)	0.93 (0.08)	0.95 (0.08)	0.93 (0.08)	0.95 (0.08)	0.93 (0.08)
Total cholesterol, mg/dL, mean (SD)	203.33 (43.30)	200.15 (43.19)	203.30 (40.78)	201.31 (41.80)	201.06 (39.47)	201.92 (42.58)	201.42 (42.05)	201.44 (41.23)
LDL-C, mg/dL, mean (SD)	128.97 (36.42)	126.08 (37.25)	129.25 (35.09)	128.55 (35.07)	126.97 (34.30)	128.43 (36.82)	127.59 (36.54)	128.25 (35.60)
HDL-C, mg/dL, mean (SD)	44.49 (13.04)	44.81 (14.36)	44.24 (12.50)	45.24 (14.06)	44.78 (12.45)	45.44 (14.12)	45.04 (13.18)	44.81 (13.91)
Triglycerides, mg/dL, median (IQR)	127.43 (92.04–182.30)	127.43 (92.04–182.30)	134.51 (100.00–181.42)	125.70 (91.15–172.57)	130.09 (94.69–182.30)	124.10 (92.04–174.52)	127.88 (92.92–171.68)	125.30 (92.20–175.22)
Triglycerides, mg/dL, mean (SD)	152.47 (108.66)	151.15 (102.13)	152.97 (93.56)	142.77 (82.13)	151.09 (94.57)	144.83 (84.43)	149.23 (108.39)	144.65 (80.33)
ApoB, g/L, mean (SD)	1.04 (0.26)	1.02 (0.27)	1.04 (0.26)	1.02 (0.26)	1.01 (0.24)	1.02 (0.27)	1.02 (0.26)	1.02 (0.25)
FPG, mg/dL, mean (SD)	100.14 (23.02)	99.09 (21.77)	99.54 (23.10)	98.86 (21.38)	99.75 (23.00)	98.95 (22.99)	98.99 (20.51)	98.77 (22.25)
Serum creatinine, mg/dL, mean (SD)	0.90 (0.22)	0.90 (0.22)	0.88 (0.21)	0.90 (0.22)	0.89 (0.21)	0.90 (0.22)	0.89 (0.22)	0.90 (0.21)
CRP, mg/L, median (IQR)	2.20 (1.10–4.16)	2.02 (1.00–4.15)	2.20 (1.20–4.18)	1.90 (1.00–3.76)	2.03 (1.10–4.20)	2.00 (1.00–3.82)	2.10 (1.08–3.91)	1.93 (0.97–3.80)
Low HDL-C, n (%)	382 (37.2)	797 (37.9)	372 (35.6)	748 (35.8)	345 (32.9)	731 (35.1)	361 (33.7)	773 (37.7)
IFG or IGT, n (%)	123 (12.0)	268 (12.7)	135 (12.9)	279 (13.3)	128 (12.2)	273 (13.1)	125 (11.7)	269 (13.1)
Diabetes mellitus, n (%)	63 (6.1)	131 (6.2)	49 (4.7)	125 (6.0)	71 (6.8)	117 (5.6)	48 (4.5)	117 (5.7)
Renal dysfunction, n (%)	34 (3.3)	54 (2.6)	24 (2.3)	56 (2.7)	30 (2.9)	65 (3.1)	27 (2.5)	58 (2.8)
Other Hypolipidemic agents (ezetibimbe or niacin), n (%)	5 (0.5)	5 (0.2)	3 (0.3)	3 (0.1)	2 (0.2)	3 (0.1)	1 (0.1)	4 (0.2)
Other BP-lowering agents	229 (22.3)	441 (21.0)	249 (23.8)	454 (21.9)	237 (22.6)	458 (22.0)	249 (23.3)	416 (20.3)

ApoB indicates apolipoprotein B; FPG, fasting plasma glucose; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CH, candesartan/hydrochlorothiazide; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; WHR, waist/hip ratio.

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Table 3. Permanent Discontinuation for the Study Medications by Lifestyle Factor Score at Baseline: Test Across All 4 Groups and Test Homogeneity Between Randomized Treatment

	Lifestyle Factor At Baseline*						
	Score 4, n (%)	Score 3, n (%)	Score 2, n (%)	Score 1, n (%)	Score 0, n (%)	Overall, *P* Value	Homogeneity, *P* Value†
Nonmissing lifestyle score at baseline, n	174	2222	4343	2909	465	. . .	. . .
Permanent discontinuation of study medication, n (%)							
Off CH/placebo	31 (17.82)	525 (23.63)	980 (22.57)	674 (23.17)	102 (21.94)	0.43	0.91
Off rosuvastatin/placebo	31 (17.82)	521 (23.45)	969 (22.31)	697 (23.96)	107 (23.01)	0.23	0.88
Off either CH/placebo or rosuvastatin/placebo	33 (18.97)	588 (26.46)	1060 (24.41)	739 (25.40)	111 (23.87)	0.12	0.94
Off both CH/placebo and rosuvastatin/placebo	29 (16.67)	458 (20.61)	889 (20.47)	632 (21.73)	98 (21.08)	0.45	0.84

CH indicates candesartan/hydrochlorothiazide.
*Participants were excluded if they died or had one of the following debilitating diseases during the study: cognitive decline, cancer, or a cardiovascular event such as myocardial infarction, stroke, cardiac arrest, revascularization, heart failure, or angina.
†Breslow–Day test.

intervals (CIs). The HRs presented comparing healthy versus less healthy lifestyles were adjusted for age, sex, ethnicity, and education. No adjustment was made to assess the impact of treatments. A *P* value for interaction comparing the effects of the interventions between subgroups was calculated, and a value of 0.05 was considered significant. Because in the overall trial the benefit of blood pressure lowering was observed only in those in the highest tertile group, we examined whether in this subgroup the effect of blood pressure lowering varied by the degree of adherence to lifestyles.

Results

In the HOPE-3 trial, rosuvastatin 10 mg daily reduced the relative risk (RR) of CVD outcomes by 23% compared with placebo. Candesartan 16 mg/hydrochlorothiazide 12.5 mg daily did not reduce the RR of CVD in the total population but reduced RR by 28% only in those with systolic blood pressure in the highest tertile (≥143.5 mm Hg). The combined medications reduced the RR of CVD by 29% in the overall population and by 44% in those with the highest tertile of systolic blood pressure.

Baseline Characteristics

Of the 12 705 HOPE-3 randomized participants, 12 521 (98.6%) had all 4 lifestyle factors recorded at baseline and constitute the population of this analysis (Table S1). Of these, 8329 (66.5%) had ≥2 healthy lifestyle factors and 4192 (33.5%) had <2 healthy lifestyle factors. The distribution of the lifestyle factors and their prevalence and combined scores at baseline were similar among the 4 randomized treatment groups (Table 1). The baseline characteristics of the participants in each of the 4 treatment groups subdivided in <2 and ≥2 healthy lifestyle factors are shown in Table 2. Participants with ≥2 healthy lifestyle factors compared with those with <2 were older, more often women, and most often of European ethnicity and had higher education, more frequent family history of coronary artery disease, lower systolic blood pressure, fewer concomitant antihypertensive

Table 4. Changes in Healthy Lifestyle Factors Between Baseline and the End of the Study

	Overall, n (%)	Both Treatments, n (%)	Rosuvastatin Alone, n (%)	CH Alone, n (%)	Both Placebos, n (%)
Participants with both evaluations*	8376	2115	2105	2114	2042
Score change from baseline to study end					
Improved (score increased)	2494 (29.78)	639 (30.21)	642 (30.50)	613 (29.00)	600 (29.38)
Score remained the same	3696 (44.13)	922 (43.59)	923 (43.85)	956 (45.22)	895 (43.83)
Deteriorated (score decreased)	2186 (26.10)	554 (26.19)	540 (25.65)	545 (25.78)	547 (26.79)

CH indicates candesartan/hydrochlorothiazide.
*Patients who died during the study or had a cardiovascular disease or a debilitating disease such as cancer or dementia were excluded.

medications, and lower waist/hip ratio and C-reactive protein levels.

Lifestyles and Adherence to the Study Medications

During follow-up, 691 participants died. At the end of the trial, in the cholesterol lowering study arm, 23.7% had permanently stopped taking rosuvastatin and 26.2% had stopped taking the matching placebo. In the blood pressure lowering study arm, 24.4% had permanently discontinued the antihypertensive medication and 25.2% had discontinued the matching placebo. There was no significant difference in trial medication adherence between participants who adhered to more versus fewer healthy lifestyle factors. (Table 3) Likewise, the numbers of participants maintaining or changing their healthy lifestyle scores at the study end were similar between groups (Table 4). Vital status at the end of the trial was ascertained in 99.1%.

Observational Analysis of Lifestyles and Outcome

In the total population, participants with ≥2 compared with <2 healthy lifestyle factors had 15% lower adjusted HR for the cardiovascular composite outcome. This lower risk was primarily driven by the lower rates of CVD outcome among nonsmokers compared with smokers (Figure 1).

Randomized Medications and Lifestyle Factors

The impact of the randomized treatment by different levels of healthy lifestyle in the total population is shown in Figure 2. Rosuvastatin compared with placebo reduced the composite outcome adjusted HR by 26% in participants with more healthy lifestyle factors (HR: 0.74; 95% CI, 0.62–0.90) and by 21% in participants with fewer healthy lifestyle factors (HR: 0.79; 95% CI, 0.61–1.01; *P*=0.749 for interaction). In contrast, candesartan/hydrochlorothiazide, compared with placebo, reduced the HR by 22% in participants with fewer healthy lifestyle factors (HR: 0.78; 95% CI, 0.61–1.00) but not in participants with more healthy factors (HR: 1.00; 95% CI, 0.83–1.20; *P*=0.126 for interaction). In participants with combined rosuvastatin and candesartan/hydrochlorothiazide versus combined placebos, the adjusted HR was reduced by 26% in participants with more healthy lifestyle factors (HR: 0.74; 95% CI, 0.57–0.97) and by 39% in those with fewer healthy lifestyle factors (HR: 0.61; 95% CI, 0.43–0.88; *P*=0.398 for interaction).

Randomized Medications and Lifestyle Factors in Participants With Elevated Systolic Pressure

In the prespecified subgroup of participants in the highest systolic blood pressure tertile (≥143.5 mm Hg), candesartan/hydrochlorothiazide compared with placebo was associated

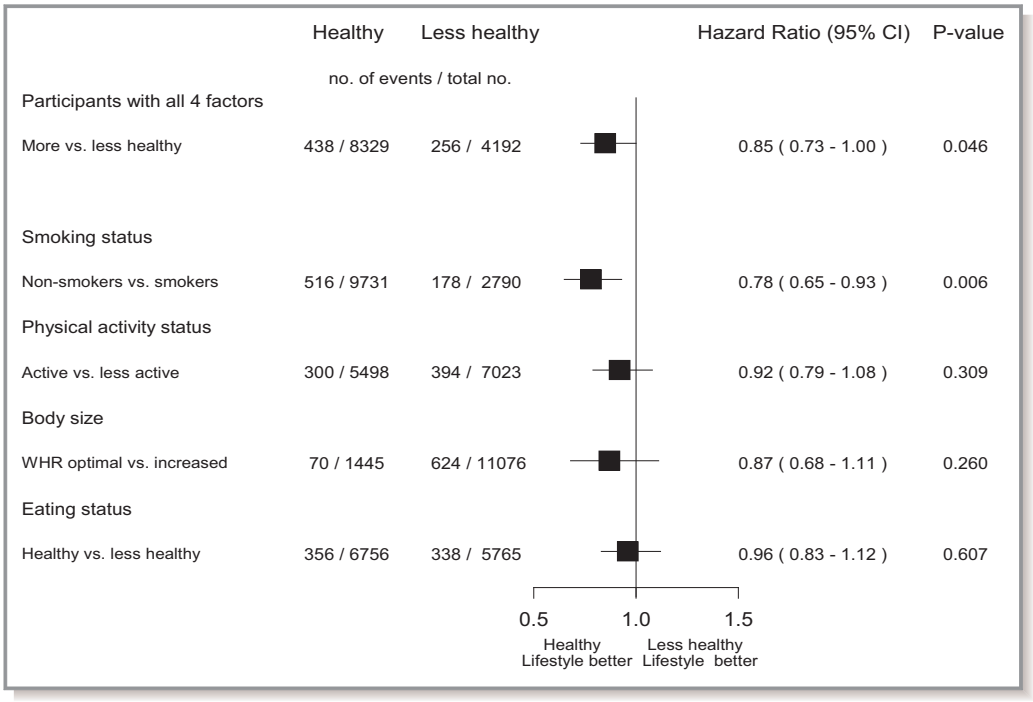

Figure 1. Cardiovascular outcome by healthy lifestyle factors (≥2=healthy, <2=less healthy). Hazard ratios are adjusted for age, sex, ethnicity, and education. CI indicates confidence interval; WHR, waist/hip ratio.

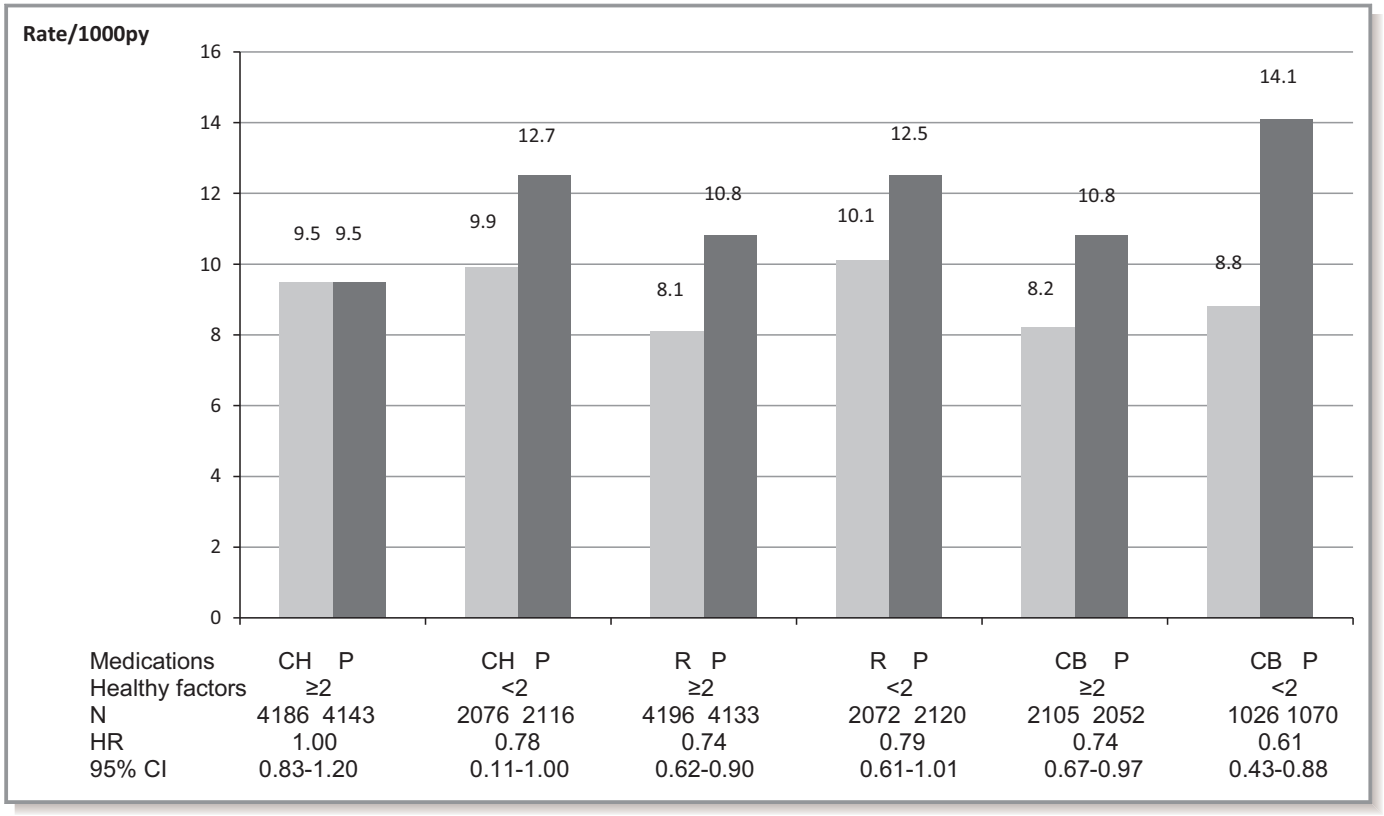

Figure 2. Event rates according to randomized medication and healthy and less healthy lifestyle factors. Rates are in 1000 person-years (py). HR is adjusted for age, sex, ethnicity, and education. CB indicates combination therapy (candesartan/hydrochlorothiazide plus rosuvastatin); CH, candesartan/hydrochlorothiazide; CI, confidence interval; HR, hazard ratio; P, placebo; R, rosuvastatin.

with directionally consistent lower CVD event rates compared with placebo in both lifestyle subgroups, more healthy (6.30% versus 8.13%; HR: 0.76; 95% CI, 0.58–1.01) and less healthy (5.55 versus 8.69%; HR, 0.65, 95% CI, 0.44–0.97; *P* for interaction, 0.546). Rosuvastatin compared with placebo lowered the CVD risk similarly in both lifestyle factor subgroups with elevated systolic pressure (more healthy: 6.44% versus 7.94%; HR: 0.77; 95% CI, 0.58–1.02; less healthy: 6.10% versus 8.13%; HR: 0.73; 95% CI, 0.50–1.08; *P*=0.787 for interaction). In the comparison of combined treatment versus matched placebos, there was a similar and significant reduction in outcomes in both lifestyle subsets with elevated systolic blood pressure (more healthy: 5.21% versus 8.60%; HR: 0.55; 95% CI, 0.36–0.84; less healthy: 5.01% versus 10.11%; HR: 0.48; 95% CI, 0.27–0.83; *P*=0.654 for interaction; Table 5).

Discussion

This analysis of the primary-prevention HOPE-3 trial performed in 12 705 participants at risk for CVD and followed for 5.6 years has 3 principal findings. First, in an observational analysis, participants who adhered to ≥2 healthy lifestyle factors at enrollment had lower CVD risk than those with <2 factors. Second, in all participants randomized to candesartan/hydrochlorothiazide, this medication versus placebo was associated with a trend for benefit limited to participants with less healthy lifestyles; however, in participants with systolic blood pressure ≥143.5 mm Hg, a directionally consistent reduction in CVD was documented in the subgroups with healthier and less healthy lifestyles. Third, and in contrast, rosuvastatin versus placebo and combined treatments versus combined placebos were beneficial in participants with both healthier and less healthy lifestyles.

In observational studies, adherence to healthy lifestyles has been associated with reduced CVD risk.[1–11] Our study confirms this association in a large and contemporaneous primary-prevention trial; however, only 2% of study participants adhered to all 4 healthy lifestyle factors, and a third had <2 of these 4 factors. Despite reinforcement of the need for adherence to a healthy lifestyle at each visit, only 30% increased their score (indicating improved rates of healthy lifestyle) at study end, 44% of participants maintained the same score and disappointingly, 26% decreased their score. These observations were consistent in each treatment group (Table 4). However, healthier lifestyle did not appear to be associated with improved adherence to the study medications. This study highlights the major challenge of improving lifestyle, even in the setting of a randomized clinical trial in

Table 5. Subgroup Analysis by Healthy and Less Healthy Lifestyles in the SBP Highest Tertile (≥143.5 mm Hg)

							Cardiovascular Outcomes					
	Medications			Placebo			Unadjusted			Adjusted*		
Lifestyle	n	n (%)	Rate/100 Person-Years	n	n (%)	Rate/100 Person-Years	HR	95% CI	*P* (Interaction)	HR	95% CI	*P* (Interaction)
CH vs placebo												
Healthy	1382	87 (6.30)	1.14	1341	109 (8.13)	1.48	0.77	0.58–1.02		0.76	0.58–1.01	
Less healthy	739	41 (5.55)	1.02	725	63 (8.69)	1.62	0.63	0.43–0.94	0.433	0.65	0.44–0.97	0.546
Rosuvastatin vs placebo												
Healthy	1350	87 (6.44)	1.16	1373	109 (7.94)	1.44	0.81	0.61–1.07		0.77	0.58–1.02	
Less healthy	738	45 (6.10)	1.13	726	59 (8.13)	1.51	0.76	0.52–1.13	0.797	0.73	0.50–1.08	0.787
CH+rosuvastatin vs placebo												
Lifestyle												
Healthy	672	35 (5.21)	0.93	663	57 (8.60)	1.56	0.60	0.39–0.91		0.55	0.36–0.84	
Less healthy	379	19 (5.01)	0.93	366	37 (10.11)	1.89	0.50	0.29–0.87	0.583	0.48	0.27–0.83	0.654

Healthy=score 2–4. Less healthy=score 0–1. CH indicates candesartan/hydrochlorothiazide; CI, confidence interval; HR, hazard ratio; SBP, systolic blood pressure.
*Adjusted for age, sex, ethnicity, and education.
n represents the total population and n(%) represents the number and % of events.

which structured advice was provided throughout the study. Clearly, new approaches to improving healthy lifestyle adherence are needed.

In the HOPE-3 trial, candesartan/hydrochlorothiazide compared with placebo significantly reduced CVD only in participants with systolic blood pressure ≥143.5 mm Hg. In this analysis of HOPE-3 across all ranges of systolic blood pressure, antihypertensive medication reduced CVD in participants with less healthy lifestyles but not in those with healthier lifestyles. The lack of benefit of the antihypertensive medication in participants with healthier lifestyles across the whole range of blood pressures is not clear; it may be due to lower risk at entry in participants with healthier versus less healthy lifestyle, considering the rates of events in the placebo arm (5.26% versus 6.85%, respectively). Indeed, compared with participants with fewer healthy factors, those with healthier lifestyles at entry had lower systolic blood pressure, waist/hip ratio, and C-reactive protein despite being older and more often having a family history of premature coronary disease. These findings highlight the favorable impact of a healthier lifestyle. In participants with systolic blood pressure ≥143.5 mm Hg, the placebo event rates were higher in those with healthier lifestyles and similar to those with less healthy lifestyles (8.13% versus 8.68%, respectively); antihypertensive medication significantly reduced CVD in the subgroup with less healthy lifestyle and was associated with a trend in lowering CVD in the healthier lifestyle subgroup. Similar findings have been reported in hypertensive participants in observational studies.[7–9]

Although the event rates were lower in participants with healthier lifestyles than those with less healthy lifestyles, both groups benefited similarly from lipid-lowering therapy and the combined treatment of rosuvastatin and candesartan/hydrochlorothiazide compared with placebos.

Limitations

Our study has some limitations. The lifestyle factors were self-reported except for the measured waist/hip ratio; for the 3 self-reported factors, ascertainment errors are possible but were likely minimized by the use of standardized questionnaires in this trial. Participants were not randomized by lifestyle status, although in evaluating CVD events in the treatment groups, we adjusted for baseline differences among the treatment and lifestyle status subgroups; such subgroups limit the power of the study for further subgroup analyses Each healthy lifestyle factor was identically weighted, although respective impacts may differ. The dietary pattern assessed with the Mediterranean diet score is well established in several developed countries but not in Asian countries, and the sodium content of the diet was not estimated. Detailed nonrecreational physical activities were not documented. As documented at the end of the study, the lifestyle factor distribution changed during the course of the study, and we do not know when such change occurred; however, the changes were not different among the randomized groups. Our study has several strengths. It involves a large multiethnic cohort with well-defined baseline characteristics and regular visits during 5.6-year follow-up. All events were adjudicated, and vital status was determined in 99%. To our

knowledge, our study is the first to address whether randomized allocation to lipid-lowering or antihypertensive medications or both compared with placebos has similar or different effects in participants with healthier versus less healthy lifestyle factors.

Conclusions

Rosuvastatin alone and combined with candesartan/hydrochlorothiazide is beneficial regardless of the health-related lifestyle status; however, the benefit of antihypertensive treatment, although nonsignificant, appears limited to participants with less healthy lifestyle profiles who were at greater risk than those with more healthy factors. This latter observation requires independent confirmation. These findings have implications for therapeutic decision-making in the primary prevention of CVD. Healthy lifestyle approaches should be improved and integrated with pharmacologic strategies for the primary prevention of CVD and the prevention of other major chronic diseases such as diabetes mellitus and cancers.

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SUPPLEMENTAL MATERIAL

Table S1. Available Healthy Lifestyle Factor Distribution by Randomized Medication.

	Overall	Both treatments	Rosuvastatine alone	Candesartan/ HCT alone	Both placebos
	N (%)	N (%)	N (%)	N (%)	N (%)
Randomized in HOPE-3	12705	3180	3181	3176	3168
Non-smokers	12700 (99.96)	3178 (99.94)	3180 (99.97)	3175 (99.97)	3167 (99.97)
Physical activities	12696 (99.93)	3178 (99.94)	3178 (99.91)	3174 (99.97)	3166 (99.94)
Optimal body size	12668 (99.71)	3170 (99.69)	3168 (99.59)	3168 (99.75)	3162 (99.81)
Healthy eating	12540 (98.70)	3137 (98.65)	3142 (98.77)	3135 (98.71)	3126 (98.67)