ORIGINAL ARTICLE

Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease

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ABSTRACT

BACKGROUND

Elevated blood pressure and elevated low-density lipoprotein (LDL) cholesterol increase the risk of cardiovascular disease. Lowering both should reduce the risk of cardiovascular events substantially.

METHODS

In a trial with 2-by-2 factorial design, we randomly assigned 12,705 participants at intermediate risk who did not have cardiovascular disease to rosuvastatin (10 mg per day) or placebo and to candesartan (16 mg per day) plus hydrochlorothiazide (12.5 mg per day) or placebo. In the analyses reported here, we compared the 3180 participants assigned to combined therapy (with rosuvastatin and the two antihypertensive agents) with the 3168 participants assigned to dual placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and the second coprimary outcome additionally included heart failure, cardiac arrest, or revascularization. The median follow-up was 5.6 years.

RESULTS

The decrease in the LDL cholesterol level was 33.7 mg per deciliter (0.87 mmol per liter) greater in the combined-therapy group than in the dual-placebo group, and the decrease in systolic blood pressure was 6.2 mm Hg greater with combined therapy than with dual placebo. The first coprimary outcome occurred in 113 participants (3.6%) in the combined-therapy group and in 157 (5.0%) in the dual-placebo group (hazard ratio, 0.71; 95% confidence interval [CI], 0.56 to 0.90; P=0.005). The second coprimary outcome occurred in 136 participants (4.3%) and 187 participants (5.9%), respectively (hazard ratio, 0.72; 95% CI, 0.57 to 0.89; P=0.003). Muscle weakness and dizziness were more common in the combined-therapy group than in the dual-placebo group, but the overall rate of discontinuation of the trial regimen was similar in the two groups.

CONCLUSIONS

The combination of rosuvastatin (10 mg per day), candesartan (16 mg per day), and hydrochlorothiazide (12.5 mg per day) was associated with a significantly lower rate of cardiovascular events than dual placebo among persons at intermediate risk who did not have cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; ClinicalTrials.gov number, NCT00468923.)

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Cardiovascular diseases are major causes of death and illness worldwide.[1] Both systolic blood pressure and low-density lipoprotein (LDL) cholesterol show graded associations with cardiovascular disease and together account for two thirds of the population-attributable risk of cardiovascular disease.[2-4] Therefore, combined lowering of LDL cholesterol and blood pressure can potentially have a bigger effect in reducing cardiovascular events than either intervention alone. Because the majority of cardiovascular events occur in persons at average risk with no previous cardiovascular disease, a strategy of broad population-based treatment of LDL cholesterol and blood pressure could be more effective than targeting only high-risk persons.[5] These considerations form the basis for the polypill concept, which theorizes large reductions in cardiovascular events with systematic use of combination-drug therapy in middle-aged and older persons in the general population.[6,7]

We therefore evaluated the effects of a moderate dose of a potent statin (without lipid monitoring) versus placebo, a fixed combination of moderate doses of an angiotensin-receptor blocker plus a diuretic (without blood-pressure targets) versus placebo, and the combination of both treatments versus dual placebo on the prevention of major cardiovascular events. This report focuses on the efficacy and safety of the combination of LDL cholesterol lowering and blood-pressure lowering versus placebo.

METHODS

TRIAL DESIGN AND OVERSIGHT

The Heart Outcomes Prevention Evaluation (HOPE)–3 trial is a multicenter, long-term, international, double-blind, randomized, placebo-controlled trial with a 2-by-2 factorial design. We evaluated cholesterol lowering with rosuvastatin versus placebo, blood-pressure lowering with a combination of candesartan and hydrochlorothiazide versus placebo, and the combination of lipid and blood-pressure lowering versus dual placebo in preventing cardiovascular events among persons who did not have cardiovascular disease and who were at intermediate risk (defined as an annual risk of major cardiovascular events of approximately 1%)[8] (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The results of the blood-pressure–lowering analysis and the lipid-lowering analysis are reported in accompanying articles in the *Journal*.[9,10] A detailed description of the trial methods is provided in the article that focuses on the effects of blood-pressure lowering.

The trial was designed by the steering committee who, along with staff at the Population Health Research Institute, oversaw the conduct of the trial, the collection and analysis of the data, and the interpretation of the results. The first author along with three other authors from the Population Health Research Institute had full access to the data and vouch for the accuracy and completeness of the data and analysis and for the fidelity of this report to the protocol. The first author drafted the manuscript, and all the authors made the decision to submit the manuscript for publication. Funding was provided by the Canadian Institutes of Health Research and AstraZeneca. AstraZeneca provided the trial drug, served as a single voting member on the 24-member steering committee, and had no other role in the trial. The trial was conducted at 228 centers in 21 countries and received regulatory and ethics approval for each participating site or from a central board that provided approval for multiple sites. All participants provided written informed consent.

ELIGIBILITY

The trial included men 55 years of age or older and women 65 years of age or older without cardiovascular disease and with at least one additional risk factor besides age (Table S2 in the Supplementary Appendix). We also included women 60 years of age or older who had at least two such risk factors. Persons with cardiovascular disease and those with an indication for or contraindication to statins, angiotensin-receptor blockers, angiotensin-converting–enzyme inhibitors, or thiazide diuretics were excluded. The trial did not mandate specific lipid or blood-pressure levels for entry. Fasting lipid and glucose levels were measured locally to inform physicians about participants' risks, but trial eligibility was based on the uncertainty principle: only those with clear indications for or contraindications to trial drugs, according to the judgment of the local physician and taking into account local guidelines and standards of practice, were excluded from participation.[11]

TRIAL PROCEDURES

Eligible persons entered a single-blind run-in phase, during which they received both active treatments (for blood-pressure lowering and for cholesterol lowering) for 4 weeks. Participants who adhered to the regimen and who did not have an unacceptable level of adverse events were randomly assigned to a fixed combination of candesartan (16 mg per day) and hydrochlorothiazide (12.5 mg per day) or placebo and to rosuvastatin (10 mg per day) or placebo.

Follow-up visits occurred at 6 weeks and 6 months after randomization and every 6 months thereafter. Individualized structured lifestyle advice was provided, on the basis of identified needs, and blood pressure was recorded at each visit in the first year and then annually. Lipid levels were measured at baseline in all participants and at 1 year, at 3 years, and at the end of the trial in 10 to 20% of the participants (with representation across geographic areas and racial and ethnic groups) (see the Supplementary Appendix for further information). Open-label statins could be prescribed at the physicians' discretion, in which case trial rosuvastatin or placebo was discontinued.

OUTCOMES

All cardiovascular events and cases of new-onset diabetes were documented and adjudicated (see the Supplementary Appendix). There were two coprimary outcomes: the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (first coprimary outcome) and the composite of these events plus resuscitated cardiac arrest, heart failure, or revascularization (second coprimary outcome). The secondary outcome was the composite of events comprising the second coprimary outcome plus angina with evidence of ischemia. This outcome was adopted by the steering committee on July 15, 2015, with no protocol amendment before unblinding of the data on November 3, 2015. At that time, a prespecified renal outcome was removed owing to limitations of statistical power. Additional prespecified outcomes included death from any cause, the components of the coprimary outcomes, new-onset diabetes, cognitive function (in participants ≥70 years of age), and erectile dysfunction in men. The latter two outcomes are not reported here. Safety reporting is described in the Supplementary Appendix.

STATISTICAL ANALYSIS

With an expected annual event rate of 1% for the first coprimary outcome in the dual-placebo group, an average duration of follow-up of 5.5 years, cumulative nonadherence rates of 23%, drop-in rates of 11%, and rates of loss to follow-up of less than 1%, we estimated that a sample of 12,700 participants (of whom 6348 would be randomly assigned to dual active treatment or dual placebo) would give the trial 80% power to detect a risk of the coprimary outcomes with combination therapy that was at least 35% lower than the risk with dual placebo.[8] No formal power calculations for this analysis were made for the comparisons of cholesterol lowering alone versus placebo, blood-pressure lowering alone versus placebo, or cholesterol lowering alone versus blood-pressure lowering alone.

The main analyses were performed according to the intention-to-treat principle. Survival curves were computed with the use of the Kaplan–Meier procedure. A Cox proportional-hazards model was used to estimate treatment effects and to evaluate effects in subgroups. No significant interaction between the two treatments was observed. The strategy used to preserve an overall type I error rate of 5% for the entire trial is described in the Supplementary Appendix; on the basis of this strategy, a nominal P value of less than 0.05 was used to test both coprimary outcomes in a comparison of the combined-therapy group with the dual-placebo group in the 6348 trial participants included in these two groups. Prespecified hypothesis-based subgroup analyses were conducted according to thirds of baseline risk (determined by the INTERHEART Risk Score),[12] of systolic blood pressure, and of LDL cholesterol concentration (with P values for trend). A post hoc recurrent-events analysis[13] was performed to describe the effect on the risk of total cardiovascular events.

RESULTS

TRIAL PARTICIPANTS AND FOLLOW-UP

A total of 12,705 participants who adhered to the regimen and did not have an unacceptable level of adverse events during the run-in period underwent randomization. Of these, 3180 were assigned to candesartan–hydrochlorothiazide plus rosuvastatin (combined therapy), 3181 to rosuvastatin plus placebo, 3176 to candesartan–hydrochlorothiazide plus placebo, and 3168 to placebo

plus placebo (Fig. S3 in the Supplementary Appendix). Baseline characteristics are described in Table 1. The mean age of the participants was 65.7 years, and 46.2% of the participants were women. The mean systolic blood pressure was 138.1 mm Hg, and the mean LDL cholesterol level was 127.8 mg per deciliter (3.3 mmol per liter). The median follow-up was 5.6 years. At the end of the trial, vital status was available for 12,587 participants (99.1%).

ADHERENCE TO TRIAL DRUGS

Among participants who were assigned to receive candesartan–hydrochlorothiazide and rosuvastatin, 83.6% were taking both trial medications at 2 years, and 74.6% were taking both at the end of the trial; the corresponding rates in the dual-placebo group were 83.3% and 71.8% (Table S5 in the Supplementary Appendix). In the combined-therapy group, an additional 1.6% were taking rosuvastatin only at 2 years, and 2.9% were taking rosuvastatin only at the end of the trial; an additional 1.4% and 1.5% were taking candesartan–hydrochlorothiazide only at the respective visits. In the dual-placebo group, 1.2% of the participants were taking the rosuvastatin placebo only at 2 years and 1.6% were taking the rosuvastatin placebo only at the end of the trial; 1.9% and 3.5% of the participants, respectively, were taking the candesartan–hydrochlorothiazide placebo only at the two time points. The use of open-label and nontrial drugs is presented in Table S5 in the Supplementary Appendix.

BLOOD PRESSURE AND LIPID LEVELS

On average over the course of the trial, the mean systolic blood pressure was lower by 6.2 mm Hg in the combined-therapy group than in the dual-placebo group, the mean diastolic blood pressure was lower by 3.2 mm Hg, and the mean LDL cholesterol level was lower by 33.7 mg per deciliter (0.87 mmol per liter) (Fig. 1) ($P<0.001$ for all comparisons). The difference in blood pressure was similar for participants assigned to candesartan–hydrochlorothiazide alone versus placebo; the difference in LDL cholesterol level was similar for participants assigned to rosuvastatin alone versus placebo.

CLINICAL OUTCOMES

The first coprimary outcome occurred in 113 participants (3.6%) in the combined-therapy group and in 157 participants (5.0%) in the dual-placebo group (hazard ratio, 0.71; 95% confidence interval [CI], 0.56 to 0.90; $P=0.005$; relative difference, 29%; absolute difference, 1.4 percentage points; number needed to treat to prevent one outcome event, 72) (Table 2, and Fig. S9 in the Supplementary Appendix). The second coprimary outcome occurred in 136 participants (4.3%) in the combined-therapy group and in 187 (5.9%) in the dual-placebo group (hazard ratio, 0.72; 95% CI, 0.57 to 0.89; $P=0.003$; relative difference, 28%; absolute difference, 1.6 percentage points; number needed to treat, 63) (Table 2 and Fig. 2A).

There were also significant between-group differences in the incidence of the secondary outcome (147 participants [4.6%] in the combined-therapy group vs. 205 [6.5%] in the dual-placebo group; hazard ratio, 0.71; 95% CI, 0.57 to 0.87; $P=0.001$) (Fig. S10 in the Supplementary Appendix) and in the incidence of any kind of stroke (31 participants [1.0%] vs. 55 [1.7%]; hazard ratio, 0.56; 95% CI, 0.36 to 0.87; $P=0.009$). There were 163 deaths in the combined-therapy group and 178 in the dual-placebo group; there were fewer deaths from cardiovascular causes in the combined-group group than in the dual-placebo group (75 vs. 91), but no difference was seen in the number of deaths from other causes (88 and 87, respectively) (Table S18 in the Supplementary Appendix). In a post hoc analysis, there were fewer first and recurrent events of the first coprimary outcome with combined therapy than with dual placebo (hazard ratio, 0.68; 95% CI, 0.53 to 0.87; $P=0.002$) and fewer first and recurrent events of the second coprimary outcome (hazard ratio, 0.66; 95% CI, 0.52 to 0.84; $P=0.001$).

SUBGROUP ANALYSES

There were no significant treatment-by-subgroup interactions with respect to the first and second coprimary outcomes in the three prespecified subgroups defined according to stroke risk, LDL cholesterol level, and systolic blood pressure at baseline (Fig. S16 and S17 in the Supplementary Appendix). In a post hoc analysis of the first coprimary outcome comparing the upper third of systolic blood pressure (>143.5 mm Hg) with the lower two thirds, the point estimate for the hazard ratio was lower in the upper third (hazard ratio, 0.59; 95% CI, 0.40 to 0.85) than in the lower two thirds (hazard ratio, 0.82; 95% CI, 0.59 to 1.12), although the P value for interaction of 0.19 was not nominally significant. There was

Table 1. Characteristics of the 12,705 Participants in the Heart Outcomes Prevention Evaluation–3 Trial at Baseline.*

Characteristic	Candesartan–Hydrochlorothiazide plus Rosuvastatin (N=3180)	Rosuvastatin plus Placebo (N=3181)	Candesartan–Hydrochlorothiazide plus Placebo (N=3176)	Placebo plus Placebo (N=3168)
Age — yr	65.7±6.3	65.8±6.4	65.6±6.4	65.7±6.3
Female sex — no. (%)	1465 (46.1)	1486 (46.7)	1445 (45.5)	1478 (46.7)
Cardiovascular risk factor — no. (%)†				
Elevated waist-to-hip ratio	2771 (87.1)	2769 (87.0)	2740 (86.3)	2754 (86.9)
Recent or current smoking	889 (28.0)	851 (26.8)	893 (28.1)	891 (28.1)
Low concentration of HDL cholesterol	1201 (37.8)	1143 (35.9)	1096 (34.5)	1148 (36.2)
Impaired fasting glucose or impaired glucose tolerance	392 (12.3)	417 (13.1)	407 (12.8)	400 (12.6)
Early diabetes mellitus	196 (6.2)	178 (5.6)	190 (6.0)	167 (5.3)
Family history of premature coronary heart disease	834 (26.2)	841 (26.4)	834 (26.3)	826 (26.1)
Early renal dysfunction	89 (2.8)	80 (2.5)	95 (3.0)	86 (2.7)
Hypertension	1200 (37.7)	1203 (37.8)	1198 (37.7)	1213 (38.3)
2 Risk factors	1486 (46.7)	1516 (47.7)	1486 (46.8)	1438 (45.4)
≥3 Risk factors	795 (25.0)	750 (23.6)	743 (23.4)	780 (24.6)
Blood pressure — mm Hg				
Systolic	138.2±14.8	137.9±15.0	138.2±14.7	137.9±14.6
Diastolic	81.9±9.4	81.8±9.3	82.0±9.3	81.8±9.2
Heart rate — beats/min	73.0±10.3	72.6±10.2	72.9±10.1	72.5±10.3
Body-mass index‡	27.2±4.8	27.1±4.8	27.1±4.8	27.1±4.7
Waist-to-hip ratio	0.94±0.08	0.94±0.08	0.94±0.08	0.94±0.09
Cholesterol — mg/dl				
Total	201.3±43.5	201.8±41.6	201.5±41.7	201.2±41.7
LDL	127.0±37.0	128.6±35.2	127.9±36.0	127.9±36.0
HDL	44.7±14.1	44.8±13.7	45.1±13.7	44.8±13.8
Triglycerides — mg/dl				
Median	128.3	129.2	126.5	126.5
Interquartile range	92.0–182.3	93.8–176.1	92.9–178.8	92.9–174.9
Fasting plasma glucose — mg/dl				
Median	96.0	95.4	95.4	95.4
Interquartile range	87.0–106.2	86.4–106.0	86.4–106.0	87.0–106.0
Apolipoprotein B — g/liter	1.02±0.27	1.03±0.26	1.02±0.26	1.02±0.26
Apolipoprotein A1 — g/liter	1.46±0.34	1.46±0.34	1.47±0.34	1.46±0.33
Ratio of apolipoprotein B to apolipoprotein A	0.75±0.36	0.75±0.31	0.74±0.31	0.74±0.32
High-sensitivity C-reactive protein — mg/liter				
Median	2.1	2.0	2.0	2.0
Interquartile range	1.0–4.1	1.0–3.9	1.0–4.0	1.0–3.8
Serum creatinine — mg/dl	0.90±0.22	0.89±0.22	0.90±0.22	0.90±0.21
INTERHEART Risk Score§	14.6±5.2	14.5±5.2	14.5±5.1	14.3±5.2
Race or ethnic group — no. (%)¶				
Chinese	922 (29.0)	932 (29.3)	922 (29.0)	915 (28.9)

Table 1. (Continued.)

Characteristic	Candesartan–Hydrochlorothiazide plus Rosuvastatin (N=3180)	Rosuvastatin plus Placebo (N=3181)	Candesartan–Hydrochlorothiazide plus Placebo (N=3176)	Placebo plus Placebo (N=3168)
Hispanic	864 (27.2)	880 (27.7)	875 (27.6)	877 (27.7)
White	651 (20.5)	635 (20.0)	633 (19.9)	627 (19.8)
South Asian	465 (14.6)	462 (14.5)	467 (14.7)	460 (14.5)
Other Asian	169 (5.3)	172 (5.4)	173 (5.4)	182 (5.7)
Black	58 (1.8)	55 (1.7)	58 (1.8)	54 (1.7)
Other	51 (1.6)	45 (1.4)	48 (1.5)	53 (1.7)
Medication use — no. (%)				
Ezetimibe	7 (0.2)	4 (0.1)	3 (0.1)	3 (0.1)
Niacin	4 (0.1)	2 (0.1)	2 (0.1)	3 (0.1)
Aspirin	358 (11.3)	328 (10.3)	381 (12.0)	326 (10.3)
Beta-blocker	259 (8.1)	245 (7.7)	265 (8.3)	251 (7.9)
Calcium-channel blocker	444 (14.0)	497 (15.6)	484 (15.2)	460 (14.5)
Alpha-blocker	38 (1.2)	38 (1.2)	34 (1.1)	31 (1.0)
Nonthiazide diuretic	23 (0.7)	16 (0.5)	13 (0.4)	13 (0.4)
Aldosterone antagonist	3 (0.1)	9 (0.3)	3 (0.1)	2 (0.1)
Oral hypoglycemic agent	92 (2.9)	75 (2.4)	84 (2.6)	86 (2.7)

* Plus–minus values are means ±SD. There were no significant differences in the baseline characteristics among the four groups. Data on blood pressure were missing for 2 participants in the dual-placebo group, and data on central core laboratory measurements of low-density lipoprotein (LDL) cholesterol concentration for 321 in the combined-therapy group, 335 in the rosuvastatin-plus-placebo group, 328 in the group assigned to candesartan–hydrochlorothiazide plus placebo, and 323 in the dual-placebo group. Data on age and sex were complete. Data on other characteristics were available for 99.7% or more of the trial participants, except that some laboratory variables measured at the central core laboratory had rates of missing data similar to that for LDL cholesterol concentration. To convert the values for cholesterol to millimoles per liter, multiply by 0.0259. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for creatinine to micromoles per liter, multiply by 88.4. HDL denotes high-density lipoprotein.

† Case definitions for the cardiovascular risk factors are provided in Table S2 in the Supplementary Appendix.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The scale of the INTERHEART Risk Score ranges from 0 to 49; low cardiovascular risk corresponds to a score of 9 or less, medium risk to a score of 10 to 15, and high risk to a score of 16 or more.[12]

¶ Race and ethnic group were determined by self-report.

no significant heterogeneity in the effects of combination therapy in subgroups defined according to age, sex, or race or ethnic group.

CHOLESTEROL LOWERING ALONE VERSUS BLOOD-PRESSURE LOWERING ALONE

There was a nonsignificant trend toward a lower risk of the first coprimary outcome with rosuvastatin plus placebo than with candesartan–hydrochlorothiazide plus placebo (122 participants [3.8%] and 147 [4.6%], respectively; hazard ratio, 0.82; 95% CI, 0.65 to 1.05; P=0.11) (Table 2). There was a nominally significant difference in the risk of the second coprimary outcome (141 participants [4.4%] with rosuvastatin plus placebo vs. 176 [5.5%] with candesartan–hydrochlorothiazide plus placebo; hazard ratio, 0.79; 95% CI, 0.64 to 0.99; P=0.04).

ADVERSE EFFECTS

Muscle weakness and dizziness were more common in the combined-therapy group than in the dual-placebo group. The incidence of muscle weakness or pain was similar in the combined-therapy group and the rosuvastatin-plus-placebo group, and the incidence of dizziness, lightheadedness, or hypotension was similar in the combined-therapy group and the group assigned to

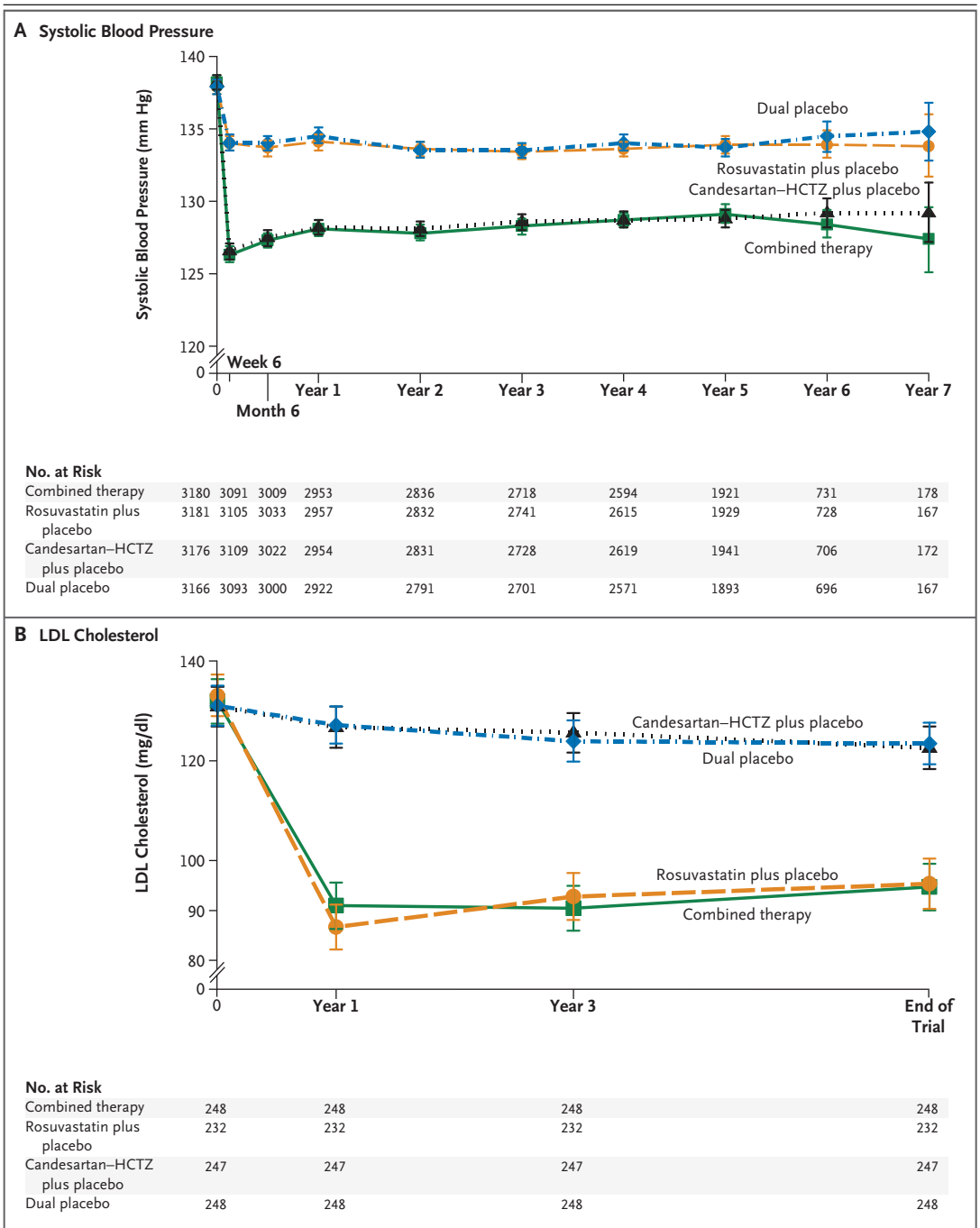

Figure 1. Levels of Systolic Blood Pressure and Low-Density Lipoprotein (LDL) Cholesterol, According to Trial Group.
Combined therapy is candesartan–hydrochlorothiazide (HCTZ) plus rosuvastatin. To convert the values for LDL cholesterol to millimoles per liter, multiply by 0.0259. I bars represent 95% confidence intervals.

candesartan–hydrochlorothiazide plus placebo. The rates of permanent discontinuation for any reason did not differ significantly between the combined-therapy group and the dual-placebo group (26.3% and 28.8%, respectively), nor did the rates of serious adverse events. (For more on safety outcomes, see Tables S19 through S23 in the Supplementary Appendix.)

Table 2. Primary, Secondary, and Other Outcomes.*

Outcome	Candesartan–Hydrochlorothiazide plus Rosuvastatin (N=3180)	Rosuvastatin plus Placebo (N=3181)	Candesartan–Hydrochlorothiazide plus Placebo (N=3176)	Placebo plus Placebo (N=3168)	Candesartan–Hydrochlorothiazide plus Rosuvastatin vs. Placebo plus Placebo	
					Hazard Ratio (95% CI)	P Value
Coprimary outcomes — no. (%)						
First coprimary outcome	113 (3.6)	122 (3.8)†	147 (4.6)‡	157 (5.0)	0.71 (0.56–0.90)	0.005
Second coprimary outcome	136 (4.3)	141 (4.4)§	176 (5.5)¶	187 (5.9)	0.72 (0.57–0.89)	0.003
Secondary outcome — no. (%)‖	147 (4.6)	159 (5.0)	188 (5.9)	205 (6.5)	0.71 (0.57–0.87)	0.001
Components of the coprimary and secondary outcomes — no. (%)						
Death from cardiovascular causes	75 (2.4)	79 (2.5)	80 (2.5)	91 (2.9)	0.82 (0.60–1.11)	
Fatal or nonfatal myocardial infarction	21 (0.7)	24 (0.8)	31 (1.0)	38 (1.2)	0.55 (0.32–0.93)	
Fatal or nonfatal stroke	31 (1.0)	39 (1.2)	44 (1.4)	55 (1.7)	0.56 (0.36–0.87)	
Resuscitated cardiac arrest	1 (<0.1)	3 (0.1)	1 (<0.1)	3 (0.1)	0.33 (0.03–3.18)	
Revascularization	27 (0.8)	29 (0.9)	37 (1.2)	45 (1.4)	0.59 (0.37–0.95)	
Heart failure	10 (0.3)	11 (0.3)	11 (0.3)	18 (0.6)	0.55 (0.25–1.19)	
Angina with objective evidence of ischemia‖	25 (0.8)	31 (1.0)	26 (0.8)	38 (1.2)	0.65 (0.39–1.08)	
Other outcomes						
Death from any cause — no. (%)	163 (5.1)	171 (5.4)	179 (5.6)	178 (5.6)	0.91 (0.73–1.12)	
New-onset diabetes — no./total no. (%)	123/2982 (4.1)	109/3001 (3.6)	113/2984 (3.8)	113/2999 (3.8)	1.09 (0.85–1.41)	
Hospitalization — no. (%)**						
For cardiovascular causes	141 (4.4)	140 (4.4)	178 (5.6)	191 (6.0)	0.73 (0.59–0.91)	0.005
For noncardiovascular causes	463 (14.6)	418 (13.1)	436 (13.7)	443 (14.0)	1.04 (0.92–1.19)	0.52
First and recurrent events of the second coprimary outcome††						
No. of participants with ≥1 event	136	141	176	187		
No. of participants with ≥2 events	29	39	30	59		
No. of participants with ≥3 events	2	4	3	13		
Total no. of events	169	184	211	262	0.66 (0.52–0.84)	0.001

* The first coprimary outcome was the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; the second coprimary outcome was the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, heart failure, or revascularization; and the secondary outcome was the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, heart failure, revascularization, or angina with objective evidence of ischemia. CI denotes confidence interval.

† The hazard ratio for rosuvastatin plus placebo versus placebo plus placebo was 0.77 (95% CI, 0.61 to 0.97) and for rosuvastatin plus placebo versus candesartan–hydrochlorothiazide plus placebo was 0.82 (95% CI, 0.65 to 1.05).

‡ The hazard ratio for candesartan–hydrochlorothiazide plus placebo versus placebo plus placebo was 0.93 (95% CI, 0.75 to 1.17).

§ The hazard ratio for rosuvastatin plus placebo versus placebo plus placebo was 0.74 (95% CI, 0.60 to 0.93) and for rosuvastatin plus placebo versus candesartan–hydrochlorothiazide plus placebo was 0.79 (95% CI, 0.64 to 0.99).

¶ The hazard ratio for candesartan–hydrochlorothiazide plus placebo versus placebo plus placebo was 0.94 (95% CI, 0.76 to 1.15).

‖ The secondary outcome — a composite of events comprising the second coprimary outcome plus angina with evidence of ischemia — and the individual outcome of angina with objective evidence of ischemia were not included in the original protocol but were added by the steering committee before data lock and analysis.

** Hospitalizations were a prespecified safety outcome.

†† These outcomes were not prespecified in the trial protocol.

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DISCUSSION

In the HOPE-3 trial, which involved a primary prevention population at intermediate risk and with average lipid and blood pressure levels, combination therapy with rosuvastatin (10 mg per day), candesartan (16 mg per day), and hydrochlorothiazide (12.5 mg per day) for a median of 5.6 years was associated with a significantly lower risk of cardiovascular events than dual placebo (29% lower relative risk and 1.4-percentage-point lower absolute risk of the first primary outcome). The number needed to treat for 5.6 years to prevent one event of the first coprimary outcome was 72, and the number needed to treat to prevent one event of the second coprimary outcome was 63. In a post hoc recurrent-events analysis, the benefit was slightly larger.

The reduction in LDL cholesterol concentration was approximately 33.7 mg per deciliter over the course of the trial (which is similar to the 38.6 mg per deciliter [1.00 mmol per liter] that was expected),[8] and the reduction in systolic blood pressure was 6.2 mm Hg (which is lower than the expected 8 mm Hg reduction). Rates of adherence to rosuvastatin and to candesartan–hydrochlorothiazide were high, and so the degree of cholesterol and blood-pressure lowering that we observed, in a large population treated over a median of 5.6 years, is probably more representative than that observed in small, short-term trials involving persons with elevated blood pressure or high lipid levels. Greater reductions in LDL cholesterol and in systolic blood pressure could be achieved with a more intensive regimen, and the reductions in cardiovascular outcomes could be larger,[14,15] but the safety of such an approach would need to be established.

We performed a post hoc subgroup analysis comparing participants in the upper third of baseline systolic blood pressure with those in the lower two thirds. Among participants in the upper third, the risk of the two coprimary outcomes was approximately 40% lower with combined therapy than with dual placebo, whereas the relative risk was only about 20% lower among participants with lower systolic blood pressure. Although the test for interaction between these two effects was not significant, these results (comparing combined therapy with dual placebo) are based on only half the entire trial cohort. In the overall trial, a significant treatment-by-subgroup interaction was seen according to thirds of baseline systolic blood pressure for the comparison of candesartan–hydrochlorothiazide with placebo; only those in the highest third of systolic blood pressure benefited from treatment to lower blood pressure.[10] These results are consistent with those of two meta-analyses of trials of blood-pressure lowering, which showed that there was a clear benefit of antihypertensive therapy in persons with a systolic blood pressure of 140 mm Hg or more but no benefit on cardiovascular events (as a composite) in those with an initial systolic blood pressure of less than 140 mm Hg.[16,17] By contrast, the effects of rosuvastatin in the HOPE-3 trial were independent of blood-pressure or lipid levels. These different lines of evidence suggest that combination therapy (with a statin and blood-pressure-lowering treatment) would perform best in persons with elevated blood pressure, whereas statins alone would perform best in those without elevated blood pressure.

We also found that the rate of myocardial infarction was lower in the combined-therapy group than in the placebo group (relative difference, 45%; absolute difference, 0.5 percentage points), as was the rate of stroke (relative difference, 44%; absolute difference, 0.8 percentage points). These estimates are similar to those from the Anglo-Scandinavian Cardiac Outcomes Trial[18] with combined lipid and blood-pressure lowering (albeit with a different regimen for blood-pressure lowering) but were substantially lower than the 80% relative risk reduction projected by Wald and Law for the effect of a polypill (consisting of three blood-pressure-lowering agents, a statin, folate, and aspirin).[6] We did not use three blood-pressure-lowering drugs together because of limited data on long-term safety in persons without hypertension. Aspirin was not used because its role in primary prevention is unclear,[19] and trials of folate in Western countries have been disappointing[20] (although in a recent trial in China, where dietary folate intake is low, stroke rates were reduced[21]).

There were no significant differences between the combined-therapy group and the dual-placebo group in the rate of new-onset diabetes, renal dysfunction, syncope, liver-function abnormalities, eye problems, or cancers. Although the rates of muscle weakness or pain and of dizziness were higher in the combined-therapy group than

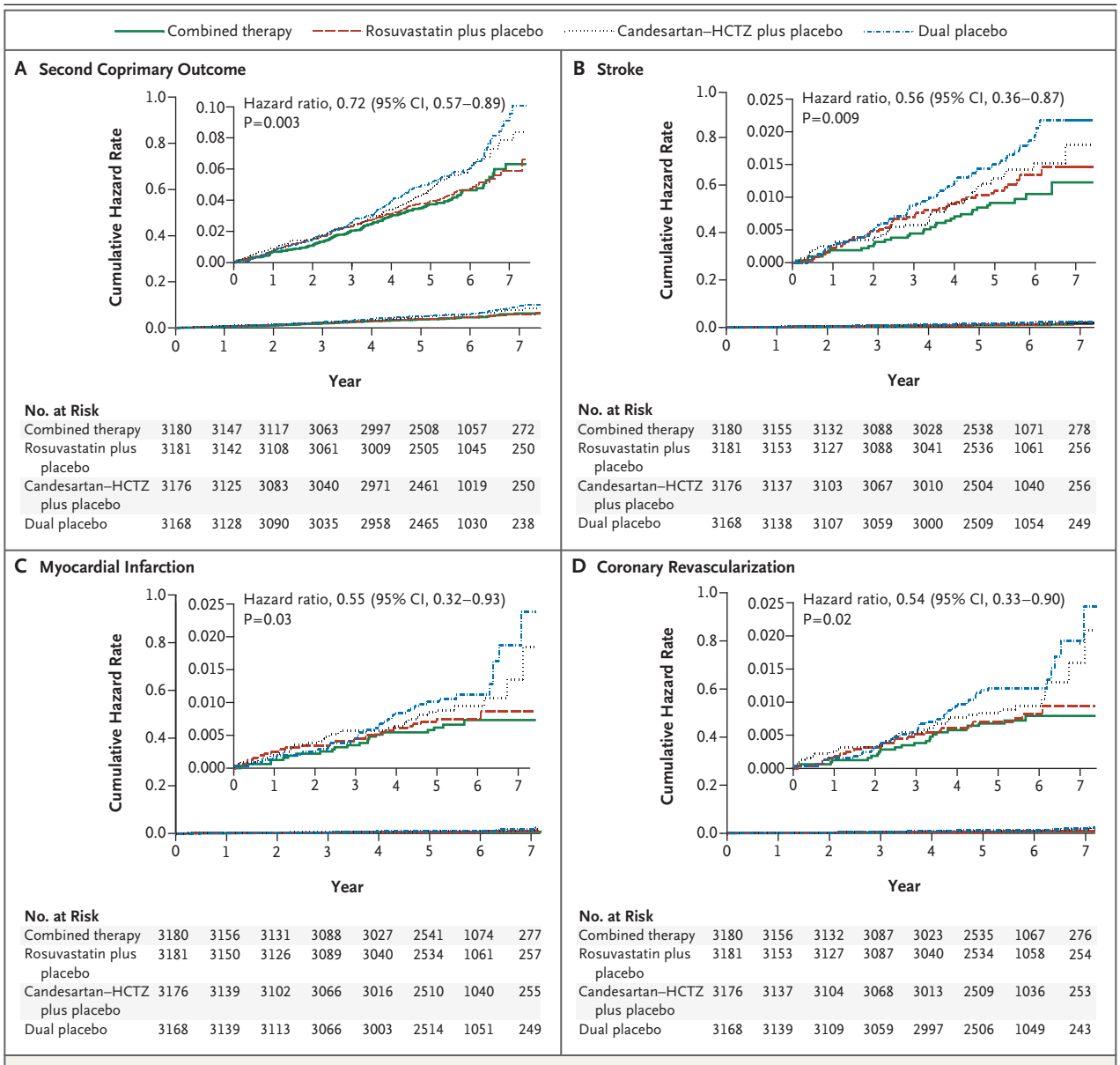

Figure 2. Kaplan–Meier Curves for the Second Coprimary Outcome, Stroke, Myocardial Infarction, and Coronary Revascularization.

Shown are cumulative hazard curves for the second coprimary outcome (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, heart failure, or revascularization; Panel A), stroke (Panel B), myocardial infarction (Panel C), and coronary revascularization (Panel D). The hazard ratios, 95% confidence intervals, and P values are presented for the comparison between combined therapy (rosuvastatin plus candesartan–hydrochlorothiazide) and dual placebo. The insets show the same data on an enlarged y axis.

in the dual-placebo group (by 0.9 percentage points and 2.2 percentage points, respectively), these effects were reversible by temporary discontinuation of the trial drug. There was only one case of rhabdomyolysis (in the rosuvastatin-plus-placebo group), which was detected clinically, indicating that there is little need for routine blood testing with a combined-treatment strategy. Furthermore, our approach of selecting persons on the basis of age and easily measured risk factors means that neither complex screening nor blood tests are required to initiate treatment with low doses of combination therapy. Our trial included persons of diverse racial and

ethnic groups from 21 countries with broadly consistent benefits and safety.

In conclusion, in the HOPE-3 trial, treatment with fixed doses of rosuvastatin and two antihypertensive agents was associated with a significantly lower risk of cardiovascular events than the risk with placebo among intermediate-risk persons without previous cardiovascular disease.

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APPENDIX

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