ORIGINAL ARTICLE

Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease

S. Yusuf, J. Bosch, G. Dagenais, J. Zhu, D. Xavier, L. Liu, P. Pais,
P. López-Jaramillo, L.A. Leiter, A. Dans, A. Avezum, L.S. Piegas, A. Parkhomenko,
K. Keltai, M. Keltai, K. Sliwa, R.J.G. Peters, C. Held, I. Chazova, K. Yusoff,
B.S. Lewis, P. Jansky, K. Khunti, W.D. Toff, C.M. Reid, J. Varigos,
G. Sanchez-Vallejo, R. McKelvie, J. Pogue,* H. Jung, P. Gao, R. Diaz,
and E. Lonn, for the HOPE-3 Investigators†

ABSTRACT

BACKGROUND

Previous trials have shown that the use of statins to lower cholesterol reduces the risk of cardiovascular events among persons without cardiovascular disease. Those trials have involved persons with elevated lipid levels or inflammatory markers and involved mainly white persons. It is unclear whether the benefits of statins can be extended to an intermediate-risk, ethnically diverse population without cardiovascular disease.

METHODS

In one comparison from a 2-by-2 factorial trial, we randomly assigned 12,705 participants in 21 countries who did not have cardiovascular disease and were at intermediate risk to receive rosuvastatin at a dose of 10 mg per day or 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 revascularization, heart failure, and resuscitated cardiac arrest. The median follow-up was 5.6 years.

RESULTS

The overall mean low-density lipoprotein cholesterol level was 26.5% lower in the rosuvastatin group than in the placebo group. The first coprimary outcome occurred in 235 participants (3.7%) in the rosuvastatin group and in 304 participants (4.8%) in the placebo group (hazard ratio, 0.76; 95% confidence interval [CI], 0.64 to 0.91; P=0.002). The results for the second coprimary outcome were consistent with the results for the first (occurring in 277 participants [4.4%] in the rosuvastatin group and in 363 participants [5.7%] in the placebo group; hazard ratio, 0.75; 95% CI, 0.64 to 0.88; P<0.001). The results were also consistent in subgroups defined according to cardiovascular risk at baseline, lipid level, C-reactive protein level, blood pressure, and race or ethnic group. In the rosuvastatin group, there was no excess of diabetes or cancers, but there was an excess of cataract surgery (in 3.8% of the participants, vs. 3.1% in the placebo group; P=0.02) and muscle symptoms (in 5.8% of the participants, vs. 4.7% in the placebo group; P=0.005).

CONCLUSIONS

Treatment with rosuvastatin at a dose of 10 mg per day resulted in a significantly lower risk of cardiovascular events than placebo in an intermediate-risk, ethnically diverse population without cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; HOPE-3 ClinicalTrials.gov number, NCT00468923.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Yusuf at the Population Health Research Institute, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada, or at yusufs@mcmaster.ca.

*Deceased.

CARDIOVASCULAR DISEASES CAUSE 18 million deaths per year globally and a similar number of nonfatal cardiovascular events.[1] Elevated low-density lipoprotein (LDL) cholesterol levels account for approximately half the population-attributable risk of myocardial infarction[2] and approximately one quarter of the risk of ischemic stroke.[3] In previous trials, lowering LDL cholesterol levels with statins has been shown to reduce the risk of cardiovascular diseases, but most of the patients enrolled in those trials had vascular disease, elevated lipid levels, elevated inflammatory markers, hypertension, or diabetes.[4,5] The association between LDL cholesterol level and cardiovascular disease is graded and has no documented threshold.[2,3] Yet the role of lowering LDL cholesterol levels with statins in the primary prevention of cardiovascular events among persons without cardiovascular disease, regardless of lipid levels, inflammatory markers, hypertension status, or diabetes status, has not been established.

Although 80% of the global burden of cardiovascular disease occurs in low- and middle-income countries, the majority of trials have been conducted in North America or Europe and involve mainly white persons.[4] The pattern of dyslipidemia can vary among different races or ethnic groups,[6] and Asian persons are thought to be at higher risk for the adverse effects of statin use than are white persons.[7] We therefore conducted the Heart Outcomes Prevention Evaluation (HOPE)–3 trial, which was a large trial evaluating the long-term effects of rosuvastatin at a dose of 10 mg per day (without dose adjustment or lipid targets) among persons of various ethnic backgrounds on six continents who did not have cardiovascular disease and were at intermediate risk.

METHODS

TRIAL DESIGN

We conducted this pragmatic, multicenter, long-term, international, double-blind, randomized, placebo-controlled trial at 228 centers in 21 countries. The trial had a 2-by-2 factorial design. The trial evaluated cholesterol lowering with rosuvastatin at a dose of 10 mg per day, blood-pressure lowering with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day, and the combination of both interventions for the prevention of cardiovascular events among persons who did not have cardiovascular disease and 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 analysis of blood-pressure lowering and the analysis of the combination of blood-pressure lowering and cholesterol lowering 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.[9]

TRIAL OVERSIGHT

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 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 after regulatory and ethical approvals were obtained 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 who had at least one of the following cardiovascular risk factors: elevated waist-to-hip ratio, history of a low level of high-density lipoprotein cholesterol, current or recent tobacco use, dysglycemia, family history of premature coronary disease, and mild renal dysfunction (details of the eligibility criteria are provided in Table S2 in the Supplementary Appendix). We also included women 60 years of age or older who had at least two such risk factors. Participants 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 to inform physicians about participants' risks, but trial eligibility was based on the uncertainty principle, which asserts that only persons with clear indications for or contraindications to trial drugs were excluded from participation, and those persons were identified on the basis of the clinical judgment of local physicians, usual practice, and guidelines.[11]

TRIAL PROCEDURES

Eligible participants entered a single-blind run-in phase, during which they received active treatments (both for blood-pressure lowering and for cholesterol lowering) for 4 weeks. Participants who adhered to the assigned regimen and who did not have an unacceptable level of adverse events were randomly assigned to receive a fixed combination of candesartan at a dose of 16 mg per day and hydrochlorothiazide at a dose of 12.5 mg per day or placebo; participants were also randomly assigned to receive rosuvastatin at a dose of 10 mg per day or placebo (Fig. S2 in the Supplementary Appendix).

Follow-up visits occurred at 6 weeks and 6 months after randomization and every 6 months thereafter. Individualized structured lifestyle advice was provided to the participants, according to identified needs. The blood pressure was recorded at each visit during the first year and annually thereafter. Lipid levels were measured at baseline in all participants and at 1 year, 3 years, and the end of the trial in a subsample of 10 to 20% of the participants (with representation across geographic regions and races or ethnic groups) (see the Supplementary Appendix for further information). Open-label statins could be prescribed at the physicians' discretion, but in those cases, the assigned regimen was discontinued.

EFFICACY AND SAFETY OUTCOMES

All cardiovascular events and cases of new-onset diabetes were documented and adjudicated. 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 resuscitated cardiac arrest, heart failure, and revascularization. The secondary outcome was the second coprimary outcome plus angina with evidence of ischemia. This outcome was adopted by the steering committee in July 2015 without a protocol amendment before unblinding of the data on November 3, 2015. At the same time, a prespecified renal outcome was removed because of limitations of statistical power. Additional outcomes include death from any cause, the components of the coprimary and secondary 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. Definitions of all events and the approach to safety reporting are described in the Supplementary Appendix.

STATISTICAL ANALYSIS

With an expected event rate of 1% per year for the first coprimary outcome in the dual-placebo group (i.e., persons assigned to receive placebo in both the blood-pressure and cholesterol comparisons), a mean follow-up of 5.5 years, cumulative nonadherence rates of 23% in the groups receiving active treatment, and drop-in rates of 11% over a 5-year period, we estimated that a sample of 12,700 participants would provide the trial with more than 80% power to detect a risk with rosuvastatin that was 22.5% lower than the risk with placebo. To preserve the overall type I error rate of 5% for the testing of both coprimary outcomes in both factorial comparisons, the first coprimary outcome was tested at a P value of 0.04 and the second at a P value of 0.02. A nominal P value of less than 0.05 was used for all other analyses (further details are provided in the Supplementary Appendix).

The analyses were performed with the use of an intention-to-treat approach. Survival curves are shown as Kaplan–Meier curves. A Cox proportional-hazards model, stratified according to the opposite group of the factorial design, was used to estimate treatment effects and to evaluate effects in subgroups. No significant interaction between the two treatments was observed. Prespecified, hypothesis-based subgroup analyses were conducted according to thirds of baseline cardiovascular risk, of LDL cholesterol level, and of systolic blood pressure. A post hoc recurrent-events analysis[12] was performed to assess the

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Rosuvastatin Group (N=6361)	Placebo Group (N=6344)
Age — yr	65.8±6.4	65.7±6.3
Female sex — no. (%)	2951 (46.4)	2923 (46.1)
Cardiovascular risk factors — no. (%)		
Elevated waist-to-hip ratio	5540 (87.1)	5494 (86.6)
Recent or current smoking	1740 (27.4)	1784 (28.1)
Low HDL cholesterol level	2344 (36.8)	2244 (35.4)
Impaired fasting glucose or impaired glucose tolerance	809 (12.7)	807 (12.7)
Early diabetes mellitus	374 (5.9)	357 (5.6)
Family history of premature coronary heart disease	1675 (26.3)	1660 (26.2)
Early renal dysfunction	169 (2.7)	181 (2.9)
Hypertension	2403 (37.8)	2411 (38.0)
Presence of 2 risk factors	3002 (47.2)	2924 (46.1)
Presence of ≥3 risk factors	1545 (24.3)	1523 (24.0)
Blood pressure — mm Hg		
Systolic	138.04±14.92	138.06±14.62
Diastolic	81.85±9.38	81.90±9.26
Heart rate — beats/min	72.75±10.25	72.72±10.19
Body-mass index†	27.15±4.78	27.07±4.77
Waist-to-hip ratio	0.94±0.08	0.94±0.08
Cholesterol — mg/dl‡		
Total	201.5±42.6	201.3±41.7
LDL	127.8±36.1	127.9±36.0
HDL	44.7±13.9	44.9±13.8
Triglycerides — mg/dl‡		
Median	128.8	126.5
Interquartile range	92.9–179.6	92.9–176.1
Fasting plasma glucose — mg/dl		
Median	95.4	95.4
Interquartile range	87.0–106.2	86.4–106.0
Apolipoprotein B — g/liter	1.03±0.26	1.02±0.26
Apolipoprotein A1 — g/liter	1.46±0.34	1.46±0.33
Ratio of apolipoprotein B to apolipoprotein A	0.75±0.33	0.74±0.31
High-sensitivity C-reactive protein — mg/liter‡		
Median	2.0	2.0
Interquartile range	1.0–4.0	1.0–3.9
Serum creatinine — mg/dl	0.89±0.22	0.90±0.22
INTERHEART Risk Score§	14.5 (5.2)	14.4 (5.2)
Race or ethnic group — no. (%)¶		
Chinese	1854 (29.1)	1837 (29.0)
Hispanic	1744 (27.4)	1752 (27.6)
White	1286 (20.2)	1260 (19.9)
South Asian	927 (14.6)	927 (14.6)

Table 1. (Continued.)		
Characteristic	Rosuvastatin Group (N = 6361)	Placebo Group (N = 6344)
Other Asian	341 (5.4)	355 (5.6)
Black	113 (1.8)	112 (1.8)
Other	96 (1.5)	101 (1.6)
Medication use — no. (%)		
Ezetimibe	11 (0.2)	6 (0.1)
Niacin	6 (0.1)	5 (0.1)
Aspirin	686 (10.8)	707 (11.1)
Beta-blocker	504 (7.9)	516 (8.1)
Calcium-channel blocker	941 (14.8)	944 (14.9)
Alpha-blocker	76 (1.2)	65 (1.0)
Nonthiazide diuretic	39 (0.6)	26 (0.4)
Aldosterone antagonist	12 (0.2)	5 (0.1)
Oral hypoglycemic agent	167 (2.6)	170 (2.7)

* Plus–minus values are means ±SD. There were no significant between-group differences. Definitions for the cardiovascular risk factors are provided in Table S2 in the Supplementary Appendix. Data on blood pressure were missing for 2 participants in the placebo group, and data on low-density lipoprotein (LDL) cholesterol level for 656 in the rosuvastatin group and for 651 in the 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 level. To convert values for cholesterol to millimoles per liter, multiply by 0.0259. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for creatinine to micromoles per liter, multiply by 88.4. HDL denotes high-density lipoprotein.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The measurements were made at the central core laboratory.
§ The scale for the INTERHEART Risk Score[13] 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 higher.
¶ Race and ethnic group were self-reported.

effect of rosuvastatin use on the risk of total cardiovascular events.

RESULTS

PARTICIPANTS AND ADHERENCE TO THE TRIAL REGIMEN

From April 2007 through November 2010, a total of 12,705 persons who adhered to the assigned regimen during the run-in period and did not have an unacceptable level of adverse events were randomly assigned to rosuvastatin (6361 persons) or to placebo (6344 persons) (Fig. S2 in the Supplementary Appendix). The mean age of the participants was 65.7 years, the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 27.1, the mean systolic blood pressure was 138.1 mm Hg, and the median fasting plasma glucose level was 95.4 mg per deciliter (5.3 mmol per liter) (Table 1). A total of 46.2% of the participants were women.

Only 5.8% had diabetes (with 44% of those participants receiving diabetes medications). A total of 20% of the participants were white, 49.1% were Asian, 27.5% were Hispanic, and 3.3% were black or belonged to another ethnic group. The median follow-up was 5.6 years. At the end of the trial, vital status was available for 99.1% of the participants (12,587).

In the rosuvastatin group, 88.0% were taking the assigned regimen at 1 year, 83.5% at 3 years, and 75.5% at 5 years; the corresponding rates in the placebo group were 87.8%, 83.0%, and 73.2% (Table S4 in the Supplementary Appendix). The percentages of participants in the rosuvastatin group who were taking open-label statins were 0.6% at 1 year, 1.7% at 3 years, and 2.5% at 5 years; the corresponding percentages in the placebo group were 1.2%, 3.3%, and 5.6%. Rosuvastatin was permanently discontinued in fewer participants than was placebo (1510 [23.7%] vs. 1664 [26.2%], P=0.001).

LIPID AND HIGH-SENSITIVITY C-REACTIVE PROTEIN LEVELS

At baseline, the mean total cholesterol level was 201.4 mg per deciliter (5.22 mmol per liter), the mean LDL cholesterol level was 127.8 mg per deciliter (3.31 mmol per liter), and the mean apolipoprotein B level was 1.02 g per liter (Table 1). The LDL cholesterol level (measured in the subsample of participants described in the Methods section) was 39.6 mg per deciliter (1.02 mmol per liter) lower in the rosuvastatin group than in the placebo group at 1 year, 34.7 mg per deciliter (0.90 mmol per liter) lower at 3 years, and 29.5 mg per deciliter (0.76 mmol per liter) lower at the end of the trial (overall mean difference, 34.6 mg per deciliter [0.90 mmol per liter] or 26.5%; P<0.001) (Fig. 1). The overall mean triglyceride level was 21.2 mg per deciliter (0.24 mmol per liter) lower and the overall mean apolipoprotein B level was 0.23 g per liter lower in the rosuvastatin group than in the placebo group (P<0.001 for both comparisons). The median high-sensitivity C-reactive protein level at baseline was 2.0 mg per liter; the overall C-reactive protein level was significantly lower in the rosuvastatin group than in the placebo group (log-transformed mean difference, 0.19 mg per liter; P<0.001).

OUTCOMES

The first coprimary outcome occurred in 235 participants (3.7%) in the rosuvastatin group and in 304 participants (4.8%) in the placebo group (hazard ratio, 0.76; 95% confidence interval [CI], 0.64 to 0.91; P=0.002; number needed to treat with rosuvastatin to prevent one coprimary outcome event, 91) (Table 2, and Fig. S7 in the Supplementary Appendix). The second coprimary outcome occurred in 277 participants (4.4%) in the rosuvastatin group and in 363 participants (5.7%) in the placebo group (hazard ratio, 0.75; 95% CI, 0.64 to 0.88; P<0.001; number need to treat, 73) (Table 2 and Fig. 2).

In a post hoc analysis, the total number of events of the second coprimary outcome was substantially lower in the rosuvastatin group than in the placebo group (353 vs. 473; difference, 120; hazard ratio, 0.75; 95% CI, 0.64 to 0.89; P=0.001) (Table 2). The secondary outcome occurred in 306 participants (4.8%) in the rosuvastatin group and in 393 participants (6.2%) in the placebo group (hazard ratio, 0.77; 95% CI, 0.66 to 0.89;

P<0.001) (Table 2, and Fig. S8 in the Supplementary Appendix).

Significantly fewer participants in the rosuvastatin group than in the placebo group had strokes (Table 2 and Fig. 2). Fewer ischemic strokes occurred in the rosuvastatin group than in the placebo group (41 vs. 77), but slightly more hemorrhagic strokes occurred (11 vs. 8), and the same number of cases of subarachnoid hemorrhage occurred in both groups (4). (The type of stroke was unclassified for 15 cases of stroke in the rosuvastatin group and 11 cases in the placebo group.) Significantly fewer myocardial infarctions and coronary revascularizations occurred in the rosuvastatin group than in the placebo group (Table 2 and Fig. 2). There was no significant difference between the two groups in the number of participants who had new-onset diabetes (Table 2). Death from cardiovascular causes occurred in 154 participants (2.4%) in the rosuvastatin group and in 171 (2.7%) in the placebo group, and death from noncardiovascular causes occurred in 180 participants (2.8%) in the rosuvastatin group and in 186 (2.9%) in the placebo group. The total number of deaths was 334 in the rosuvastatin group and 357 in the placebo group (Table 2, and Table S12 in the Supplementary Appendix).

SAFETY

A significantly smaller number of participants in the rosuvastatin group than in the placebo group were hospitalized for cardiovascular causes (281 [4.4%] vs. 369 [5.8%], P<0.001) (Table 2, and Tables S13 through S17 in the Supplementary Appendix); in addition, the total number of hospitalizations for cardiovascular causes was lower in the rosuvastatin group than in the placebo group (444 vs. 596). More participants in the rosuvastatin group than in the placebo group had muscle pain or weakness (367 [5.8%] vs. 296 [4.7%], P=0.005). There was no significant difference between the two groups in the number of participants in whom the assigned treatment was permanently discontinued because of muscle symptoms (83 [1.3%] in the rosuvastatin group and 76 [1.2%] in the placebo group, P=0.63) or in the number of cases of rhabdomyolysis or myopathy (2 and 1, respectively) or cancer (267 and 286, respectively). More participants in the rosuvastatin group than in the
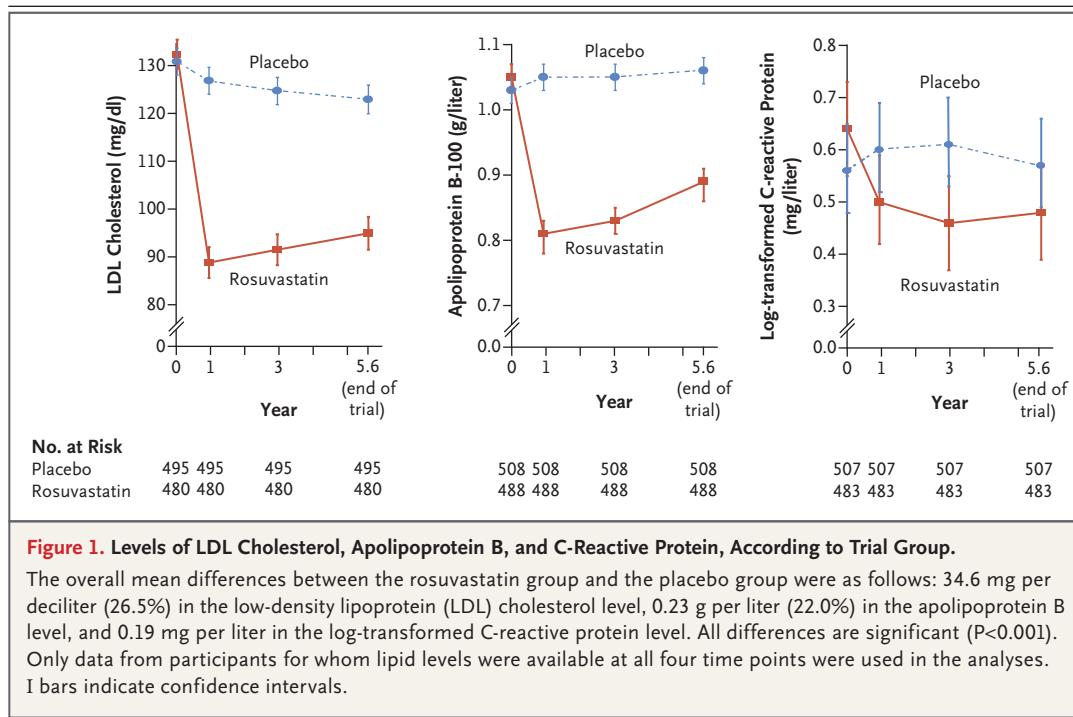
Figure 1. Levels of LDL Cholesterol, Apolipoprotein B, and C-Reactive Protein, According to Trial Group.

The overall mean differences between the rosuvastatin group and the placebo group were as follows: 34.6 mg per deciliter (26.5%) in the low-density lipoprotein (LDL) cholesterol level, 0.23 g per liter (22.0%) in the apolipoprotein B level, and 0.19 mg per liter in the log-transformed C-reactive protein level. All differences are significant (P<0.001). Only data from participants for whom lipid levels were available at all four time points were used in the analyses. I bars indicate confidence intervals.

placebo group underwent cataract surgery (241 [3.8%] vs. 194 [3.1%], P=0.02). Fewer participants in the rosuvastatin group than in the placebo group had deep-vein thrombosis or pulmonary embolism (14 vs. 31; hazard ratio, 0.45; 95% CI, 0.24 to 0.84; P=0.01).

SUBGROUPS

The benefits of rosuvastatin, as compared with placebo, were consistent in subgroups defined according to cardiovascular risk at baseline, LDL cholesterol level, blood pressure, and C-reactive protein level (Fig. S14 and S15 in the Supplementary Appendix; additional subgroup data are not reported here). There was also no evidence of heterogeneity of effect in subgroups defined according to sex, age, and race or ethnic group.

DISCUSSION

In the HOPE-3 trial, treatment with rosuvastatin at a dose of 10 mg per day for a period of 5.6 years in intermediate-risk persons who did not have cardiovascular disease and who had baseline lipid levels within the normal range resulted in a lower risk of cardiovascular events than that with placebo, including the risk of a composite

of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, revascularization, and heart failure. Treatment with rosuvastatin also resulted in significantly lower risks of strokes and myocardial infarctions than those with placebo.

The HOPE-3 trial included persons of diverse ethnic backgrounds in 21 countries on six continents. Approximately half the participants were women and 80% were nonwhite. Therefore, the results are broadly applicable. The benefits of rosuvastatin were consistent across subgroups defined according to LDL cholesterol level, blood pressure, C-reactive protein level, cardiovascular risk at baseline, age, sex, and race or ethnic group. HOPE-3 thus provides new evidence of a benefit of statin therapy in Chinese and other Asian populations and in Hispanic populations, in addition to white populations.

JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin),[5] which included only patients with elevated levels of C-reactive protein (>2.0 mg per liter) and with LDL cholesterol levels of 130 mg per deciliter (3.37 mmol per liter) or less, showed a substantially lower risk of cardiovascular events with the use of rosuvastatin at a dose of 20 mg

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

Outcome	Rosuvastatin Group (N = 6361)	Placebo Group (N = 6344)	Hazard Ratio (95% CI)	P Value
Coprimary outcomes — no. (%)				
First coprimary outcome	235 (3.7)	304 (4.8)	0.76 (0.64–0.91)	0.002
Second coprimary outcome	277 (4.4)	363 (5.7)	0.75 (0.64–0.88)	<0.001
Secondary outcome — no. (%)	306 (4.8)	393 (6.2)	0.77 (0.66–0.89)	<0.001
Components of the coprimary and secondary outcomes — no. (%)				
Death from cardiovascular causes	154 (2.4)	171 (2.7)	0.89 (0.72–1.11)	
Myocardial infarction	45 (0.7)	69 (1.1)	0.65 (0.44–0.94)	
Stroke	70 (1.1)	99 (1.6)	0.70 (0.52–0.95)	
Resuscitated cardiac arrest	4 (0.1)	4 (0.1)	0.99 (0.25–3.97)	
Revascularization	56 (0.9)	82 (1.3)	0.68 (0.48–0.95)	
Heart failure	21 (0.3)	29 (0.5)	0.72 (0.41–1.26)	
Angina with evidence of ischemia	56 (0.9)	64 (1.0)	0.87 (0.61–1.24)	
Death from any cause — no. (%)	334 (5.3)	357 (5.6)	0.93 (0.80–1.08)	0.32
New-onset diabetes — no. (%)	232 (3.9)	226 (3.8)	1.02 (0.85–1.23)	0.82
Coronary heart disease — no. (%)†	105 (1.7)	140 (2.2)	0.74 (0.58–0.96)	0.02
First and recurrent events of the second coprimary outcome‡				
No. of participants with ≥1 event	277	363		
No. of participants with ≥2 events	68	89		
No. of participants with ≥3 events	6	16		
Total no. of events	353	473	0.75 (0.64–0.89)	0.001
Hospitalizations — no. (%)§				
For cardiovascular causes	281 (4.4)	369 (5.8)	0.75 (0.64–0.88)	<0.001
For noncardiovascular causes	881 (13.9)	879 (13.9)	1.00 (0.91–1.10)	0.99

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

† Coronary heart disease was a post hoc outcome that included fatal or nonfatal myocardial infarction, coronary revascularization, and angina with evidence of ischemia.

‡ The analysis of the recurrent events of the second coprimary outcome was a post hoc analysis that used a proportional-means model. The second coprimary outcome is shown because it comprises all events that were included in the first coprimary outcome as well as resuscitated cardiac arrest, heart failure, and revascularization.

§ Hospitalizations were a prespecified safety outcome.

per day than with placebo. The LDL cholesterol level was 46.3 mg per deciliter (1.20 mmol per liter) lower at 12 months in the rosuvastatin group than in the placebo group; this difference is larger than the difference observed in HOPE-3 (39.6 mg per deciliter) at the same time point. The reduction in the risk of cardiovascular events in JUPITER was also larger (relative risk reduction, 44%, vs. 24% in HOPE-3), but the confi-dence intervals of the two estimates overlap, and the early termination of JUPITER may have in-flated the apparent benefits. In HOPE-3, similar benefits were observed with rosuvastatin regard-less of C-reactive protein level.

The results of our trial in an intermediate-risk, primary-prevention population are consis-tent with those of a Japanese trial[14] in a primary-prevention population with elevated lipid levels
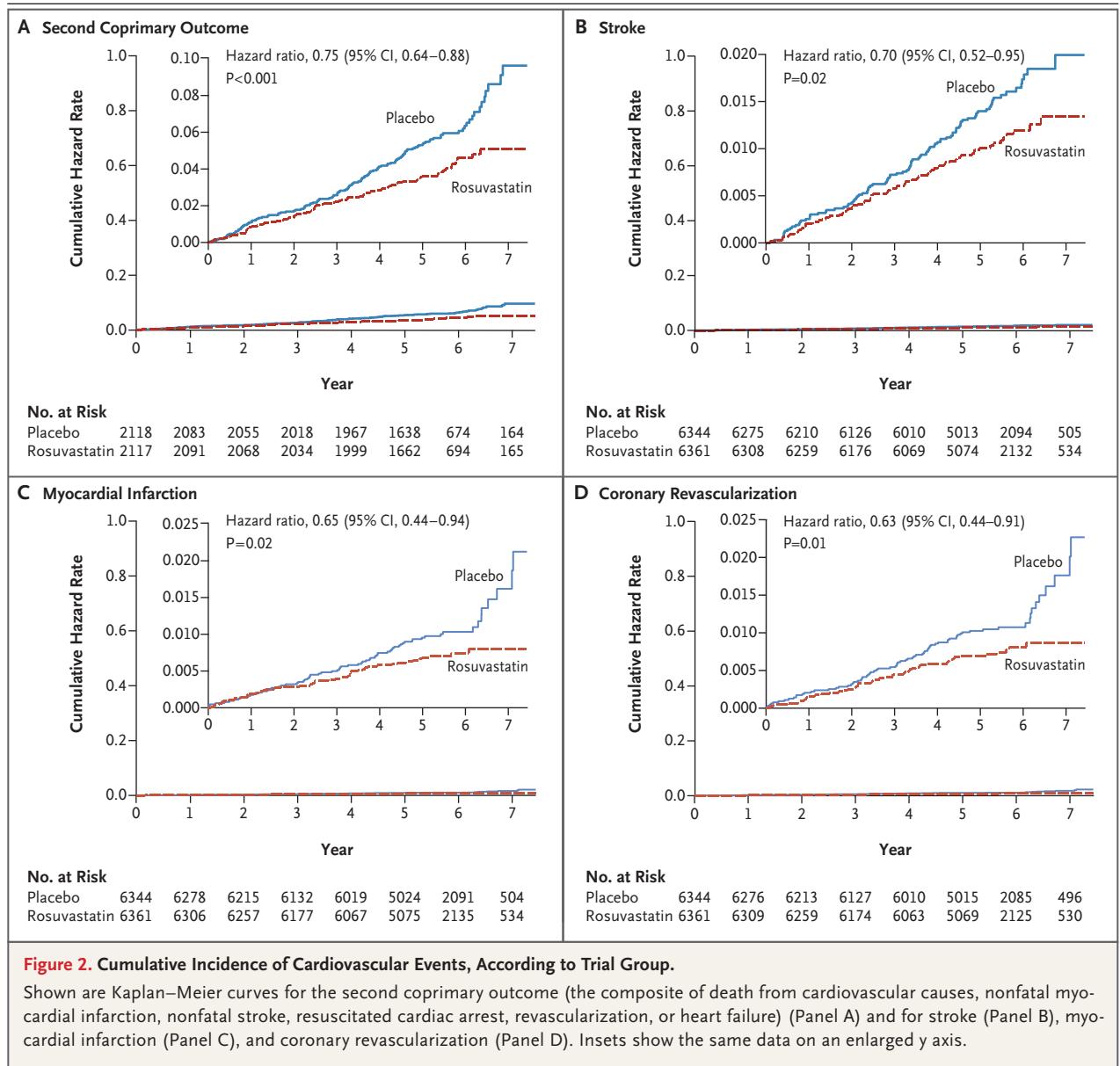
Figure 2. Cumulative Incidence of Cardiovascular Events, According to Trial Group.

Shown are Kaplan–Meier curves for the second coprimary outcome (the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, revascularization, or heart failure) (Panel A) and for stroke (Panel B), myocardial infarction (Panel C), and coronary revascularization (Panel D). Insets show the same data on an enlarged y axis.

and also consistent with the Cholesterol Treatment Trialists' Collaboration trial in a higher-risk population.[4] The degree of reduction of cardiovascular risk in HOPE-3 is consistent with the degree of reduction of LDL cholesterol levels in previous statin trials[4,15] (Fig. S18 in the Supplementary Appendix).

HOPE-3 and other statin trials, which typically have a relatively short mean duration of treatment, may underestimate the real benefits of longer-term treatment. Furthermore, the absolute benefits of treatment are underestimated in a time-to-first-event analysis, as compared with an analysis that also considers the effect of treatment on recurrent events (e.g., for the second coprimary outcome in HOPE-3, there was a between-group difference of 86 first events vs. 120 total events). Also, in HOPE-3, the difference in statin use between the rosuvastatin group and the placebo group was approximately 82% (in the middle of the trial), and thus the benefits in patients who actually took the statins is most likely larger. The differences between the rosuvastatin group and the placebo group in LDL cho-

lesterol level and apolipoprotein B level were approximately one quarter smaller by the end of the trial than they were at 1 year, which may be explained largely by the moderate reductions in adherence to the assigned regimen in the rosuvastatin group and by the use of statins in the placebo group. Despite these factors, the reduction in the risk of cardiovascular disease continued to increase over time.

The rate of discontinuation for adverse events was lower among the participants who received rosuvastatin (at a dose of 10 mg daily) than among those who received placebo, and there was no excess in diabetes or functional abnormalities of the liver in the rosuvastatin group. There was a higher rate of muscle weakness or pain in the rosuvastatin group than in the placebo group, but these conditions were generally reversible with temporary discontinuation. There was only one case of rhabdomyolysis (in the rosuvastatin group) and two episodes of myopathy (one each in the rosuvastatin group and the placebo group). There were more cases of cataract surgery in the rosuvastatin group than in the placebo group. This effect has not been reported in trials but has been seen in observational studies.[16] However, one trial of ezetimibe plus statins reported fewer cases of cataracts in the active-treatment group than in the placebo group.[17] Determining whether the excess in cataracts is related to the treatment requires a systematic analysis of all statin trials.

The results of HOPE-3 and other trials of statins collectively provide an extensive body of evidence of a significant clinical benefit in a broad group of persons of diverse ethnic backgrounds. In particular, trials of low-dose statins, such as HOPE-3, suggest that the risks associated with such therapy are low. Given that generic statins are now widely available and affordable in high-income and upper-middle-income countries,[18] a case may be made for their broader use in these countries. Efforts to make them more widely available and affordable in poorer countries should facilitate wider use for both primary and secondary prevention. Our trial of a fixed dose of rosuvastatin indicates that a simple approach to treatment, without routine blood tests to initiate or monitor statin therapy, is effective. This approach avoids the costs of frequent clinic visits, thereby facilitating the use of rosuvastatin in primary care, and may have the potential to substantially reduce the rates of premature cardiovascular events globally.

In summary, HOPE-3 evaluated cholesterol lowering with the use of a low dose of rosuvastatin in a diverse population of persons who did not have cardiovascular disease and who were at intermediate risk. There was a significant reduction in the risk of cardiovascular events with the use of rosuvastatin.

APPENDIX

The authors' full names and academic degrees are as follows: Salim Yusuf, M.B., B.S., D.Phil., Jackie Bosch, Ph.D., Gilles Dagenais, M.D., Jun Zhu, M.D., Denis Xavier, M.D., Lisheng Liu, M.D., Prem Pais, M.D., Patricio López-Jaramillo, M.D., Ph.D., Lawrence A. Leiter, M.D., Antonio Dans, M.D., Alvaro Avezum, M.D., Ph.D., Leopoldo S. Piegas, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Katalin Keltai, M.D., Ph.D., Matyas Keltai, M.D., Ph.D., Karen Sliwa, M.D., Ph.D., Ron J.G. Peters, M.D., Ph.D., Claes Held, M.D., Ph.D., Irina Chazova, M.D., Ph.D., Khalid Yusoff, M.D., Basil S. Lewis, M.D., Petr Jansky, M.D., Kamlesh Khunti, M.D., Ph.D., William D. Toff, M.D., Christopher M. Reid, Ph.D., John Varigos, B.Sc., Gregorio Sanchez-Vallejo, M.D., Robert McKelvie, M.D., Ph.D., Janice Pogue, Ph.D., Hyejung Jung, M.Sc., Peggy Gao, M.Sc., Rafael Diaz, M.D., and Eva Lonn, M.D.

The authors' affiliations are as follows: the Population Health Research Institute, Hamilton Health Sciences (S.Y., J.B., R.M., J.P., H.J., P.G., E.L.), Departments of Medicine (S.Y., R.M., E.L.) and Clinical Epidemiology and Biostatistics (J.P.), and School of Rehabilitation Science (J.B.), McMaster University, Hamilton, ON, Institut Universitaire de Cardiologie et Pneumologie de Québec, Université Laval, Quebec, QC (G.D.), and Li Ka Shing Knowledge Institute and Keenan Research Centre for Biomedical Science, St. Michael's Hospital, University of Toronto, Toronto (L.A.L.) — all in Canada; Fu Wai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing (J.Z., L.L.); St. John's Medical College (D.X.) and St. John's Research Institute (D.X., P.P.), Bangalore, India; Fundacion Oftalmológica de Santander and Instituto Masira, Medical School, Universidad de Santander, Bucaramanga (P.L.-J.), and University of Quindio, Armenia (G.S.-V.) — both in Colombia; College of Medicine, University of the Philippines, Manila (A.D.); Dante Pazzanese Institute of Cardiology (A.A.) and HCor-Heart Hospital (L.S.P.), São Paulo; Institute of Cardiology, Kiev, Ukraine (A.P.); Hungarian Institute of Cardiology, Semmelweis University, Budapest (K. Keltai, M.K.); Hatter Institute for Cardiovascular Research in Africa, Department of Medicine, University of Cape Town, Soweto Cardiovascular Research Group, Cape Town, South Africa (K.S.); Department of Cardiology, Academic Medical Center, Amsterdam (R.J.G.P.); Department of Medical Sciences, Cardiology, Clinical Research Center, Uppsala University, Uppsala, Sweden (C.H.); Institute of Clinical Cardiology in the Russian Cardiology Research Com-

plex, Moscow (I.C.); Universiti Teknologi Majlis Amansh Rakyat, Selayang, and University College Sedaya International University, Kuala Lumpur — both in Malaysia (K.Y.); Lady Davis Carmel Medical Center, Ruth and Bruce Rappaport School of Medicine, Technion–Israel Institute of Technology, Haifa (B.S.L.); University Hospital Motol, Prague, Czech Republic (P.J.); Diabetes Research Centre (K. Khunti) and Department of Cardiovascular Sciences (W.D.T.), University of Leicester, and National Institute for Health Research, Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital (W.D.T.), Leicester, United Kingdom; School of Public Health, Curtin University, Perth, WA (C.M.R.), and Primary Care Diabetes and Vascular Medicine, Monash Centre of Cardiovascular Research and Education in Therapeutics (C.M.R.), and Department of Epidemiology and Preventive Medicine (J.V.), Monash University, Melbourne, VIC (J.V.) — both in Australia; and Instituto Cardiovascular de Rosario, Rosario, Argentina (R.D.).

REFERENCES

1. GBD 2013 Risk factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386:2287-323.
2. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937-52.
3. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010;376:112-23.
4. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.
5. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359:2195-207.
6. McQueen MJ, Hawken S, Wang X, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study):

a case-control study. Lancet 2008;372: 224-33.
7. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, prespecified muscle and liver outcomes, and reasons for stopping study treatment. Eur Heart J 2013;34:1279-91.
8. Lonn E, Bosch J, Pogue J, et al. Novel approaches in primary cardiovascular disease prevention: the HOPE-3 trial rationale, design, and participants' baseline characteristics. Can J Cardiol 2016;32:311-8.
9. Lonn EM, Bosch J, López-Jaramillo P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2009-20.
10. Yusuf S, Lonn E, Pais P, et al. Blood-pressure and cholesterol lowering in persons without cardiovascular disease. N Engl J Med 2016;374:2032-43.
11. Sackett DL. Why randomized controlled trials fail but needn't: 1. Failure to gain "coal-face" commitment and to use the uncertainty principle. CMAJ 2000;162: 1311-4.
12. Lin D, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. J R Stat Soc B 2000;62:711-30.
13. McGorrian C, Yusuf S, Islam S, et al. Estimating modifiable coronary heart disease risk in multiple regions of the world:

the INTERHEART Modifiable Risk Score. Eur Heart J 2011;32:581-9.
14. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet 2006;368:1155-63.
15. Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581-90.
16. Wise SJ, Nathoo NA, Etminan M, Mikelberg FS, Mancini GBJ. Statin use and risk for cataract: a nested case-control study of 2 populations in Canada and the United States. Can J Cardiol 2014;30: 1613-9.
17. Bang CN, Greve AM, La Cour M, et al. Effect of randomized lipid lowering with simvastatin and ezetimibe on cataract development (from the Simvastatin and Ezetimibe in Aortic Stenosis Study). Am J Cardiol 2015;116:1840-4.
18. Khatib R, McKee M, Shannon H, et al. Availability and affordability of cardiovascular disease medicines and their effect on use in high-income, middle-income, and low-income countries: an analysis of the PURE study data. Lancet 2016;387:61-9.
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