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Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*

ABSTRACT

BACKGROUND

Statin therapy reduces low-density lipoprotein (LDL) cholesterol levels and the risk of cardiovascular events, but whether the addition of ezetimibe, a nonstatin drug that reduces intestinal cholesterol absorption, can reduce the rate of cardiovascular events further is not known.

METHODS

We conducted a double-blind, randomized trial involving 18,144 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days and had LDL cholesterol levels of 50 to 100 mg per deciliter (1.3 to 2.6 mmol per liter) if they were receiving lipid-lowering therapy or 50 to 125 mg per deciliter (1.3 to 3.2 mmol per liter) if they were not receiving lipid-lowering therapy. The combination of simvastatin (40 mg) and ezetimibe (10 mg) (simvastatin–ezetimibe) was compared with simvastatin (40 mg) and placebo (simvastatin monotherapy). The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke. The median follow-up was 6 years.

RESULTS

The median time-weighted average LDL cholesterol level during the study was 53.7 mg per deciliter (1.4 mmol per liter) in the simvastatin–ezetimibe group, as compared with 69.5 mg per deciliter (1.8 mmol per liter) in the simvastatin-monotherapy group ($P<0.001$). The Kaplan–Meier event rate for the primary end point at 7 years was 32.7% in the simvastatin–ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (absolute risk difference, 2.0 percentage points; hazard ratio, 0.936; 95% confidence interval, 0.89 to 0.99; $P=0.016$). Rates of prespecified muscle, gallbladder, and hepatic adverse effects and cancer were similar in the two groups.

CONCLUSIONS

When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes. Moreover, lowering LDL cholesterol to levels below previous targets provided additional benefit. (Funded by Merck; IMPROVE-IT ClinicalTrials.gov number, NCT00202878.)

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Brigham and Women's Hospital, and Harvard Medical School, Boston (C.P.C., R.P.G., A.M., K.I., E.A.B., S.D.W., E.B.); Duke Clinical Research Institute (DCRI), Durham, NC (M.A.B., J.A.W., C.R., R.M.C.); Montreal Heart Institute, Montreal (P.T.); Vivantes Neukölln Medical Center, Berlin (H.D.); Lady Davis Carmel Medical Center, Haifa, Israel (B.S.L.); Canisius-Wilhelmina Ziekenhuis, Nijmegen (T.O.O.), and the Netherlands Leiden University Medical Center, Leiden (J.W.J.) — both in the Netherlands; Fondazione IRCCS Policlinico San Matteo and University of Pavia, Pavia, Italy (G.M.D.F.); National Institute of Cardiology, Warsaw, Poland (W.R.); and Merck, Kenilworth, NJ (P.D.L., A.M.T., T.A.M.). Address reprint requests to Dr. Cannon at the Cardiovascular Division, Brigham and Women's Hospital, 350 Longwood Ave., 1st Fl., Boston, MA 02115, or at cpcannon@partners.org.

*A complete list of investigators in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is provided in the Supplementary Appendix, available at NEJM.org.

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The use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) reduces both low-density lipoprotein (LDL) cholesterol levels and the risk of cardiovascular events in patients with and those without cardiovascular disease.[1-4] Intensive statin therapy, as compared with moderate-dose statin therapy, incrementally lowers LDL cholesterol levels and rates of nonfatal cardiovascular events.[5-9] Because of the residual risk of recurrent cardiovascular events and safety concerns associated with high-dose statin therapy,[10] additional lipid-modifying therapies have been sought.[11-14]

A Quick Take summary is available at NEJM.org

Ezetimibe targets the Niemann–Pick C1–like 1 (NPC1L1) protein, thereby reducing absorption of cholesterol from the intestine.[15,16] When added to statins, ezetimibe reduces LDL cholesterol levels by an additional 23 to 24%, on average.[17,18] Polymorphisms affecting NPC1L1 are associated with both lower levels of LDL cholesterol and a lower risk of cardiovascular events.[19] Whether further lowering of LDL cholesterol levels achieved with the addition of ezetimibe to statin therapy leads to a benefit in clinical outcomes is unknown. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) evaluated the effect of ezetimibe combined with simvastatin, as compared with that of simvastatin alone, in stable patients who had had an acute coronary syndrome and whose LDL cholesterol values were within guideline recommendations.[20-24]

Methods

Study Oversight

The trial was designed and led by an executive committee that included representatives from the Thrombolysis in Myocardial Infarction (TIMI) Study Group, the Duke Clinical Research Institute (DCRI), and the study sponsor (Merck), in collaboration with an international steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org).[22-24] The ethics committee at each participating center approved the protocol and amendments. A data and safety monitoring board oversaw the study. DCRI managed the database and performed the primary analyses independently using raw data; TIMI and the sponsor verified the analyses. All the authors vouch for the completeness and accuracy of the data and all analyses, as well as for the fidelity of this report to the trial protocol, which is available at NEJM.org.

Patient Population

Men and women who were at least 50 years of age were eligible for inclusion if they had been hospitalized within the preceding 10 days for an acute coronary syndrome (an acute myocardial infarction, with or without ST-segment elevation on electrocardiography, or high-risk unstable angina[22-24]; detailed definitions are provided in the Supplementary Appendix). Patients were required to have an LDL cholesterol level of 50 mg per deciliter (1.3 mmol per liter) or higher. For participants who were not receiving long-term lipid-lowering therapy, the maximum LDL cholesterol level for enrollment was 125 mg per deciliter (3.2 mmol per liter); for participants who were receiving lipid-lowering therapy, the maximum level was 100 mg per deciliter (2.6 mmol per liter). The LDL cholesterol level for eligibility was measured locally within the first 24 hours after onset of the acute coronary syndrome. Key exclusion criteria were planned coronary-artery bypass grafting for the acute coronary syndrome event, creatinine clearance of less than 30 ml per minute, active liver disease, or use of statin therapy that had LDL cholesterol–lowering potency greater than 40 mg of simvastatin (see the Supplementary Appendix). Each patient provided written informed consent.

Study Protocol

Patients received standard medical and interventional treatment for acute coronary syndrome[22] and were randomly assigned, in a 1:1 ratio and in a double-blind fashion, to receive, once daily, either simvastatin (at a dose of 40 mg) plus ezetimibe (at a dose of 10 mg) (simvastatin–ezetimibe group) or simvastatin (at a dose of 40 mg) plus placebo (simvastatin-monotherapy group). Randomization was stratified according to prior use of lipid-lowering therapy, type of acute coronary syndrome, and status with respect to enrollment in the concurrent Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) trial.[25]

Patients had follow-up visits at 30 days, at 4 months, and every 4 months thereafter. Patients who discontinued the study drug during the trial were generally followed by means of telephone

calls. Blood samples were obtained at randomization, at 1, 4, 8, and 12 months, and yearly thereafter for those attending clinic visits.

For patients in either study group who had LDL cholesterol levels higher than 79 mg per deciliter (2.0 mmol per liter) on two consecutive measurements, the simvastatin dose was increased to 80 mg in a double-blind manner. In June 2011, in accordance with Food and Drug Administration guidance for limiting new prescriptions of 80 mg of simvastatin, patients were no longer eligible for an increased dose of simvastatin to 80 mg, and any patient who had been receiving the 80-mg dose for less than 1 year had the dose reduced to 40 mg.[23] If an LDL cholesterol measurement on the new regimen was confirmed to be higher than 100 mg per deciliter, the study drug could be discontinued and more potent therapy initiated. The study continued until each patient had been followed for a minimum of 2.5 years and until the target number of events (5250) was reached. Five amendments to the protocol were implemented during the course of the study, including an increase in the sample size.[23]

END POINTS

The primary efficacy end point was a composite of death from cardiovascular disease, a major coronary event (nonfatal myocardial infarction, documented unstable angina requiring hospital admission, or coronary revascularization occurring at least 30 days after randomization), or nonfatal stroke, assessed from the time of randomization until the first occurrence of one of the events. The three secondary efficacy end points were a composite of death from any cause, major coronary event, or nonfatal stroke; a composite of death from coronary heart disease, nonfatal myocardial infarction, or urgent coronary revascularization 30 days or more after randomization; and a composite of death from cardiovascular causes, nonfatal myocardial infarction, hospitalization for unstable angina, all revascularization 30 days or more after randomization, or nonfatal stroke. All end-point definitions are described in the Supplementary Appendix.[22-24] Prespecified safety variables included liver enzyme levels and creatine kinase levels, episodes of myopathy or rhabdomyolysis, gallbladder-related adverse events, and cancer. Independent clinical-events committees, whose members were unaware of the study-group assignments, adjudicated primary end-point events (excluding revascularization), cancer, and muscle-related events (details are provided in the Supplementary Appendix).

STATISTICAL ANALYSIS

In the final protocol, we estimated that 5250 events would be required to give the study 90% power to detect a 9.375% lower relative risk for the primary end point with simvastatin–ezetimibe than with simvastatin monotherapy. All efficacy and safety analyses were performed in the intention-to-treat population. Rules for stopping the study early at interim analyses were prespecified.[22-24] The data and safety monitoring board conducted 10 safety reviews. In addition, three interim efficacy analyses were performed, after 45.7%, 76.1%, and 86.9% of the required events had occurred; adjustment of the level of significance to account for the three interim analyses was determined by the Lan–DeMets approximation of the O'Brien–Fleming boundaries for group sequential testing, with a final two-sided P value for significance of 0.0394 or less. The false positive error rate for the three secondary end points was controlled with the use of the Hochberg method.[26] A nominal P value of 0.05 or less without adjustment for multiple testing was used for other end points. Estimates of the hazard ratios and associated 95% confidence intervals for the comparison of simvastatin–ezetimibe with simvastatin monotherapy were obtained with the use of a Cox proportional-hazards model, with study group and stratification factors as covariates. Event rates are Kaplan–Meier failure rates at 7 years. Data for the analyses in this report were based on the database that was locked on October 21, 2014. Additional updating of data on serious adverse events and hospitalizations was carried out after this database lock (see the Supplementary Appendix).

RESULTS

PATIENTS

Between October 26, 2005, and July 8, 2010, a total of 18,144 patients underwent randomization at 1147 sites in 39 countries. The disposition of the patients is shown in Figure S1 in the Supplementary Appendix; 9077 were assigned to the simvastatin-monotherapy group, and 9067 to the

Table 1. Baseline Characteristics.*

Variable	Simvastatin Monotherapy (N=9077)	Simvastatin–Ezetimibe (N=9067)
Demographic characteristic		
Age — yr	63.6±9.8	63.6±9.7
Male — no. (%)	6886 (75.9)	6842 (75.5)
White race — no. (%)†	7624 (84.0)	7578 (83.6)
Weight — kg	83.0±17.4	82.9±17.4
Body-mass index‡	28.3±5.2	28.3±5.2
Region — no. (%)		
North America	3487 (38.4)	3486 (38.4)
Western Europe	3641 (40.1)	3633 (40.1)
Eastern Europe	707 (7.8)	709 (7.8)
Asia Pacific	448 (4.9)	448 (4.9)
South America	794 (8.7)	791 (8.7)
Coexisting conditions — no./total no. (%)		
Diabetes	2474/9077 (27.3)	2459/9067 (27.1)
Hypertension	5557/9072 (61.3)	5580/9063 (61.6)
Congestive heart failure	371/9077 (4.1)	419/9067 (4.6)
Peripheral arterial disease	518/9077 (5.7)	487/9067 (5.4)
Current smoker — no./total no. (%)	3035/9072 (33.5)	2943/9067 (32.5)
Previous MI — no./total no. (%)	1881/9077 (20.7)	1925/9054 (21.3)
Previous PCI — no. (%)	1796 (19.8)	1766 (19.5)
Previous CABG — no. (%)	842 (9.3)	842 (9.3)
Before index ACS		
Medications — no./total no. (%)		
Lipid-lowering agent	3207/9063 (35.4)	3227/9067 (35.6)
Statin	3111/9077 (34.3)	3135/9067 (34.6)
Aspirin	3855/9077 (42.5)	3799/9067 (41.9)
Creatinine clearance — ml/min		
Median	84.7	84.4
Interquartile range	65.8–107.4	65.8–106.5
At index event		
Type of event — no./total no. (%)		
MI with ST-segment elevation	2606/9077 (28.7)	2584/9067 (28.5)
MI without ST-segment elevation	4253/9077 (46.9)	4302/9061 (47.5)
Unstable angina	2211/9077 (24.4)	2175/9067 (24.0)
Diagnostic catheterization — no./total no. (%)	7936/9069 (87.5)	7988/9059 (88.2)
Prerandomization PCI — no./total no. (%)	6321/9071 (69.7)	6385/9061 (70.5)
Mean LDL cholesterol — mg/dl§	93.8	93.8
Time from ACS to randomization — days		
Median	5.0	5.0
Interquartile range	3.0–8.0	3.0–8.0
Medications at time of randomization — no./total no. (%)		
Aspirin	8794/9077 (96.9)	8798/9063 (97.1)

Table 1. (Continued.)

Variable	Simvastatin Monotherapy (N=9077)	Simvastatin–Ezetimibe (N=9067)
Thienopyridine	7813/9077 (86.1)	7869/9067 (86.8)
Beta-blocker	7879/9077 (86.8)	7912/9067 (87.3)
ACE inhibitor or ARB	6878/9077 (75.8)	6822/9063 (75.3)

* Plus–minus values are means ±SD. No significant differences were noted between the groups. ACE denotes angiotensin-converting enzyme, ACS acute coronary syndrome, ARB angiotensin-receptor blocker, CABG coronary-artery bypass grafting, LDL low-density lipoprotein, MI myocardial infarction, and PCI percutaneous coronary intervention.
† Race was determined by the investigators.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Data on baseline levels were available for 9009 participants in the simvastatin-monotherapy group and for 8990 participants in the simvastatin–ezetimibe group; data on 1-year levels were available for 6939 participants in the simvastatin-monotherapy group and for 6864 participants in the simvastatin–ezetimibe group. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

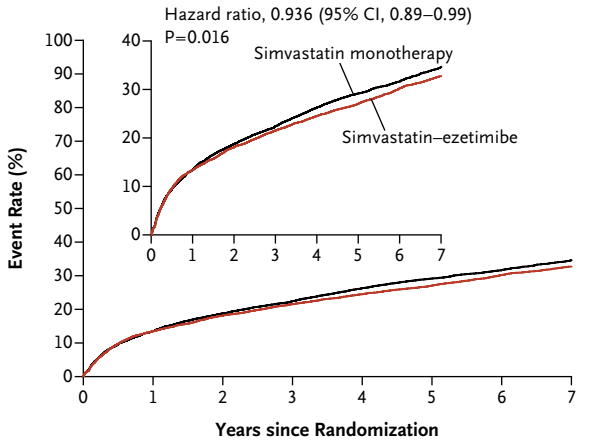
simvastatin–ezetimibe group. The baseline characteristics of the patients in the two study groups were well matched (Table 1). The average age of the patients was 64 years, 24% were women, 27% had diabetes mellitus, 88% had undergone coronary angiography and 70% had undergone percutaneous coronary intervention during the index hospitalization, 34% were taking statin drugs at the time of the index event, and 77% received statin therapy during hospitalization.

The simvastatin dose was increased to 80 mg for elevated LDL cholesterol levels in 27% of the patients in the simvastatin-monotherapy group and in 6% of the patients in the simvastatin–ezetimibe group. The numbers of patients who discontinued the study drug, withdrew consent, or were lost to follow-up were similar in the two groups (Fig. S1 in the Supplementary Appendix). After a median of 6 years, 42% of the patients in each group had discontinued the study medication without having died or without having had a primary end-point event. The percentage of potential follow-up that was achieved — calculated as (number of patient-years of follow-up ÷ potential patient-years of follow-up) × 100 — was 91% for the primary end point and 97% for all-cause mortality.

LIPID DATA

At the time of hospitalization for the index event, the mean LDL cholesterol level was 93.8 mg per deciliter (2.4 mmol per liter) in each group (Table 1). Among patients who had blood samples obtained at 1 year, the mean LDL cholesterol level was 69.9 mg per deciliter (1.8 mmol per liter) in the simvastatin-monotherapy group and 53.2 mg per deciliter (1.4 mmol per liter) in the simvastatin–ezetimibe group (P<0.001) (Table S1 in the Supplementary Appendix). This difference of 16.7 mg per deciliter (0.43 mmol per liter) (P<0.001) represented a 24% further lowering of LDL cholesterol level when ezetimibe was combined with simvastatin than when simvastatin was administered alone. Over the course of the entire trial, the median time-weighted average LDL cholesterol level was 69.5 mg per deciliter (1.8 mmol per liter) in the simvastatin-monotherapy group and 53.7 mg per deciliter (1.4 mmol per liter) in the simvastatin–ezetimibe group. To account for patients in the two groups who discontinued treatment and did not have blood samples obtained, LDL cholesterol levels were imputed with the use of the LDL cholesterol levels measured at randomization (the approach used by the Cholesterol Treatment Trialists [CTT] collaborators).[3,4] The between-group difference in LDL cholesterol level at 1 year with imputation was 12.8 mg per deciliter (0.33 mmol per liter).

At 1 year, levels of total cholesterol, triglycerides, non–high-density lipoprotein (HDL) cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein were all significantly lower in the simvastatin–ezetimibe group than in the simvastatin-monotherapy group (Table S1 in the Supplementary Appendix). A greater proportion of patients in the simvastatin–ezetimibe group than in the simvastatin-monotherapy group achieved the dual goal of an LDL cholesterol level of less than 70 mg per deciliter (1.8 mmol per liter) and a high-sensitivity C-reactive protein



No. at Risk								
Simvastatin–ezetimibe	9067	7371	6801	6375	5839	4284	3301	1906
Simvastatin	9077	7455	6799	6327	5729	4206	3284	1857

Figure 1. Kaplan–Meier Curves for the Primary Efficacy End Point.

Shown are the cumulative event rates for the primary composite end point of death from cardiovascular disease, a major coronary event (nonfatal myocardial infarction, documented unstable angina requiring hospital admission, or coronary revascularization occurring at least 30 days after randomization), or nonfatal stroke in the intention-to-treat population during the overall study period (i.e., beginning from the time of randomization to the day of the first occurrence of a primary end-point event, the day of the last office or phone visit, or the day of death during follow-up). The inset shows the same data on an enlarged y axis.

level of less than 2.0 at 1 month (50.6% vs. 30.5%) (Table S2 in the Supplementary Appendix).

EFFICACY END POINTS

Kaplan–Meier event rates for the primary end point at 7 years were 32.7% in the simvastatin–ezetimibe group and 34.7% in the simvastatin-monotherapy group (absolute risk reduction, 2.0 percentage points; hazard ratio, 0.936; 95% confidence interval, 0.89 to 0.99; P=0.016) (Fig. 1). The benefit appeared to emerge after 1 year. The rate of each of the three secondary end points was significantly lower in the simvastatin–ezetimibe group than in the simvastatin-monotherapy group (Table 2).

The rates of death from cardiovascular causes and from any cause were similar in the two groups. The risk of any myocardial infarction was significantly lower with simvastatin–ezetimibe than with simvastatin monotherapy (difference, 1.7 percentage points; hazard ratio, 0.87; P=0.002), as was the risk of ischemic stroke (difference, 0.7 percentage points; hazard ratio, 0.79; P=0.008) (Table 2). There was a nonsignificantly higher risk of hemorrhagic stroke with simvastatin–ezetimibe than with simvastatin monotherapy (difference, 0.2 percentage points; hazard ratio, 1.38; P=0.11), although the number of hemorrhagic strokes was low.

The rate of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke was significantly lower, by 1.8 percentage points, in the simvastatin–ezetimibe group than in the simvastatin-monotherapy group (hazard ratio, 0.90; P=0.003) (Table 2). The rate of major vascular events as defined by the CTT collaborators[3,4] (a composite of death from coronary heart disease, myocardial infarction, stroke, or coronary revascularization 30 days or more after randomization) was also significantly lower in the simvastatin–ezetimibe group (difference, 2.2 percentage points; hazard ratio, 0.928; P=0.007).

The benefit of simvastatin–ezetimibe was consistent across nearly all prespecified subgroups (Fig. S2 in Supplementary Appendix). The benefit appeared to be particularly pronounced in patients with diabetes mellitus and in patients 75 years of age or older.

SAFETY

No significant between-group differences were seen in the percentage of patients who had elevations in alanine aminotransferase levels that exceeded three times the upper limit of the normal range or in the rates of gallbladder-related adverse events, cholecystectomy, muscle-related adverse events, or new, relapsing, or worsening cancer (Table 3). Discontinuation of study medication owing to an adverse event occurred in 10.1% of the patients in the simvastatin-monotherapy group and in 10.6% of those in the simvastatin–ezetimibe group.

DISCUSSION

In IMPROVE-IT, the addition to statin therapy of a nonstatin agent, ezetimibe, which reduces the absorption of cholesterol from the gastrointestinal tract, lowered LDL cholesterol by approximately 24%. The combination of simvastatin and ezetimibe also resulted in a significantly lower risk of cardiovascular events than that with statin monotherapy, with a 2.0-percentage-point lower rate of the primary composite end point of

Table 2. Primary, Secondary, and Individual End Points.*

Outcome	Simvastatin Monotherapy (N=9077)	Simvastatin–Ezetimibe (N=9067)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Primary end point: death from cardiovascular causes, major coronary event, or nonfatal stroke	2742 (34.7)	2572 (32.7)	0.936 (0.89–0.99)	0.016
Secondary end points				
Death from any cause, major coronary event, or nonfatal stroke	3246 (40.3)	3089 (38.7)	0.95 (0.90–1.0)	0.03
Death from coronary heart disease, nonfatal MI, urgent coronary revascularization ≥30 days	1448 (18.9)	1322 (17.5)	0.91 (0.85–0.98)	0.02
Death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, all revascularization ≥30 days, nonfatal stroke	2869 (36.2)	2716 (34.5)	0.95 (0.90–1.0)	0.04
Tertiary end points†				
Death from any cause	1231 (15.3)	1215 (15.4)	0.99 (0.91–1.07)	0.78
Death from cardiovascular causes	538 (6.8)	537 (6.9)	1.00 (0.89–1.13)	1.00
Death from coronary heart disease	461 (5.8)	440 (5.7)	0.96 (0.84–1.09)	0.50
Any MI	1118 (14.8)	977 (13.1)	0.87 (0.80–0.95)	0.002
Nonfatal MI	1083 (14.4)	945 (12.8)	0.87 (0.80–0.95)	0.002
Fatal MI	49 (0.7)	41 (0.5)	0.84 (0.55–1.27)	0.41
Any stroke	345 (4.8)	296 (4.2)	0.86 (0.73–1.00)	0.05
Ischemic stroke	297 (4.1)	236 (3.4)	0.79 (0.67–0.94)	0.008
Hemorrhagic stroke	43 (0.6)	59 (0.8)	1.38 (0.93–2.04)	0.11
Coronary revascularization ≥30 days after randomization	1793 (23.4)	1690 (21.8)	0.95 (0.89–1.01)	0.11
Urgent coronary revascularization ≥30 days after randomization	626 (8.6)	510 (7.0)	0.81 (0.72–0.91)	0.001
Any revascularization ≥30 days after randomization	1962 (25.6)	1871 (24.2)	0.96 (0.90–1.02)	0.18
Hospitalization for unstable angina	148 (1.9)	156 (2.1)	1.06 (0.85–1.33)	0.62
Other prespecified end points				
Death from cardiovascular causes, MI, or stroke	1704 (22.2)	1544 (20.4)	0.90 (0.84–0.96)	0.003
Major vascular events: death from coronary heart disease, MI, stroke, or coronary revascularization ≥30 days after randomization‡	2685 (34.0)	2498 (31.9)	0.928 (0.88–0.98)	0.007

* The database for the analysis presented here was locked on October 21, 2014. Percentages are 7-year Kaplan–Meier estimates. Major coronary events included MI, hospitalization for unstable angina, and coronary revascularization 30 or more days after randomization.
† The individual end points listed are the first occurrence of that event.
‡ The end point of major vascular events was defined according to the definition used by the Cholesterol Treatment Trialists' collaborators.

Table 3. Prespecified Safety End Points.*

End Point	Simvastatin Monotherapy (N = 9077)	Simvastatin–Ezetimibe (N = 9067)	P Value
	no. of patients (%)		
ALT, AST, or both ≥3×ULN	208 (2.3)	224 (2.5)	0.43
Cholecystectomy	134 (1.5)	133 (1.5)	0.96
Gallbladder-related adverse events	321 (3.5)	281 (3.1)	0.10
Rhabdomyolysis	18 (0.2)	13 (0.1)	0.37
Myopathy	10 (0.1)	15 (0.2)	0.32
Rhabdomyolysis or myopathy	28 (0.3)	27 (0.3)	0.90
Rhabdomyolysis, myopathy, myalgia with creatine kinase elevation ≥5×ULN	58 (0.6)	53 (0.6)	0.64
Cancer†	732 (10.2)	748 (10.2)	0.57
Death from cancer†	272 (3.6)	280 (3.8)	0.71

* Adverse events were assessed in the intention-to-treat population. The database for the analysis presented here was locked on October 21, 2014. All muscle and cancer events were adjudicated by a clinical events committee, whose members were unaware of the study-group assignments. Detailed definitions of the adverse events are provided in the Supplementary Appendix. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.

† Percentages for cancer are 7-year Kaplan–Meier estimates. Cancer includes any new, relapsing, or progressing cancer, excluding nonmelanoma skin cancer. Death from cancer includes death from nonmelanoma skin cancer.

cardiovascular death, major coronary events, or nonfatal stroke (hazard ratio, 0.936). No between-group differences in cardiovascular mortality or in the rate of death from any cause were anticipated or observed in IMPROVE-IT, findings that are consistent with those in trials of intensive-dose versus standard-dose statin therapy.[5-9] However, significant reductions were observed in the rates of myocardial infarction and ischemic stroke.

The extent of benefit afforded by the simvastatin–ezetimibe combination is consistent with that seen in previous statin trials, with a similar reduction in cardiovascular events according to the degree of LDL cholesterol lowering (Fig. 2).[1,2,27-38] Using the approach and end point that were used by the CTT collaborators,[3,4] we observed a between-group difference in LDL cholesterol levels (with imputation for missing values) of 12.8 mg per deciliter and a proportional 7.2% lower rate of major vascular events, a finding consistent with the reduction produced by statins. The hazard ratio for clinical benefit per millimole of LDL cholesterol reduction with ezetimibe in IMPROVE-IT was 0.80, as compared with 0.78 observed with statins in the CTT meta-analysis.[3,4] This trial cannot prove that the effect was mediated by the lowering of LDL cholesterol levels alone, since changes in other lipoproteins and high sensitivity C-reactive protein may have played a role. However, the consistency with expectations from the CTT analysis, in which a different class of drug was used, provides further evidence for a relationship between lipid lowering and improved outcomes. The observation that a nonstatin lipid-lowering agent can also reduce cardiovascular risk does indirectly support the LDL hypothesis (i.e., that lowering LDL cholesterol leads to a reduction in cardiovascular events), but most importantly it undercuts the "statin hypothesis," that somehow only statins are beneficial. This finding is notable in that several previous trials have failed to show a significant benefit of nonstatin lipid-modifying agents when added to statins.[11-14]

According to practice guidelines in place at the time of patient enrollment in IMPROVE-IT, treatment of hypercholesterolemia was based on lowering LDL cholesterol to target levels,[20,21] which were set on the basis of a patient's risk of cardiovascular events. Over the past two decades, statin trials have shown clinical benefit when LDL cholesterol was lowered to progressively lower levels.[1-9] On the basis of these trials, a target LDL cholesterol of less than 70 mg per deciliter has been recommended for patients

after an acute coronary syndrome.[20,21] Whether additional clinical benefit would be observed with further reductions of LDL cholesterol to levels below 70 mg per deciliter has not been clear. The benefit of ezetimibe in IMPROVE-IT suggests that there is additional clinical benefit, and it appeared to be similar in patients with lower LDL cholesterol levels as well as in those with higher LDL cholesterol levels at baseline.

There were no significant differences between the two study groups in any of the prespecified safety end points or in the rate of discontinuation of study medication owing to adverse events, albeit with a higher use of the 80-mg simvastatin dose in the simvastatin-monotherapy group than in the simvastatin–ezetimibe group. The rate of hemorrhagic stroke was higher, although not significantly so, with simvastatin–ezetimibe than with simvastatin monotherapy, a finding similar to that seen with statin therapy as compared with placebo.[3,4] Although cautions had been raised about the safety of ezetimibe,[39,40] we observed no significant between-group difference in the incidence of cancer or cancer deaths during up to 7 years of follow-up and no significant difference in the incidence of rhabdomyolysis or myopathy.

Several limitations of our study should be considered. First, we evaluated patients who had had an acute coronary syndrome, and our results are most relevant to that population. However, the treatment period extended for an average of 6 years, and the differences between the two treatment groups emerged after about 1 year, by which time most of the data were from patients in the chronic phase of their disease. Second, we used 40 mg and 80 mg of simvastatin as background statin therapy (categorized as "moderate" and "intensive" statin therapy, respectively) with an upper limit for LDL cholesterol level at study entry to ensure that this statin regimen would be likely to reduce LDL cholesterol levels to less than 70 mg per deciliter (on average), as recommended at the time of patient enrollment in the trial.[20,21] Although we studied only this regimen, current data indicate that the same relationship between reduction in LDL cholesterol levels and clinical benefit is seen across different statins and statin doses.[4] It is possible, as others have suggested,[41] that greater benefits from ezetimibe might have been seen if baseline LDL cholesterol levels had been higher. Finally, 42% of the patients discontinued the study medication for any reason prematurely, with an equal proportion in the two groups. This rate of approximately 7% per year is similar to or better than that achieved

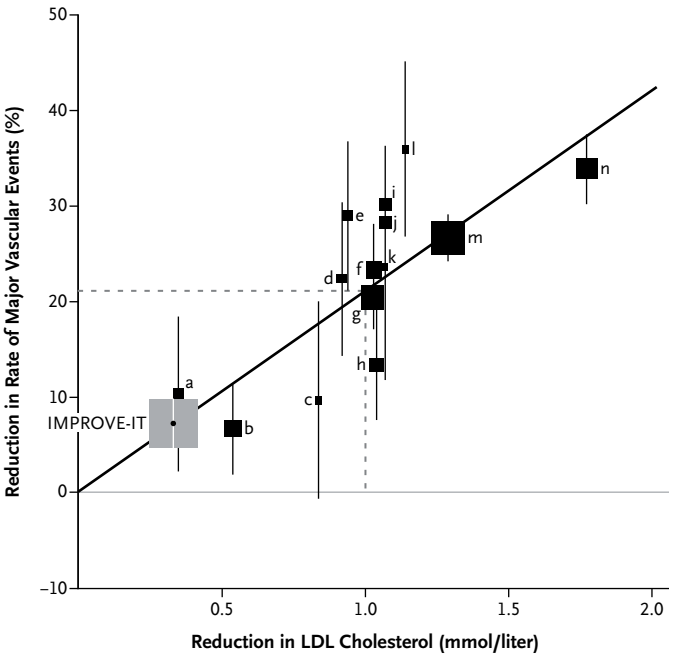


Figure 2. Plot of the IMPROVE-IT Trial Data and Statin Trials for Change in Low-Density Lipoprotein (LDL) Cholesterol versus Clinical Benefit.

The hazard ratio (obtained with the use of a Cox proportional-hazards model) for the reduction in major vascular events in the simvastatin–ezetimibe group as compared with the simvastatin-monotherapy group in IMPROVE-IT is plotted against data from other trials of statins that assessed the association between change in LDL and clinical benefit. Major vascular events were defined as a composite of death from coronary heart disease, myocardial infarction, stroke, or revascularization more than 30 days after randomization. Vertical bars indicate 1 SE. The size of the box is proportional to the number of end points in the study. In IMPROVE-IT, the between-group difference in LDL cholesterol was calculated as the difference in the observed LDL cholesterol level in patients from whom blood samples were obtained at 1 year, with imputation of the value measured at the time of randomization for patients from whom a blood sample was not obtained or was missing (including those who had died). Letters from a to n denote the following trials: a: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI Prevenzione)[27]; b: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid Lowering Trial (ALLHAT-LLT)[28]; c: Assessment of Lescol in Renal Transplantation (ALERT)[29]; d: Lescol Intervention Prevention Study (LIPS)[30]; e: Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[31]; f: Cholesterol and Recurrent Events (CARE)[32]; g: Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID)[33]; h: Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)[34]; i: Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA)[35]; j: West of Scotland Coronary Prevention Study (WOSCOPS)[36]; k: Post–Coronary Artery Bypass Graft (Post CABG)[37]; l: Collaborative Atorvastatin Diabetes Study (CARDS)[38]; m: Heart Protection Study (HPS)[2]; and n: Scandinavian Simvastatin Survival Study (4S)[1].

in some prior studies,[5-7] but this trial had a particularly long duration of follow-up. We nonetheless found a significant benefit; if adherence had been higher, one might anticipate that a greater clinical benefit might have been seen.

In conclusion, the addition of ezetimibe to statin therapy in stable patients who had had an acute coronary syndrome and who had LDL cholesterol levels within guideline recommendations further lowered the risk of cardiovascular events. The event reduction was consistent with the predicted effects seen with statins, even in the range of low LDL cholesterol levels in this trial, and no offsetting adverse events or toxic effects were observed.

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