JAMA Cardiology | Original Investigation

Effect of Simvastatin-Ezetimibe Compared With Simvastatin Monotherapy After Acute Coronary Syndrome Among Patients 75 Years or Older

A Secondary Analysis of a Randomized Clinical Trial

Richard G. Bach, MD; Christopher P. Cannon, MD; Robert P. Giugliano, MD, SM; Jennifer A. White, MS; Yuliya Lokhnygina, PhD; Erin A. Bohula, MD, DPhil; Robert M. Califf, MD; Eugene Braunwald, MD; Michael A. Blazing, MD

IMPORTANCE Limited evidence is available regarding the benefit and hazard of higher-intensity treatment to lower lipid levels among patients 75 years or older. As a result, guideline recommendations differ for this age group compared with younger patients.

OBJECTIVE To determine the effect on outcomes and risks of combination ezetimibe and simvastatin compared with simvastatin monotherapy to lower lipid levels among patients 75 years or older with stabilized acute coronary syndrome (ACS).

DESIGN, SETTING, PARTICIPANTS In this prespecified secondary analysis of the global, multicenter, prospective clinical randomized Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), outcomes and risks were compared by age among patients 50 years or older after a hospitalization for ACS. Data were collected from October 26, 2005, through July 8, 2010, with the database locked October 21, 2014. Data were analyzed May 29, 2015, through March 13, 2018, using Kaplan-Meier curves and Cox proportional hazards models.

INTERVENTIONS Double-blind randomized assignment to combined simvastatin and ezetimibe or simvastatin and placebo with follow-up for a median of 6 years (interquartile range, 4.3-7.1 years).

MAIN OUTCOMES AND MEASURES The primary composite end point consisted of death due to cardiovascular disease, myocardial infarction (MI), stroke, unstable angina requiring hospitalization, and coronary revascularization after 30 days. Individual adverse ischemic and safety end points and lipid variables were also analyzed.

RESULTS Of 18 144 patients enrolled (13 728 men [75.7%]; mean [SD] age, 64.1 [9.8] years), 5173 (28.5%) were 65 to 74 years old, and 2798 (15.4%) were 75 years or older at randomization. Treatment with simvastatin-ezetimibe resulted in lower rates of the primary end point than simvastatin-placebo, including 0.9% for patients younger than 65 years (HR, 0.97; 95% CI, 0.90-1.05) and 0.8% for patients 65 to 74 years of age (hazard ratio [HR], 0.96; 95% CI, 0.87-1.06), with the greatest absolute risk reduction of 8.7% for patients 75 years or older (HR, 0.80; 95% CI, 0.70-0.90) (P = .02 for interaction). The rate of adverse events did not increase with simvastatin-ezetimibe vs simvastatin-placebo among younger or older patients.

CONCLUSIONS AND RELEVANCE In IMPROVE-IT, patients hospitalized for ACS derived benefit from higher-intensity therapy to lower lipid levels with simvastatin-ezetimibe compared with simvastatin monotherapy, with the greatest absolute risk reduction among patients 75 years or older. Addition of ezetimibe to simvastatin was not associated with any significant increase in safety issues among older patients. These results may have implications for guideline recommendations regarding lowering of lipid levels in the elderly.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT00202878

JAMA Cardiol. doi:10.1001/jamacardio.2019.2306
Published online July 17, 2019.

Invited Commentary
Author Audio Interview
Supplemental content

Author Affiliations: Cardiovascular Division, Department of Medicine, Washington University School of Medicine, St Louis, Missouri (Bach); TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts (Cannon, Giugliano, Bohula, Braunwald); Duke Clinical Research Institute, Division of Cardiology, Department of Medicine, Duke University, Durham, North Carolina (White, Lokhnygina, Califf, Blazing).

Corresponding Author: Richard G. Bach, MD, Cardiovascular Division, Department of Medicine, Washington University School of Medicine, 660 S Euclid Ave, St Louis, MO 63110 (rgbach@wustl.edu).

For patients hospitalized with an acute coronary syndrome (ACS), the risk of adverse cardiovascular outcomes increases with age and is highest for elderly patients.[1] Although persons 75 years or older account for 6% of the population, they account for more than 65% of all deaths due to cardiovascular disease (CVD),[2] and the number of US individuals in this age group is expected to double by 2050.[3]

Although randomized trials have shown that high-intensity treatment to lower lipid levels reduces CVD events for patients after an ACS whose mean age is approximately 60 years,[4] the evidence supporting the benefit of intensive therapy to lower lipid levels among elderly patients is more limited. In epidemiologic studies, the strong positive association between elevated cholesterol levels and adverse CVD events observed in younger patients appears attenuated, absent, or reversed among elderly patients.[5-8] Although some clinical trials[9,10] have shown benefit of therapy to lower lipid levels across a wide range of ages, other trials[11] suggest that the efficacy of statin therapy to reduce the risk of recurrent events is diminished in the elderly. However, most randomized trials have explicitly excluded or enrolled few older adults. In the Cholesterol Treatment Trialists' meta-analysis of 28 trials involving more than 186 000 participants,[12] the comparison of more- vs less-intensive therapy found consistency across age categories, but fewer than 2400 patients were older than 75 years. As a result, the generalizability of the results of most major clinical trials to lower lipid levels to the elderly population remains uncertain. Moreover, concern has been raised that more intensive therapy to lower lipid levels in the elderly may be associated with greater risk of adverse effects compared with younger patients.[13] As a result, recent lipid treatment guidelines[14,15] and the recent update to recommendations on use of nonstatin therapies for lowering cholesterol levels,[16] citing the limited information available, support the use of moderate statin therapy and do not advocate the routine use of high-intensity therapy for patients older than 75 years.

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) evaluated the effect of higher-intensity treatment to lower lipid levels with ezetimibe combined with simvastatin compared with simvastatin and placebo (henceforth referred to as simvastatin monotherapy) among patients with a stabilized ACS and observed that ezetimibe added to statin therapy incrementally lowered low-density lipoprotein cholesterol (LDL-C) levels and improved CVD outcomes.[17] IMPROVE-IT enrolled patients with no upper age limit. In this secondary analysis, we examined the association of age with the benefit of intensive treatment to lower lipid levels with ezetimibe combined with simvastatin vs simvastatin monotherapy in IMPROVE-IT.

Key Points

Question Does ezetimibe plus simvastatin offer any benefit compared with simvastatin alone as a therapy to lower lipid levels among elderly patients after acute coronary syndrome?

Findings In this secondary analysis of the randomized clinical Improved Reduction of Outcomes: Vytorin Efficacy International Trial, which enrolled 18 144 patients, greater reduction of cardiovascular events with simvastatin and ezetimibe vs simvastatin and placebo was observed in the 2798 patients 75 years or older vs younger patients, with no increase in adverse events. Treatment of only 11 patients 75 years or older with simvastatin-ezetimibe appeared to be needed to prevent 1 event.

Meaning After acute coronary syndrome, elderly patients may benefit from simvastatin-ezetimibe vs simvastatin alone as a higher-intensity therapy to lower lipids with preserved safety.

Methods

Study Protocol

IMPROVE-IT was a prospective, international, multicenter, randomized, double-blind clinical trial involving 18 144 patients enrolled at 1147 sites in 39 countries (eFigure in Supplement 2). The design, detailed methods, and primary results of IMPROVE-IT have been published previously.[17,18] All patients randomized in IMPROVE-IT were included in this analysis. Briefly, patients (with no upper age limit) were enrolled who were hospitalized within the preceding 10 days for an ACS (acute myocardial infarction [MI], with or without ST-segment elevation, or high-risk unstable angina) and who had an LDL-C level of at least 50 mg/dL and a maximum LDL-C level of 125 mg/dL for patients who were not receiving prescription therapy to lower lipid levels or 100 mg/dL for patients who were (to convert LDL-C to millimoles per liter, multiply by 0.0259). Key reasons for exclusion were failure to meet ACS stability criteria within 10 days, planned coronary artery bypass grafting for the ACS event, or estimated creatinine clearance (Cockcroft-Gault equation) of less than 30 mL/min/1.73 m^2 (to convert to milliliters per second per square meter, multiply by 0.0167). The trial protocol is available in Supplement 1. Ethics committees at participating sites reviewed and approved the protocol, and all patients provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Patients were randomly assigned, in a 1:1 ratio, to once-daily simvastatin (40 mg) plus ezetimibe (10 mg) (simvastatin-ezetimibe group) or simvastatin (40 mg) plus placebo (simvastatin monotherapy group). Patients had follow-up visits at 30 days, 4 months, and every 4 months thereafter. For patients in either study group who had LDL-C levels of greater than 79 mg/dL on 2 consecutive measurements, the simvastatin dose was increased to 80 mg in a double-blind manner until June 2011, when a US Food and Drug Administration advisory placed restrictions on the use of 80 mg of simvastatin.[19] The study continued until each patient had been followed up for a minimum of 2.5 years and until the target number of events (5250) was reached. The disposition of patients according to age group during the course of the trial is provided in eTable 1 in Supplement 2.

End Points

The primary efficacy end point was a composite of CVD death, major adverse cardiac event (nonfatal MI, unstable angina leading to hospitalization, coronary revascularization after day 30), or nonfatal stroke.[17] Prespecified safety variables included abnormal liver enzyme and creatine kinase levels, myopathy, rhabdomyolysis, adverse gallbladder-related events, and cancer. Post

hoc safety events included cataracts and adverse neurocognitive events.[20] Further details are provided in the trial protocol in Supplement 1 and in the eMethods in Supplement 2.

Statistical Analysis

Data were analyzed May 29, 2015, through March 13, 2018. As previously described,[17,18] all efficacy and safety analyses were performed in the intention-to-treat population. A nominal 2-sided $P \leq .05$ without adjustment for multiple testing was used for other end points. Estimates of the hazard ratios (HRs) and associated 95% CIs for the comparison of simvastatin-ezetimibe with simvastatin monotherapy were obtained with the use of a Cox proportional hazards regression model. Cox proportional hazards regression assumptions were tested using Schoenfeld residuals. Event rates are Kaplan-Meier failure rates at 7 years. Analyses of the association between treatment effect and age, with age stratified by the categorical groups of younger than 65 vs 65 years or older and younger than 75 vs 75 years or older, were prespecified in the protocol.[17,18] Analyses stratified by ages younger than 65, 65 to 74, and 75 years or older were post hoc comparisons. In a post hoc sensitivity analysis, the association between age as a continuous variable and outcome was also assessed using Cox proportional hazards regression models, with age included as a restricted cubic spline, for each treatment group. Further details are provided in the protocol in Supplement 1 and in the eMethods in Supplement 2.

Results

Patients, Baseline Characteristics, and Clinical Presentation

A total of 18 144 patients (13 728 men [75.7%] and 4416 women [24.3%]; mean [SD] age, 64.1 [9.8] years) were enrolled in IMPROVE-IT from January 1, 2005, through December 31, 2010, of whom 10 173 (56.1%) were younger than 65 years; 5173 (28.5%), aged 65 to 75 years; and 2798 (15.4%), 75 years or older (median age of oldest group, 79.1 years [interquartile range, 77.0-91.8 years]) at randomization. By the end of the trial, the median age of patients 75 years or older at baseline was 85 years (interquartile range, 83-88 years).

The baseline characteristics of patients stratified by age at entry are shown in **Table 1** (and stratified by age and random-

Table 1. Baseline Characteristics of Patients by Age Group at Randomization

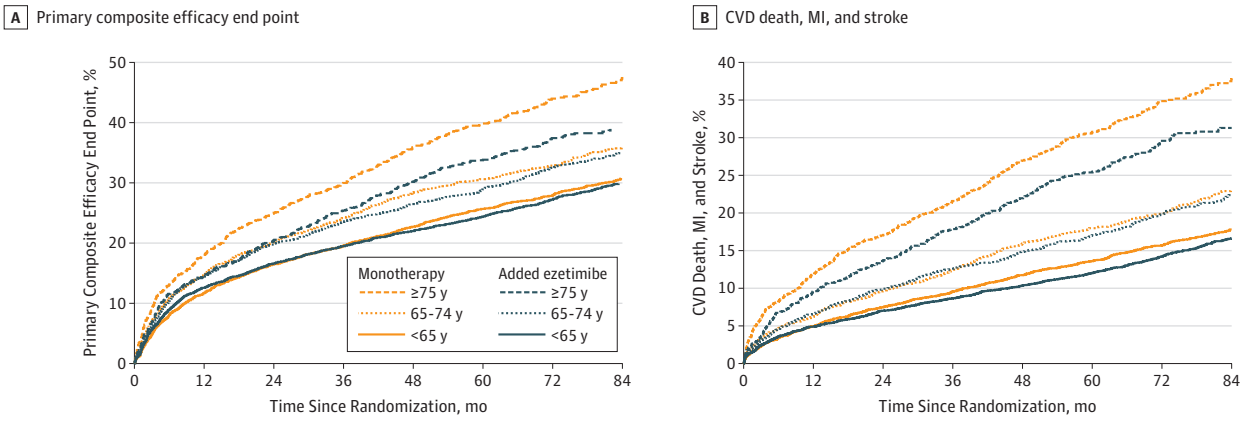
Characteristic	Patient Age Group[a]			
	<65 y (n = 10 173)	65-74 y (n = 5173)	≥75 y (n = 2798)	All (N = 18 144)
Age, y				
Mean (SD)	57.0 (5.3)	69.6 (2.9)	79.8 (3.7)	64.1 (9.8)
Median (IQR)	57.6 (53.5-61.1)	69.5 (67.2-72.1)	79.1 (77.0-81.9)	63.2 (56.8-71.1)
Male	8105 (79.7)	3772 (72.9)	1851 (66.2)	13 728 (75.7)
White	8316 (81.9)	4408 (85.2)	2478 (88.6)	15 202 (83.8)
Weight, kg				
Mean (SD)	85.8 (18.42)	81.3 (15.79)	75.8 (13.54)	83.0 (17.40)
Median (IQR)	84.0 (73.0-95.7)	80.0 (70.0-90.7)	75.0 (66.2-84.4)	81.2 (71.0-92.7)
Body mass index[b]				
Mean (SD)	28.8 (5.57)	28.1 (4.82)	26.8 (4.14)	28.3 (5.21)
Median (IQR)	27.9 (25.1-31.6)	27.5 (24.9-30.6)	26.5 (24.1-29.1)	27.5 (24.9-30.9)
Comorbidities				
Diabetes	2506 (24.6)	1607 (31.1)	820 (29.3)	4933 (27.2)
Hypertension	5622 (55.3)	3476 (67.2)	2039 (72.9)	11 137 (61.4)
Current smoker	4614 (45.4)	1100 (21.3)	264 (9.4)	5978 (32.9)
History of CVD	438 (4.3)	498 (9.6)	330 (11.8)	1266 (7.0)
History of PAD	391 (3.8)	365 (7.1)	249 (8.9)	1005 (5.5)
MI before index ACS	1864 (18.3)	1220 (23.6)	722 (25.8)	3806 (21.0)
CABG before index ACS	611 (6.0)	641 (12.4)	432 (15.4)	1684 (9.3)
Index event				
Statin use before index ACS	2951 (29.0)	2142 (41.4)	1153 (41.2)	6246 (34.4)
Index ACS event				
STEMI	3432 (33.7)	1214 (23.5)	544 (19.4)	5190 (28.6)
NSTEMI	4516 (44.4)	2532 (48.9)	1507 (53.9)	8555 (47.2)
Unstable angina	2217 (21.8)	1425 (27.5)	744 (26.6)	4386 (24.2)
Diagnostic catheterization	9193 (90.4)	4486 (86.7)	2245 (80.2)	15 924 (87.8)
Post-ACS prerandomization PCI	7487 (73.6)	3502 (67.7)	1717 (61.4)	12 706 (70.0)
Medication at randomization				
Aspirin	9935 (97.7)	4989 (96.4)	2668 (95.4)	17 592 (97.0)
β-Blocker	8969 (88.2)	4460 (86.2)	2362 (84.4)	15 791 (87.0)
ACE inhibitor	6717 (66.0)	3265 (63.1)	1762 (63.0)	11 744 (64.7)

Abbreviations:
ACE, angiotensin-converting enzyme;
ACS, acute coronary syndrome;
CABG, coronary artery bypass graft;
CVD, cardiovascular disease;
IQR, interquartile range;
MI, myocardial infarction;
NSTEMI, non–ST-segment elevation myocardial infarction (STEMI);
PAD, peripheral artery disease;
PCI, percutaneous coronary intervention.

[a] Unless otherwise specified, data are expressed as number (percentage) of patients.

[b] Calculated as weight in kilograms divided by height in meters squared.

Figure 1. Kaplan-Meier Curves for Study Outcomes



No. at risk

Monotherapy																
≥75 y	1428	1084	946	852	730	511	349	190	1428	1165	1048	959	838	592	404	224
65-74 y	2520	2043	1864	1725	1550	1093	851	487	2520	2240	2105	1987	1820	1305	1029	582
<65 y	5129	4328	3989	3750	3458	2602	2084	1180	5129	4654	4418	4220	3950	3016	2429	1408
Added ezetimibe																
≥75 y	1370	1078	964	873	774	527	389	225	1370	1142	1046	961	869	596	435	245
65-74 y	2653	2130	1954	1818	1653	1164	860	500	2653	2324	2193	2080	1914	1363	1036	603
<65 y	5044	4163	3883	3684	3421	2593	2052	1181	5044	4530	4333	4182	3941	3030	2442	1417

Outcomes were measured during 84 months of follow-up for patients randomized to simvastatin-ezetimibe (added ezetimibe) therapy vs simvastatin monotherapy (monotherapy) and stratified by age at randomization. CVD indicates cardiovascular disease; MI, myocardial infarction.

ized treatment in eTable 2 in Supplement 2). Compared with younger patients, those 75 years or older had a greater prevalence of hypertension (2039 [72.9%]) and history of CVD (330 [11.8%]) or peripheral vascular disease (249 [8.9%]) and less prevalent cigarette smoking (264 [9.4%]). Statin use before study enrollment was more common among those aged 65-74 years (2142 [41.4%]) and those 75 years or older (1153 [41.2%]). The presenting ACS was more often a non-ST-segment elevation MI or unstable angina among older patients.

Lowering of Lipid Levels According to Age and Treatment

The baseline mean LDL-C level at hospitalization for the index event and the reduction by study treatment at 1 year stratified by age group are shown in eTable 3 in Supplement 2. The percentages of LDL-C level reduction by simvastatin monotherapy and by simvastatin-ezetimibe were similar across the age groups. Within each age group, the LDL-C level achieved was 15 to 17 mg/dL lower with simvastatin-ezetimibe than with simvastatin monotherapy. Effects of treatment on other lipid levels and high-sensitivity C-reactive protein levels are shown in eTable 4 in Supplement 2. When age was considered as a continuous variable, treatment × age interactions for lowering LDL-C levels were not significant, suggesting no apparent differential effect of age on lowering lipid levels by the addition of ezetimibe to simvastatin.

Cardiovascular Outcomes According to Age and Treatment

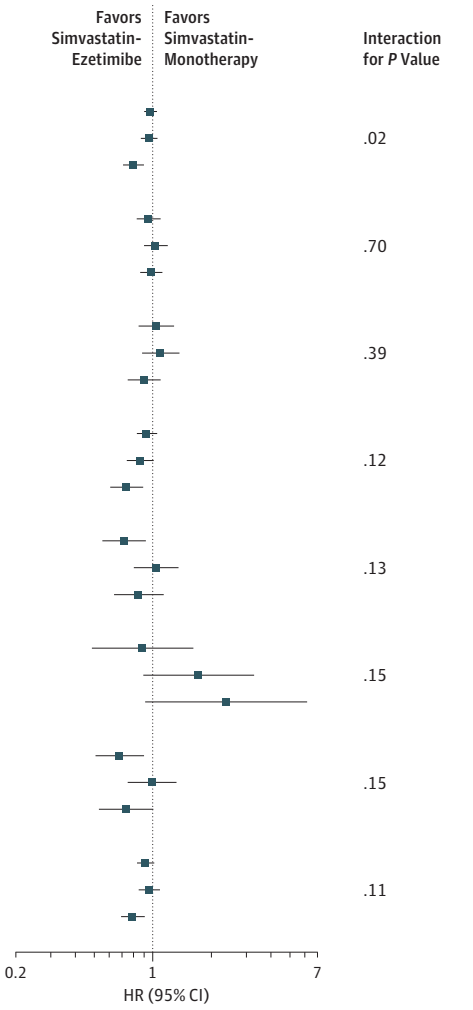
As previously reported, in the overall population of IMPROVE-IT, higher-intensity therapy to lower lipid levels with combined simvastatin-ezetimibe was effective in reducing the primary end point compared with simvastatin monotherapy (32.7% vs 34.7%; HR 0.94; 95% CI, 0.89-0.99; P = .02). As age increased, the rate of the primary end point at 7 years increased in the simvastatin-monotherapy arm to 30.8% for patients younger than 65 years, 35.8% for patients aged 65 to 74 years, and 47.6% for patients 75 years or older (**Figure 1**). For patients 75 years or older, the rate of CVD death, nonfatal MI, unstable angina leading to hospitalization, coronary revascularization after day 30, or nonfatal stroke was lower with simvastatin-ezetimibe within the first 12 months, and the curves continued to diverge during the 7 years of follow-up.

The incidence of the primary end point, select individual and composite end points, and the HR comparing treatment with simvastatin-ezetimibe vs simvastatin monotherapy among patients stratified by age group are shown in **Figure 2**. Treatment with simvastatin-ezetimibe resulted in an absolute reduction of the primary composite end point (7-year Kaplan-Meier rates) for patients younger than 65 years of 0.9% (29.9% vs 30.8%; HR, 0.97; 95% CI, 0.90-1.05), for patients aged 65 to 74 years of 0.8% (35.1% vs 35.9%; HR, 0.96; 95% CI, 0.87-1.06), and for patients 75 years or older of 8.7% (38.9% vs 47.6%; HR, 0.80; 95% CI, 0.70-0.90). When age was analyzed as a categorical variable, the interaction between age and treatment effect for simvastatin-ezetimibe for the primary end point was significant (P = .02 for interaction).

Among patients younger than 75 vs 75 years or older, the numbers needed to treat to prevent 1 primary end point event by treatment with simvastatin-ezetimibe were 125 (95% CI, 113-∞) and 11 (95% CI, 8-23), respectively. Regarding the individual CVD end points of MI and ischemic stroke and the composite end point of CVD death, MI, and stroke, random assignment to simvastatin-ezetimibe was associated with favorable HRs for pa-

Figure 2. Forest Plot of Study Therapy and Event Rates

Event	Total No. of Events	Event Rate at 7 y[a] Simvastatin-Ezetimibe	Event Rate at 7 y[a] Simvastatin-Monotherapy	HR (95% CI)[b]	Interaction for *P* Value
Primary composite end point, age, y					
<65	2707	29.9	30.8	0.97 (0.90-1.05)	
65-74	1590	35.1	35.9	0.96 (0.87-1.06)	.02
≥75	1017	38.9	47.6	0.80 (0.70-0.90)	
All-cause death, age, y					
<65	770	8.4	8.6	0.95 (0.83-1.10)	
65-74	782	18.2	16.9	1.04 (0.90-1.19)	.70
≥75	894	36.3	37.1	0.98 (0.86-1.12)	
CVD, age y					
<65	350	4.0	3.8	1.04 (0.85-1.29)	
65-74	317	8.1	6.8	1.10 (0.88-1.37)	.39
≥75	408	16.3	19.1	0.90 (0.74-1.10)	
Myocardial infarction, age, y					
<65	1070	12.1	13.0	0.93 (0.83-1.05)	
65-74	610	13.5	15.3	0.86 (0.74-1.01)	.12
≥75	415	16.4	21.3	0.74 (0.61-0.89)	
Stroke, age y					
<65	240	2.6	3.4	0.71 (0.55-0.92)	
65-74	221	5.5	5.4	1.04 (0.80-1.36)	.13
≥75	180	8.2	9.3	0.85 (0.63-1.14)	
Hemorrhagic stroke, age, y					
<65	43	0.5	0.6	0.89 (0.49-1.62)	
65-74	39	1.1	0.6	1.72 (0.89-3.31)	.15
≥75	20	1.5	0.6	2.38 (0.91-6.19)	
Ischemic stroke, age, y					
<65	195	2.1	2.8	0.68 (0.51-0.90)	
65-74	185	4.7	4.7	0.99 (0.74-1.32)	.15
≥75	153	6.6	8.4	0.73 (0.53-1.01)	
CVD death/MI, and stroke, age, y					
<65	1483	16.6	17.8	0.92 (0.83-1.02)	
65-74	971	22.4	23.0	0.96 (0.85-1.09)	.11
≥75	794	31.3	38.0	0.79 (0.69-0.91)	



Effect of simvastatin-ezetimibe therapy vs simvastatin monotherapy on 7-year cardiovascular event rates for the primary composite efficacy end point and selected individual, composite component, and safety end points, according to categorical age groups at randomization, including hazard ratios (HRs) and interaction terms. CVD indicates cardiovascular disease; MI, myocardial infarction.

[a] Indicates Kaplan-Meier percentages through 7 years of follow-up.

[b] Computed for each age subgroup level from Cox proportional hazard regression models. All models were adjusted for randomization strata (prior therapy to lower lipid levels, diagnosis of acute coronary syndrome [ACS], and participation in the EARLY ACS study[21]), age group, study treatment, and age group × treatment interaction.

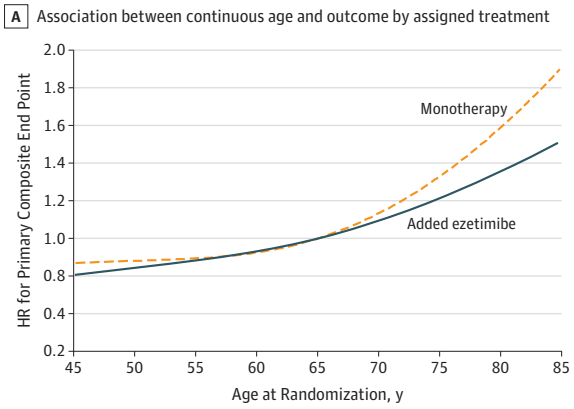
tients in varying age groups, including those 75 years or older. However, none of the formal tests for interaction between age and treatment effect for the individual or other composite end points were significant (Figure 2). No treatment-related difference in all-cause death in any age subgroup occurred.

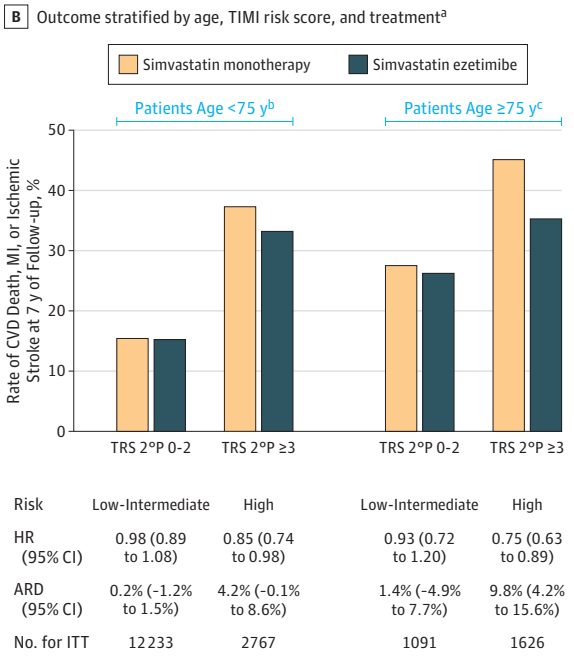
Figure 3A shows the association between age evaluated as a continuous variable and occurrence of the primary end point during follow-up. We found an increasing incidence of the primary end point with increasing age, and, in keeping with the categorical analysis, greater separation of the event curves for treatment groups favoring treatment with simvastatin-ezetimibe with increasing age. In a sensitivity analysis treating age as a continuous variable, the interaction between age and treatment effect was not significant. When patients were stratified by age and clinical risk using the TIMI Risk Score for Secondary Prevention[22] (TRS 2°P) (Figure 3B), it was evident that, compared with simvastatin monotherapy, simvastatin-ezetimibe significantly lowered the risk of CVD death, MI, and ischemic stroke among higher-risk patients (TRS 2°*P* ≥ 3) in those 75 years or older (HR, 0.75; 95% CI, 0.63-0.89; *P* = .001) and those younger than 75 years (HR, 0.85; 95% CI, 0.74-0.98; *P* = .03). The absolute risk reduction by simvastatin-ezetimibe for high-risk patients was 4.2% for patients younger than 75 years of age and 9.8% for patients 75 years or older. For the 3-way interaction among treatment, age group, and TRS 2°P, *P* = .09.

Safety Outcomes According to Age and Treatment

Safety events during treatment stratified by age and randomized treatment assignment are shown in **Table 2**. The rate of rhabdomyolysis and myopathy and the rate of elevation of se-

Figure 3. Evaluation of Age Associated With Outcomes





Risk	Low-Intermediate	High	Low-Intermediate	High
HR (95% CI)	0.98 (0.89 to 1.08)	0.85 (0.74 to 0.98)	0.93 (0.72 to 1.20)	0.75 (0.63 to 0.89)
ARD (95% CI)	0.2% (-1.2% to 1.5%)	4.2% (-0.1% to 8.6%)	1.4% (-4.9% to 7.7%)	9.8% (4.2% to 15.6%)
No. for ITT	12233	2767	1091	1626

A, Association of the primary end point with age at randomization for patients randomized to simvastatin-ezetimibe (added ezetimibe) vs simvastatin monotherapy (monotherapy) using restricted cubic spline analysis. Reference level consists of patients aged 65 years at randomization. B, Rates of cardiovascular disease (CVD) death, myocardial infarction (MI), or ischemic stroke among patients younger than 75 years and 75 years or older. Patients are stratified by TIMI Risk Score for Secondary Prevention (TRS 2°P; 0-2 indicates low-intermediate; ≥3, high) and randomized treatment. ARD indicates absolute risk decrease; HR, hazard ratio; and ITT, intention to treat.

[a] $P < .001$ for trend.

[b] $P = .11$ for interaction.

[c] $P = .18$ for interaction.

rum aspartate aminotransferase or alanine aminotransferase levels were very low, did not increase with age, and were not increased by combined simvastatin-ezetimibe compared with simvastatin monotherapy. The rates of newly diagnosed cancer, cataracts, and neurocognitive events increased with age but were not more frequent among patients assigned to simvastatin-ezetimibe compared with simvastatin monotherapy in any age group. The rates of hemorrhagic stroke were not different between the 2 arms in those 75 years or older (1.5% simvastatin-ezetimibe vs 0.6% simvastatin monotherapy; HR, 2.38; 95% CI, 0.91-6.16; $P = .15$ for interaction). The rates are based on 20 total events in this population, of which 11 occurred without the study drug (>30 days after stopping therapy), with 9 of the 11 events occurring in the simvastatin-ezetimibe arm (eTable 5 in Supplement 2).

Discussion

Recent clinical trials suggest that high-intensity therapy to lower lipid levels with a statin significantly reduces adverse CVD events for patients with established coronary heart disease. However, the use of high-intensity therapy to lower lipid levels among elderly individuals remains controversial, at least in part because of persistent uncertainty regarding whether it confers meaningful clinical benefit and is safe in persons of advanced age. As a result, recent lipid treatment guidelines do not recommend the routine use of high-intensity statin therapy for patients older than 75 years of age.[14-16] These data from IMPROVE-IT, which followed up 2798 patients 75 years or older at baseline whose mean age was older than 85 years at the end of the trial, contribute new information that is relevant to this controversy. First, we found that higher-intensity therapy to lower lipid levels by adding ezetimibe to simvastatin provided a similar reduction in LDL-C levels across all age groups. Second, age was a powerful marker for increased absolute risk of recurrent CVD events that was modifiable with higher-intensity therapy to lower lipid levels. Third, we observed that, compared with younger patients, the absolute risk reduction for the primary end point was substantially greater for patients 75 years or older. As a result, among this older group, only 11 patients need to be treated with simvastatin-ezetimibe to prevent 1 adverse ischemic event. Finally, and importantly, simvastatin-ezetimibe was well tolerated across all age groups.

As noted above, evidence supporting the benefit of lowering lipid levels in elderly individuals has been limited based on subgroup analyses,[23,24] 1 prospective randomized trial among older individuals,[25] and a recent meta-analysis.[12] In these studies, the population included patients aged 65 to 75 years and only a small percentage of patients older than 75 years, and none of the original reports provided evidence specifically among patients 75 years or older. Although the recent Cholesterol Treatment Trialists' meta-analysis[12] observed a benefit of statin therapy for reducing major vascular events among patients older than 75 years, the magnitude of benefit appeared reduced compared with that among younger patients, and the analysis of high- vs moderate-intensity therapy included fewer than 2400 patients. Thus, despite more than a decade of randomized clinical trials of high- vs moderate-intensity therapy to lower lipid levels for secondary prevention involving more than 39 000 participants,[4] reasonable uncertainty remains regarding the clinical utility of high-intensity therapy for elderly patients.

Additional concerns have been raised regarding safety. During the previous decade, several trials of therapy to lower lipid

Table 2. Safety End Points According to Age at Randomization and Treatment

	Patient Age Group by Treatment, No. (%)					
	<65 y		65-74 y		≥75 y	
	Simvastatin Monotherapy (n = 5129)	Simvastatin-Ezetimibe (n = 5044)	Simvastatin Monotherapy (n = 2520)	Simvastatin-Ezetimibe (n = 2653)	Simvastatin Monotherapy (n = 1428)	Simvastatin/Ezetimibe (n = 1370)
Liver-related events						
ALT or AST level or both ≥3 × ULN	108 (2.1)	128 (2.5)	51 (2.0)	60 (2.3)	49 (3.4)	36 (2.6)
Gallbladder-related adverse events	169 (3.3)	138 (2.7)	105 (4.2)	100 (3.8)	47 (3.3)	44 (3.2)
Muscle-related events						
Rhabdomyolysis	6 (0.1)	5 (0.1)	9 (0.4)	5 (0.2)	3 (0.2)	3 (0.2)
Myopathy	4 (0.1)	7 (0.1)	5 (0.2)	7 (0.3)	1 (0.1)	1 (0.1)
Myalgia	52 (1.0)	53 (1.1)	34 (1.3)	25 (0.9)	16 (1.1)	11 (0.8)
Myalgia with CK	17 (0.3)	16 (0.3)	9 (0.4)	5 (0.2)	5 (0.4)	5 (0.4)
Myopathy/rhabdomyolysis/myalgia with CK	27 (0.5)	28 (0.6)	22 (0.9)	16 (0.6)	9 (0.6)	9 (0.7)
Any cancer	368 (7.2)	378 (7.5)	335 (13.3)	339 (12.8)	212 (14.8)	192 (14.0)
Cataracts	106 (2.1)	116 (2.3)	134 (5.3)	151 (5.7)	85 (6.0)	81 (5.9)
Cognitive impairment	110 (2.1)	107 (2.1)	61 (2.4)	72 (2.7)	68 (4.8)	64 (4.7)

Abbreviations: ALT, alanine aminotransferase; AST, aminotransferase; CK, creatine kinase; ULN, upper limit of normal.

levels[26-28] have observed a higher incidence of abnormal liver function test results with higher-dose statin therapy in older adults. The current results from IMPROVE-IT, including more patients 75 years or older than the previous high- vs moderate-intensity statin trials combined, suggest patients 75 years or older with stabilized ACS derive substantial benefit from therapy to lower lipid levels by addition of ezetimibe to a statin regimen compared with less-intensive statin monotherapy, without any significant increase in adverse events. Given the favorable tolerability and safety profile observed in IMPROVE-IT, the addition of ezetimibe to statin therapy represents an important alternative to consider for achieving higher-intensity lowering of lipid levels for elderly patients who have difficulty tolerating higher-dose statins.

A review of randomized trials of statins compared with placebo also raised possible concern regarding an increased risk of hemorrhagic stroke with statin therapy among patients with a history of cerebrovascular disease.[29] Our analyses from IMPROVE-IT showed an excess of 1 hemorrhagic stroke per 1000 patient-years among patients receiving simvastatin-ezetimibe in the subgroup 75 years or older, which was not statistically significant. Given that fewer of the far more common ischemic strokes occurred among elderly patients receiving simvastatin-ezetimibe vs simvastatin monotherapy, no increase in the overall rate of total strokes occurred among elderly patients randomized to higher-intensity simvastatin-ezetimibe therapy.

In clinical practice, elderly patients represent the largest group of those hospitalized for an ACS,[30] and with aging of the population, that number continues to grow. Age is an important marker of increased risk after an ACS, and the risk of death and recurrent CVD events is greatest among the elderly.[2] A recent survey of patients discharged from US hospitals after an ACS found that less than half were prescribed intensive therapy to lower lipid levels, and increasing age was associated with even lower likelihood of receiving the therapy,[31] consistent with a risk-treatment paradox.[32] Of note, elderly patients are not the only high-risk group to benefit from ezetimibe. Large absolute benefits in other high-risk groups in IMPROVE-IT, such as patients with diabetes,[33] patients who have undergone coronary artery bypass graft surgery,[34] patients with prior stroke,[35] and patients with higher TRS 2°P scores,[22] have been observed (Figure 3B). In light of these observations, continuing to treat elderly patients after an ACS with moderate- rather than higher-intensity therapy to lower lipid levels will represent a missed opportunity to incrementally improve long-term outcomes for this high-risk population.

Limitations

Although the analyses of outcomes stratified by the age cutoffs of younger than 65 vs 65 years or older and younger than 75 vs 75 years or older were prespecified in the study protocol, the numbers of patients included in the subgroups may have remained underpowered for particular end points. In addition, the *P* values were not adjusted for multiple comparisons. Although IMPROVE-IT was a large multicenter, multinational trial that enrolled a broad population of patients after an ACS hospitalization, patients were selected for enrollment who fulfilled appropriate inclusion criteria and had no apparent exclusion criteria, including clinical instability. Elderly patients may have been less likely to qualify and/or willing to participate in a clinical trial. Therefore, the generalizability of the observations described to patients excluded from IMPROVE-IT is unknown.

Conclusions

In the IMPROVE-IT trial, patients 75 years or older with stabilized ACS derived substantial benefit from higher-intensity therapy to lower lipid levels with simvastatin-ezetimibe compared with simvastatin monotherapy. Higher-intensity therapy with simvastatin-ezetimibe was not associated with any significant increase in safety issues among older patients compared with simvastatin monotherapy. These results have implications for guideline recommendations regarding therapy to lower lipid levels in elderly individuals.

ARTICLE INFORMATION

Accepted for Publication: May 14, 2019.

Published Online: July 17, 2019. doi:10.1001/jamacardio.2019.2306

Author Contributions: Dr Bach had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Bach, Cannon, Giugliano, Bohula, Braunwald, Blazing.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bach, Bohula, Califf.
Critical revision of the manuscript for important intellectual content: Bach, Cannon, Giugliano, White, Lokhnygina, Califf, Braunwald, Blazing.
Statistical analysis: Cannon, White, Lokhnygina, Bohula.
Obtained funding: Cannon, Braunwald.
Administrative, technical, or material support: Cannon, Braunwald, Blazing.
Supervision: Bach, Cannon, Giugliano, Lokhnygina, Braunwald, Blazing.

Conflict of Interest Disclosures: Dr Bach reported receiving grants from Merck & Co during the conduct of the study; grants from CSL Behring and MyoKardia outside the submitted work; and personal fees from Armaron Bio, Novo Nordisk, and Pharmacosmos outside the submitted work. Dr Cannon reported receiving grants and personal fees from Merck & Co during the conduct of the study; grants from Amgen, Inc, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo Company, Ltd, Janssen Pharmaceutica, and Merck & Co outside the submitted work; and personal fees from Aegerion, Alnylam, Amarin Corporation, Amgen, Inc, Boehringer-Ingelheim, Bristol-Myers Squibb, Corvidia Therapeutics, Eisai Co, Ltd, Innovent, Janssen Pharmaceutica, Kowa Pharmaceuticals America, Inc, Merck & Co, Pfizer, Inc, Regeneron Pharmaceuticals, Inc, and Sanofi-Aventis outside the submitted work. Dr Giugliano reported grants from Merck & Co during the conduct of the study; personal fees from Akcea Therapeutics, Inc, Amarin Corporation, Amgen, Inc, Bristol-Myers Squibb, CVS Caremark, Daiichi Sankyo Company, Ltd, and Pfizer, Inc, outside the submitted work; and grants from Amgen, Inc, and Daiichi Sankyo Company, Ltd, outside the submitted work. Dr Lokhnygina reported receiving grants from Merck & Co during the conduct of the study and grants from Merck & Co, GlaxoSmithKline, and Amylin Pharmaceuticals, Inc (a wholly owned subsidiary of AstraZeneca), outside the submitted work. Dr Bohula reported receiving grants from Merck & Co during the conduct of the study; grants from Eisai Co, Ltd, and Amgen, Inc, outside the submitted work; personal fees from Merck & Co, Novartis, Novo Nordisk, Servier Laboratories, Daiichi Sankyo Company, Ltd, Lexicon, Kowa Pharmaceuticals America, Inc, and Medscape outside the submitted work; and being a member of the TIMI Study Group that has received institutional research grant support through Brigham and Women's Hospital from Abbott Laboratories, Amgen, Inc, Astra Zeneca, Critical Diagnostics, Daiichi Sankyo Company, Ltd, Eisai Co, Ltd, Genzyme, Gilead Sciences, Inc, GlaxoSmithKline, Intarcia Therapeutics, Janssen Research and Development, The Medicines Company, MedImmune, LLC, Merck & Co, Novartis, Pfizer, Inc, Poxel SA, Roche Diagnostics, and Takeda Pharmaceutical Company, Ltd. Dr Califf reported serving on the board of directors for Cytokinetics, Inc, and as chairman of the board of the People-Centered Research Foundation outside the submitted work and personal fees from Verily, Merck & Co, Amgen, Inc, Biogen, Inc, Genentech, and Eli Lilly and Company outside the submitted work. Dr Braunwald reported grants through his institution and uncompensated consultancies and lectures from Merck & Co during the conduct of the study; grants from Daiichi Sankyo Company, Ltd, Novartis, Astra Zeneca, and GlaxoSmithKline outside the submitted work; personal fees from Theravance Biopharma, Inc, Cardurion Pharmaceuticals, MyoKardia, Inc, Medscape, Verve Therapeutics, Sanofi-Aventis, and IV Communications outside the submitted work; and uncompensated consultancies and lectures from Novartis and The Medicines Company outside the submitted work. Dr Blazing reported grants and nonfinancial support from Merck & Co during the conduct of the study and personal fees from Merck & Co and Amgen, Inc, outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by Merck & Co, Inc.

Role of the Funder/Sponsor: The sponsor was involved in the design, management, and data collection of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). The sponsor had no role in the design and conduct of the current study; the analysis and interpretation of the data; the preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication. A draft of the manuscript was provided to the sponsor before submission for publication.

Data Sharing Statement: See Supplement 3.

REFERENCES

1. Avezum A, Makdisse M, Spencer F, et al; GRACE Investigators. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J*. 2005;149(1):67-73. doi:10.1016/j.ahj.2004.06.003

2. Mozaffarian D, Benjamin EJ, Go AS, et al; Writing Group Members; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation*. 2016;133(4):e38-e360.

3. Colby SL, Ortman JM. The Baby Boom Cohort in the United States: 2012 to 2060. Current Population Reports, P25-1141. Washington, DC: US Census Bureau; May 2014. available at https://www.census.gov/content/dam/Census/library/publications/2014/demo/p25-1141.pdf. Accessed October 11, 2016.

4. Fulcher J, O'Connell R, Voysey M, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet*. 2015;385(9976):1397-1405. doi:10.1016/S0140-6736(14)61368-4

5. Ulvenstam G, Bergstrand R, Johansson S, et al. Prognostic importance of cholesterol levels after myocardial infarction. *Prev Med*. 1984;13(4):355-366. doi:10.1016/0091-7435(84)90027-6

6. Kronmal RA, Cain KC, Ye Z, Omenn GS. Total serum cholesterol levels and mortality risk as a function of age: a report based on the Framingham data. *Arch Intern Med*. 1993;153(9):1065-1073. doi:10.1001/archinte.1993.00410090025004

7. Krumholz HM, Seeman TE, Merrill SS, et al. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. *JAMA*. 1994;272(17):1335-1340. doi:10.1001/jama.1994.03520170045034

8. Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. *Lancet*. 2001;358(9279):351-355. doi:10.1016/S0140-6736(01)05553-2

9. Allen Maycock CA, Muhlestein JB, Horne BD, et al; Intermountain Heart Collaborative Study. Statin therapy is associated with reduced mortality across all age groups of individuals with significant coronary disease, including very elderly patients. *J Am Coll Cardiol*. 2002;40(10):1777-1785. doi:10.1016/S0735-1097(02)02477-4

10. Armitage J, Bowman L, Wallendszus K, et al; Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet*. 2010;376(9753):1658-1669. doi:10.1016/S0140-6736(10)60310-8

11. Foody JM, Rathore SS, Galusha D, et al. Hydroxymethylglutaryl-CoA reductase inhibitors in older persons with acute myocardial infarction: evidence for an age-statin interaction. *J Am Geriatr Soc*. 2006;54(3):421-430. doi:10.1111/j.1532-5415.2005.00635.x

12. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet*. 2019;393(10170):407-415. doi:10.1016/S0140-6736(18)31942-1

13. Fleg JL, Forman DE, Berra K, et al; American Heart Association Committees on Older Populations and Exercise Cardiac Rehabilitation and Prevention of the Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Lifestyle and Cardiometabolic Health. Secondary prevention of atherosclerotic cardiovascular disease in older adults: a scientific statement from the American Heart Association. *Circulation*. 2013;128(22):2422-2446. doi:10.1161/01.cir.0000436752.99896.22

14. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25, pt B):2889-2934. doi:10.1016/j.jacc.2013.11.002

15. Grundy SM, Stone NJ, Bailey AL, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/

NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [posted online November 10, 2018]. *J Am Coll Cardiol*. 2018;S0735-1097(18)39033-8. doi:10.1016/j.jacc.2018.11.002

16. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2017;70(14):1785-1822. doi:10.1016/j.jacc.2017.07.745

17. Cannon CP, Blazing MA, Giugliano RP, et al; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387-2397. doi:10.1056/NEJMoa1410489

18. Cannon CP, Giugliano RP, Blazing MA, et al; IMPROVE-IT Investigators. Rationale and design of IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. *Am Heart J*. 2008;156(5):826-832. doi:10.1016/j.ahj.2008.07.023

19. US Food and Drug Administration. FDA Drug Safety Communication: new restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. https://www.fda.gov/drugs/drugsafety/ucm256581.htm. Updated December 15, 2011. Accessed December 13, 2013.

20. Giugliano RP, Wiviott SD, Blazing MA, et al. Long-term safety and efficacy of achieving very low levels of low-density lipoprotein cholesterol: a prespecified analysis of the IMPROVE-IT trial. *JAMA Cardiol*. 2017;2(5):547-555. doi:10.1001/jamacardio.2017.0083

21. Giugliano RP, White JA, Bode C, et al; EARLY ACS Investigators. Early versus delayed, provisional eptifibatide in acute coronary syndromes. *N Engl J Med*. 2009;360(21):2176-2190. doi:10.1056/NEJMoa0901316

22. Bohula EA, Morrow DA, Giugliano RP, et al. Atherothrombotic risk stratification and ezetimibe for secondary prevention. *J Am Coll Cardiol*. 2017;69(8):911-921. doi:10.1016/j.jacc.2016.11.070

23. Lewis SJ, Moye LA, Sacks FM, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range: results of the Cholesterol and Recurrent Events (CARE) trial. *Ann Intern Med*. 1998;129(9):681-689. doi:10.7326/0003-4819-129-9-199811010-00002

24. Hunt D, Young P, Simes J, et al. Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: results from the LIPID trial. *Ann Intern Med*. 2001;134(10):931-940. doi:10.7326/0003-4819-134-10-200105150-00007

25. Shepherd J, Blauw GJ, Murphy MB, et al; PROSPER Study Group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360(9346):1623-1630. doi:10.1016/S0140-6736(02)11600-X

26. Wenger NK, Lewis SJ, Herrington DM, Bittner V, Welty FK; Treating to New Targets Study Steering Committee and Investigators. Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. *Ann Intern Med*. 2007;147(1):1-9. doi:10.7326/0003-4819-147-1-200707030-00002

27. Deedwania P, Stone PH, Bairey Merz CN, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). *Circulation*. 2007;115(6):700-707. doi:10.1161/CIRCULATIONAHA.106.654756

28. Cannon CP, Braunwald E, McCabe CH, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350(15):1495-1504. doi:10.1056/NEJMoa040583

29. Vergouwen MDI, de Haan RJ, Vermeulen M, Roos YB. Statin treatment and the occurrence of hemorrhagic stroke in patients with a history of cerebrovascular disease. *Stroke*. 2008;39(2):497-502. doi:10.1161/STROKEAHA.107.488791

30. Steg PG, Goldberg RJ, Gore JM, et al; GRACE Investigators. Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE). *Am J Cardiol*. 2002;90(4):358-363. doi:10.1016/S0002-9149(02)02489-X

31. Javed U, Deedwania PC, Bhatt DL, et al. Use of intensive lipid-lowering therapy in patients hospitalized with acute coronary syndrome: An analysis of 65,396 hospitalizations from 344 hospitals participating in Get With The Guidelines (GWTG). *Am Heart J*. 2011;161(2):418-424.e1, 3. doi:10.1016/j.ahj.2010.12.014

32. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. *JAMA*. 2004;291(15):1864-1870. doi:10.1001/jama.291.15.1864

33. Giugliano RP, Cannon CP, Blazing MA, et al; IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation*. 2018;137(15):1571-1582. doi:10.1161/CIRCULATIONAHA.117.030950

34. Eisen A, Cannon CP, Blazing MA, et al; IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators. The benefit of adding ezetimibe to statin therapy in patients with prior coronary artery bypass graft surgery and acute coronary syndrome in the IMPROVE-IT trial. *Eur Heart J*. 2016;37(48):3576-3584. doi:10.1093/eurheartj/ehw377

35. Bohula EA, Wiviott SD, Giugliano RP, et al. Prevention of stroke with the addition of ezetimibe to statin therapy in patients with acute coronary syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation*. 2017;136(25):2440-2450. doi:10.1161/CIRCULATIONAHA.117.029095