

Baseline Low-Density Lipoprotein Cholesterol and Clinical Outcomes of Combining Ezetimibe With Statin Therapy in IMPROVE-IT



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ABSTRACT

BACKGROUND The 2018 U.S. cholesterol management guideline recommends additional lipid-lowering therapy with ezetimibe for secondary prevention in very high-risk patients with low-density lipoprotein cholesterol (LDL-C) ≥ 70 mg/dL despite maximally tolerated statin.

OBJECTIVES The purpose of this study was to evaluate the relationship between baseline LDL-C above and below 70 mg/dL and the benefit of adding ezetimibe to statin in patients post-acute coronary syndrome (ACS).

METHODS IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) was a double-blind, placebo-controlled, randomized trial of ezetimibe/simvastatin vs placebo/simvastatin in post-ACS patients followed for 6 years (median). A total of 17,999 patients were stratified by LDL-C at qualifying event into 3 groups (50- $<$ 70, 70- $<$ 100, and 100-125 mg/dL). The primary endpoint was a composite of cardiovascular death, major coronary events, or stroke.

RESULTS Absolute differences in median LDL-C achieved at 4 months between treatment arms were similar (17-20 mg/dL). The effect of ezetimibe/simvastatin vs placebo/simvastatin on primary endpoint was consistent regardless of baseline LDL-C of 50- $<$ 70 mg/dL (HR: 0.92 [95% CI: 0.80-1.05]), 70- $<$ 100 mg/dL (HR: 0.93 [95% CI: 0.87-1.01]), or 100-125 mg/dL (HR: 0.94 [95% CI: 0.86-1.03]; *P* interaction = 0.95). Normalized relative risk reductions per 1-mmol/L difference in achieved LDL-C at 4 months between treatment arms were 21% in patients with baseline LDL-C of 50- $<$ 70 mg/dL, 16% in those with 70- $<$ 100 mg/dL, and 13% in those with 100-125 mg/dL (*P* interaction = 0.91). No significant treatment interactions by baseline LDL-C were present for safety endpoints.

CONCLUSIONS Adding ezetimibe to statin consistently reduced the risk for cardiovascular events in post-ACS patients irrespective of baseline LDL-C values, supporting the use of intensive lipid-lowering therapy with ezetimibe even in patients with baseline LDL-C $<$ 70 mg/dL. (IMPROVE-IT: Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin [Ezetimibe/Simvastatin] vs Simvastatin [P04103]; [NCT00202878](https://doi.org/10.1016/j.jacc.2021.08.011)) (J Am Coll Cardiol 2021;78:1499-1507)
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Low-density lipoprotein cholesterol (LDL-C) has been well established as a modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD) (1,2). Lowering LDL-C has been an integral part of the treatment of patients with established ASCVD or a high risk for ASCVD, with statins representing the foundation of pharmacotherapy (3,4). A meta-analysis of 26 statin trials by

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ASCVD = atherosclerotic cardiovascular disease

CTTC = Cholesterol Treatment Trialists Collaboration

LDL-C = low-density lipoprotein cholesterol

MI = myocardial infarction

the Cholesterol Treatment Trialists Collaboration (CTTC) demonstrated a 22% relative risk reduction in major vascular events per 1-mmol/L reduction in LDL-C that was consistent across baseline LDL-C levels, even down to <2 mmol/L (77.3 mg/dL), although only a small proportion of patients started at such low levels of LDL-C (5). The influence of baseline LDL-C level, however, on the clinical benefit of adding nonstatin therapy on a background statin therapy remains to be fully investigated.

SEE PAGE 1508

IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) showed that the addition of ezetimibe 10 mg to simvastatin 40 mg significantly reduced recurrent cardiovascular (CV) events in patients stabilized after an acute coronary syndrome (ACS) (6). The guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA) endorsed adding ezetimibe if the LDL-C is ≥ 70 mg/dL despite maximal LDL-C-lowering therapy with statin in very high-risk patients with established ASCVD (7). Because IMPROVE-IT enrolled some patients with an LDL-C <70 mg/dL, this presents an opportunity to investigate the need for such a cutoff.

The objective of this analysis from IMPROVE-IT was to evaluate the relationship between baseline LDL-C level and the benefit of intensive lipid-lowering therapy (LLT) with the addition of ezetimibe to statin therapy in post ACS patients.

METHODS

STUDY DESIGN AND POPULATION. IMPROVE-IT was a randomized, double-blind, placebo-controlled trial that enrolled 18,144 patients hospitalized within the preceding 10 days with ACS with an LDL-C level of 50-100 mg/dL (if chronically taking prior prescription LLT) or 50-125 mg/dL (otherwise) (6,8). Patients were randomized to receive either ezetimibe 10 mg plus simvastatin 40 mg (ezetimibe/simvastatin) or matching placebo plus simvastatin 40 mg once daily (placebo/simvastatin), and were followed up for a median of 6 years (interquartile range [IQR]: 4.3-7.1 years). During the trial, patients in either treatment group who had LDL-C levels >79 mg/dL on 2 consecutive measurements had the simvastatin dose increased to 80 mg. In 2011 (after enrollment completed), in accordance with the U.S. Food and Drug Administration guidance for limiting the use of

simvastatin 80 mg, patients who had been receiving simvastatin 80 mg for <1 year were dose-reduced to 40 mg, and future uptitration to 80 mg simvastatin was not permitted. Key exclusion criteria were baseline ezetimibe use in combination with a statin, treatment with a lipid-lowering regimen more potent than simvastatin 40 mg daily, clinical instability, creatinine clearance <30 mL/min, or active liver disease. Other aspects of study design and methods were reported previously (6,8). All patients provided written informed consent, and the protocol was approved by the ethics committee at each participating center.

ENDPOINTS. In this analysis, the prespecified efficacy endpoints of the trial were used (6,8). The primary efficacy endpoint was a composite of death from CV disease, a major coronary event (nonfatal myocardial infarction [MI], documented unstable angina requiring hospital admission, or coronary revascularization occurring at least 30 days after randomization), or stroke (ischemic or hemorrhagic). The 3 secondary efficacy endpoints were as follows: 1) a composite of death from any cause, major coronary event, or stroke; 2) a composite of death from coronary heart disease, MI, or urgent coronary revascularization at least 30 days after randomization; and 3) a composite of CV death, MI, hospitalization for unstable angina, all arterial revascularization at least 30 days after randomization, or stroke.

Prespecified safety endpoints included abnormal elevations of liver enzyme and creatine kinase levels, myopathy, rhabdomyolysis, hepatobiliary events, cancer, and adverse events leading to study drug discontinuation. Neurocognitive events were identified in a post hoc manner as previously described (9). All safety endpoints, except for adverse events leading to study drug discontinuation and neurocognitive events, were independently adjudicated by a clinical events committee blinded to treatment assignment.

STATISTICAL ANALYSIS. In this analysis from the IMPROVE-IT trial, patients were categorized into 3 subgroups according to LDL-C concentration at the time of the qualifying event, hereafter "baseline LDL-C." If an LDL-C was measured within 24 hours after admission, this value was used as the baseline. However, if no measurement was available, then an LDL-C measurement obtained within the prior 6 months was used as the baseline, provided the patient had no changes in LLT and had been clinically stable until the qualifying ACS event. The baseline LDL-C concentration differed from the value at randomization, which was collected at a median of

5 days (IQR: 3-8 days) after admission for the qualifying ACS. LDL-C level at 4 months was used for acquired LDL-C value on treatment, because LDL-C was stable from month 4 through the 6-year median follow-up, as reported previously (9).

Cut points for baseline LDL-C concentration (50-<70, 70-<100, or 100-125 mg/dL) were based on the Adult Treatment Panel III Guideline Update 2004 (10) and were not prespecified. Baseline characteristics are presented as frequencies and percentages for categorical variables and as medians and IQRs for continuous variables. Comparisons between patients by LDL-C concentration at baseline were made using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Time to first event efficacy analyses were performed by intention-to-treat using Cox proportional hazards modeling with randomized treatment (ezetimibe/simvastatin vs placebo/simvastatin) and randomization stratification factors (prior use of LLT, type of ACS, and status with respect to enrollment in the concurrent EARLY ACS [Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome] trial) as covariates (8,11). The proportional hazard assumption was assessed using Schoenfeld residuals and was not violated. All presented event rates are 7-year Kaplan-Meier estimates. Effect modification of ezetimibe treatment effect by subgroup was tested by incorporating interaction terms into the Cox models. For the analysis of HR normalized for the change in LDL-C level on treatment, we used the approach previously reported by the CTT collaborators in which missing values for LDL-C at 4 months were imputed by using the baseline LDL-C in the calculation of normalized HR per 1-mmol/L difference in achieved LDL-C at 4 months between treatment arms (5,6). A competing-risk analysis based on Fine and Gray's proportional hazards model for the subdistribution of competing risks of non-CV death was performed. Negative binomial regression models were performed to compare the total number of endpoints between patients in the ezetimibe/simvastatin and placebo/simvastatin groups using methods previously described (12). Landmark analyses were performed using the primary outcome after 4 months for the ezetimibe/simvastatin vs placebo/simvastatin comparison in which the patients who experienced events prior to 4 months were excluded. All tests were 2-sided, and a P value <0.05 was considered significant. Analyses were performed using SAS version 9.4 (SAS Institute). Values of P < 0.05 were considered to signify nominal statistical significance. No adjustments were made for multiple comparisons.

RESULTS

The analysis cohort included 17,999 patients with baseline LDL-C data at the qualifying ACS event enrolled in the IMPROVE-IT. Of these, 8,990 patients were randomized to ezetimibe/simvastatin and 9,009 to placebo/simvastatin. Baseline characteristics stratified by baseline LDL-C (50-<70, 70-<100, or 100-125 mg/dL) are shown in **Table 1**. Patients with lower LDL-C at baseline were older, more likely men, had a greater prevalence of atherosclerotic risk factors and CV diseases, and were more likely on chronic statin therapy before admission. Baseline characteristics were substantially similar between treatment arms within each baseline LDL-C group (**Supplemental Table 1**).

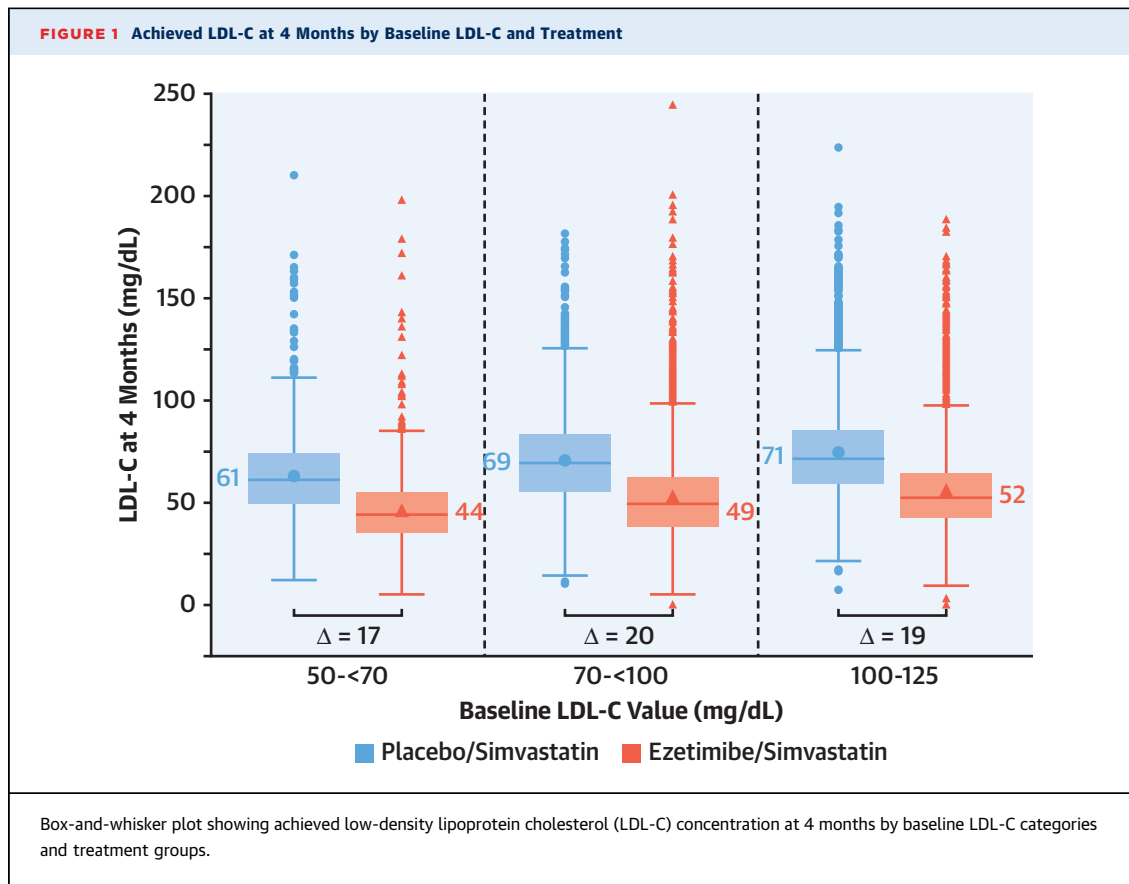
LDL-C AT BASELINE AND AFTER 4 MONTHS. The median baseline LDL-C levels were 62 mg/dL (IQR: 57-66 mg/dL), 86 mg/dL (IQR: 79-93 mg/dL), and 113 mg/dL (IQR: 106-120 mg/dL) in the 3 groups stratified by baseline LDL-C (**Table 1, Supplemental Figures 1 and 2**). A significant and progressively greater absolute reduction in LDL-C occurred from baseline to month 4 as the baseline LDL-C increased in both treatment arms (**Supplemental Figures 1 and 2**). However, the absolute differences in median LDL-C achieved at 4 months between treatment arms were similar (17-20 mg/dL), regardless of the baseline LDL-C group ($P = 0.64$) (**Figure 1**). Using the approach that was used by the CTT collaborators (5), the absolute differences in LDL-C achieved at 4 months between treatment arms were also similar (14-16 mg/dL) across the 3 baseline LDL-C groups ($P = 0.19$) (**Figure 2**).

CLINICAL EFFICACY OF EZETIMIBE/SIMVASTATIN VS PLACEBO/SIMVASTATIN BY BASELINE LDL-C. In the overall trial, the HR for the primary endpoint at 7 years with ezetimibe/simvastatin vs placebo/simvastatin was 0.93 (95% CI: 0.89-0.99). The relative risk reductions in the primary endpoint with ezetimibe/simvastatin vs placebo/simvastatin were consistent among the 3 baseline LDL-C categories ($P = 0.95$) (**Central Illustration, Supplemental Figure 3**). In the group with baseline LDL-C of 50-<70 mg/dL, the primary endpoint occurred in 38.3% vs 42.2% (HR: 0.92; 95% CI: 0.80-1.05) in the ezetimibe/simvastatin vs placebo/simvastatin arms. The absolute risk reductions in the primary endpoint were also consistent among the 3 baseline LDL-C categories ($P = 0.63$) (**Supplemental Figure 4**). A sensitivity analysis using a competing risk model for non-CV death (**Supplemental Figure 5**) and analyzing total events (**Supplemental Table 2**) showed similar

TABLE 1 Baseline Characteristics by Baseline LDL-C Categories				
	50-<70 mg/dL (n = 2,480)	70-<100 mg/dL (n = 8,097)	100-125 mg/dL (n = 7,422)	P Value
Demographics				
Age, y	66 (59-74)	64 (57-72)	62 (55-69)	<0.001
Male	1,927 (78)	6,049 (75)	5,645 (76)	0.006
White	2,075 (84)	6,716 (83)	6,284 (85)	0.01
Coexisting conditions				
Diabetes	985 (40)	2,462 (30)	1,454 (20)	<0.001
Hypertension	1,780 (72)	5,342 (66)	3,932 (53)	<0.001
Current smoking	620 (25)	2,457 (30)	2,856 (39)	<0.001
Heart failure	207 (8)	399 (5)	177 (2)	<0.001
Before index ACS event				
Cardiovascular history				
Prior myocardial infarction	957 (39)	2,120 (26)	699 (9)	<0.001
Prior percutaneous coronary intervention	916 (37)	2,040 (25)	581 (8)	<0.001
Prior coronary artery bypass graft surgery	436 (18)	974 (12)	262 (4)	<0.001
Prior stroke/transient ischemic attack	230 (9)	530 (7)	308 (4)	<0.001
Medication				
Statin	1,772 (72)	3,954 (49)	477 (6)	<0.001
At index ACS event				
Type of event				
Myocardial infarction with ST-segment elevation	474 (19)	2,060 (25)	2,623 (35)	<0.001
Myocardial infarction without ST-segment elevation	1,106 (45)	3,790 (47)	3,601 (49)	
Unstable angina	898 (36)	2,245 (28)	1,198 (16)	
Prerandomization percutaneous coronary intervention	1,517 (61)	5,527 (68)	5,575 (75)	<0.001
Medication				
Statin	2,122 (86)	6,465 (80)	5,345 (72)	<0.001
Baseline laboratory values				
Total cholesterol, mg/dL	128 (116-140)	153 (141-166)	181 (170-193)	NA
LDL-C, mg/dL	62 (57-66)	86 (79-93)	113 (106-112)	NA
HDL-C, mg/dL	39 (31-48)	39 (33-49)	41 (34-50)	<0.001
Non-HDL-C, mg/dL	85 (77-97)	110 (101-122)	138 (128-149)	NA
Triglycerides, mg/dL	115 (80-171)	119 (84-172)	123 (88-172)	0.003
C-reactive protein, mg/L	5.0 (2.0-18.2)	5.4 (2.0-19.0)	5.0 (2.0-16.0)	0.94
Creatinine clearance, mL/min	79 (61-100)	83 (64-106)	88 (70-110)	<0.001
At randomization				
Days from ACS to randomization	5.0 (3.0-8.0)	5.0 (3.0-8.0)	5.0 (3.0-7.0)	0.013
TIMI Risk Score for Secondary Prevention				
0-1	731 (30)	3,252 (41)	3,992 (55)	<0.001
2	772 (32)	2,406 (30)	2,074 (29)	
≥3	909 (38)	2,257 (29)	1,198 (17)	
Medications				
Aspirin	2,388 (96)	7,826 (97)	7,252 (98)	<0.001
Thienopyridine	2,050 (83)	6,927 (86)	6,599 (89)	<0.001
Beta-blocker	2,139 (86)	7,031 (87)	6,507 (88)	0.25
Renin-angiotensin-aldosterone inhibitor	1,909 (77)	6,171 (76)	5,520 (74)	0.006
Laboratory values				
Total cholesterol, mg/dL	129 (116-145)	146 (129-163)	159 (141-179)	NA
LDL-C, mg/dL	61 (51-72)	76 (64-89)	90 (76-106)	NA
HDL-C, mg/dL	39 (33-47)	40 (34-48)	39 (34-47)	0.005
Non-HDL-C, mg/dL	88 (75-103)	104 (89-120)	118 (100-137)	NA
Triglycerides, mg/dL	125 (94-169)	127 (97-169)	128 (100-166)	0.08
C-reactive protein, mg/L	7.9 (3.1-23.0)	9.0 (3.6-25.1)	11.6 (4.6-29.3)	<0.001

Values are median (interquartile range) or n (%). TIMI Risk Score for Secondary Prevention assigned a point for each of the following 9 risk factors: heart failure, hypertension, age ≥75 y, diabetes mellitus, prior stroke, prior coronary artery bypass graft surgery, peripheral vascular disease, estimated glomerular filtration rate <60 mL/min/1.73 m², and current smoking.

ACS = acute coronary syndrome; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NA = not applicable.



findings (P interaction = 0.91 and 0.98, respectively). Effects of ezetimibe/simvastatin vs placebo/simvastatin on individual components of primary endpoint by 3 baseline LDL-C categories were shown in Supplemental Figure 6.

When baseline LDL-C was analyzed as a continuous variable, the benefit of ezetimibe/simvastatin over placebo/simvastatin was also similar across the range of baseline LDL values from 50 to 125 mg/dL (P interaction = 0.69) (Figure 3). Using the approach that was used by the CTT collaborators, normalized relative risk reductions in the primary endpoint per 1-mmol/L difference in achieved LDL-C at 4 months between treatment arms were 16% in the overall trial, 21% in patients with baseline LDL-C of 50-<70 mg/dL, 16% in those with 70-<100 mg/dL, and 13% in those with 100-125 mg/dL (P interaction = 0.91) (Figure 2). Landmark analysis after 4 months also showed consistent normalized relative risk reductions across the 3 baseline LDL-C groups (P interaction = 0.71) (Supplemental Figure 7).

Intensive LLT with ezetimibe/simvastatin compared with placebo/simvastatin also consistently reduced the 7-year event rates of each of the 3 secondary endpoints regardless of baseline LDL-C group

(Supplemental Figure 8). Normalized relative risk reductions in the 3 secondary endpoints per 1-mmol/L difference in achieved LDL-C between treatment arms were shown in Supplemental Figure 9.

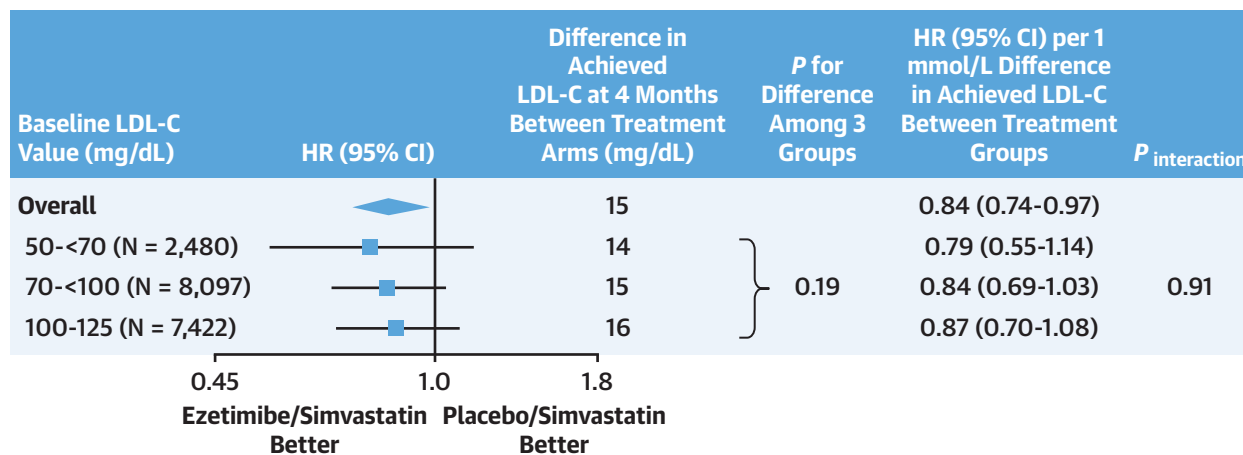
SAFETY ENDPOINTS BY BASELINE LDL-C CATEGORIES.

Rates of discontinuation caused by adverse events were similar with ezetimibe/simvastatin compared with placebo/simvastatin across baseline LDL-C categories (7.2% vs 7.8%; P = 0.53; 7.7% vs 7.2%; P = 0.39; 8.6% vs 8.0%; P = 0.43 for baseline LDL-C of 50-<70, 70-<100, and 100-125 mg/dL, respectively, with a treatment-subgroup P interaction of 0.60) (Supplemental Table 3). There were no significant treatment interactions by baseline LDL-C categories for any of the other 10 safety endpoints.

DISCUSSION

Our major finding is that intensive LLT with ezetimibe/simvastatin compared with placebo/simvastatin in patients post-ACS consistently reduced CV events regardless of baseline LDL-C. An important clinical finding is that the reductions in the primary composite endpoint of death from CV disease, major coronary events, or nonfatal stroke in patients with

FIGURE 2 Normalized Effect of Ezetimibe/Simvastatin on Primary Endpoint by Baseline LDL-C

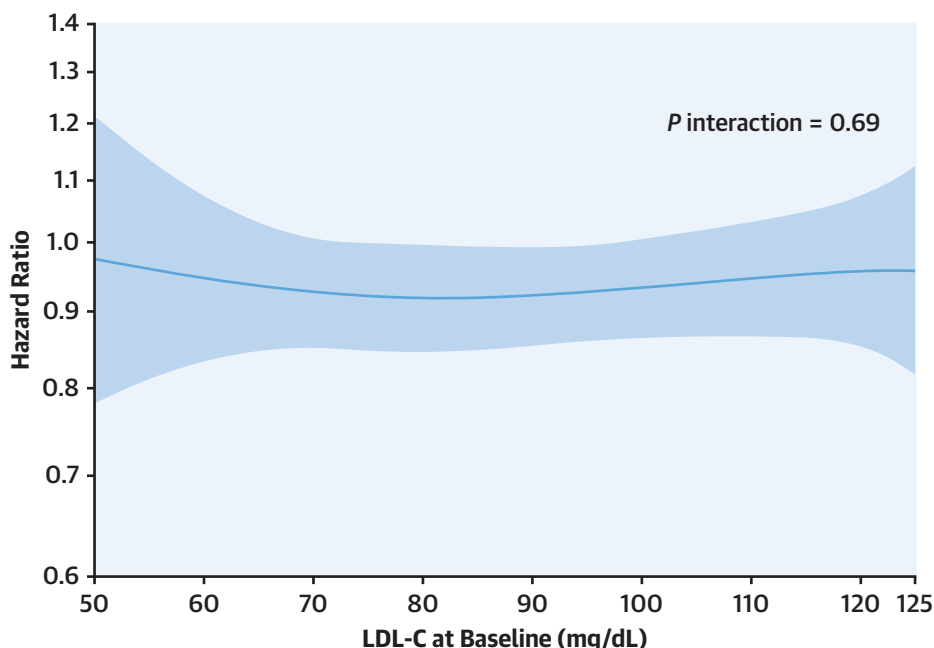


Forest plot showing normalized effect of ezetimibe/simvastatin vs placebo/simvastatin on the primary endpoint (cardiovascular death, major coronary events, or stroke) per 1-mmol/L difference in achieved low-density lipoprotein cholesterol (LDL-C) at 4 months.

baseline LDL-C of 50-<70 mg/dL were similar to the reductions observed in patients with higher baseline LDL-C. These findings suggest that the magnitude of clinical benefit of ezetimibe/simvastatin in post-ACS patients is consistent and robust across the spectrum of baseline LDL-C from 50 to 125 mg/dL. There were

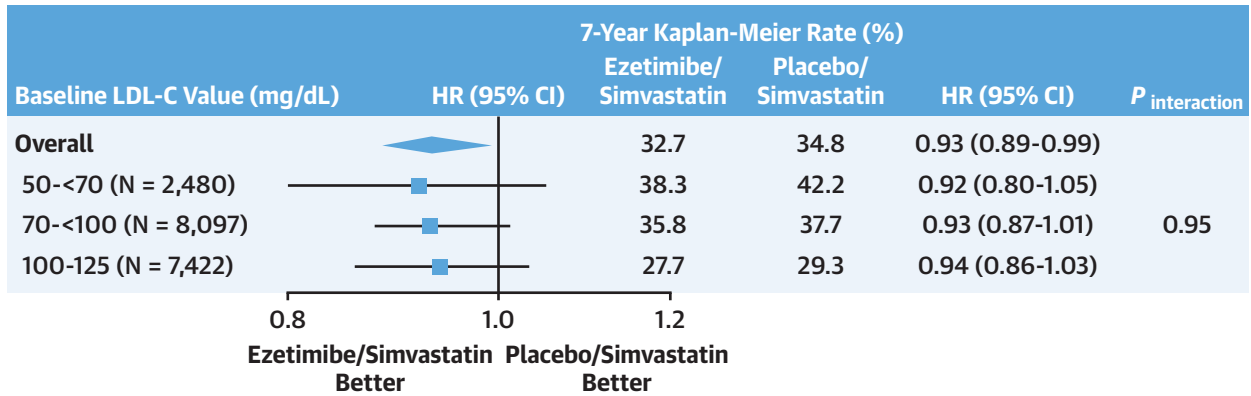
also no treatment interactions by baseline LDL-C categories for any of the 11 prespecified safety endpoints examined. Our results extend current guideline recommendations (7), which endorse the addition of ezetimibe to statin in patients post-ACS with baseline LDL-C of ≥ 70 mg/dL, demonstrating

FIGURE 3 Effect of Ezetimibe/Simvastatin on Primary Endpoint Across Baseline LDL-C Concentration



Hazard ratio for effect of ezetimibe/simvastatin vs placebo/simvastatin on the primary endpoint (cardiovascular death, major coronary events, or stroke) across baseline low-density lipoprotein cholesterol (LDL-C) concentration when baseline LDL-C was analyzed as a continuous variable.

CENTRAL ILLUSTRATION Effect of Ezetimibe/Simvastatin on Primary Endpoint by Baseline Low-Density Lipoprotein Cholesterol Categories



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Forest plot showing effect of ezetimibe/simvastatin vs placebo/simvastatin on the primary endpoint (cardiovascular death, major coronary events, or stroke) by baseline low-density lipoprotein cholesterol (LDL-C) categories.

that a similar benefit applies to patients with baseline LDL-C of 50-<70 mg/dL.

Our findings extend those reports on the PCSK9 (proprotein convertase subtilisin kexin 9) inhibitor evolocumab which showed similar reduction in CV events regardless of whether the baseline LDL-C was <70 or ≥70 mg/dL (13). Several studies have shown that aggressive reduction of LDL-C with non-statin therapies to very low achieved LDL-C levels (even below 20 mg/dL) is associated with lower rates of CV events without adversely affecting safety (14-19). However, these patients were not randomized to different achieved LDL-C levels, and thus the optimal target LDL-C remains unknown. Indeed, the ACC/AHA and European Society of Cardiology/European Atherosclerosis Society cholesterol guidelines take different approaches regarding further intensification of LLT in very high-risk patients. The ACC/AHA guideline endorses adding ezetimibe if the LDL-C is at or above the *threshold* of 70 mg/dL despite maximal tolerated statin in very high-risk patients with established ASCVD. Meanwhile the European Society of Cardiology/European Atherosclerosis Society guideline calls for further intensification of LLT to reduce the LDL-C to a *goal* of <55 mg/dL in these patients (7,20).

It is noteworthy that the 8% risk reduction in CV events with ezetimibe/simvastatin in patients with baseline LDL-C of 50-<70 mg/dL was virtually the same as the risk reductions (6%-7%) observed in the groups with higher baseline LDL-C levels. The addition of ezetimibe resulted in similar LDL-C reductions

from baseline to month 4 across the 3 categories of baseline LDL-C, which may, in part, explain the consistency for the clinical benefit observed. Indeed, we observed that normalized relative risk reduction in the primary endpoint per 1-mmol/L difference in achieved LDL-C at 4 months between treatment arms was 21% in patients with baseline LDL-C of 50-<70 mg/dL. This finding substantially corresponds with the estimate of a 22% relative risk reduction in major vascular events per 1-mmol/L reduction in LDL-C from the CTTC analysis (5). The findings that we observed with the “nonstatin” ezetimibe in IMPROVE-IT are also in line with the data with other nonstatin therapies (13,17,21,22).

Our observation that ezetimibe/simvastatin consistently reduced CV events regardless of baseline LDL-C levels has important clinical implications. Because there were no offsetting safety concerns with intensive LDL-C to achieved values well below 70 mg/dL with ezetimibe (9) or with other LLT (15,23), our data support adding ezetimibe to statin therapy in patients post-ACS with baseline LDL-C of 50-<70 mg/dL.

STUDY LIMITATIONS. First, although the IMPROVE-IT was a large trial with long follow-up, and hence a large number of patients experienced the primary endpoint, the trial was not designed to specifically detect differences in treatment effect as a function of baseline LDL-C. Second, the cut points of 70 and 100 mg/dL were post hoc, but were selected given the treatment targets and thresholds cited in guidelines

(7,10,20). Third, we only studied patients hospitalized with recent ACS with a minimum LDL-C of 50 mg/dL. Fourth, the background statin was 40 mg simvastatin (with up-titration to 80 mg in selected patients), which does not represent a maximally potent statin regimen, as is recommended in current guidelines. Fifth, the missing LDL-C values at 4 months in 2,569 patients (14.3%) were imputed by using the baseline values in the calculation of normalized HR per 1-mmol/L difference in achieved LDL-C to reproduce the CTTC approach, as is standard in the lipid field (5). Sixth, although we present some analyses with relative risk reductions normalized per 1-mmol/L reduction in LDL-C, it is important to recognize that for a given patient, the benefit of LDL-C reduction will be a function of the absolute degree of LDL-C lowering achieved in that patient. Seventh, our data are from a randomized controlled trial with strict inclusion/exclusion criteria, including that the patients have high-risk ACS, and thus may not apply to all patients seen in clinical practice. Finally, the population with baseline LDL-C of 50-<70 mg/dL was relatively smaller and at increased risk at baseline compared with those with baseline LDL-C of 70-<100 and 100-125 mg/dL.

CONCLUSIONS

Adding ezetimibe to statin therapy consistently, and in a generally well-tolerated manner, reduced the risk for CV events in patients post-ACS across a range of baseline LDL-C concentrations ranging from 50 to 125 mg/dL. These data support the use of further intensification of LLT by adding ezetimibe to statin in ACS patients with baseline LDL-C of <70 mg/dL.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL OUTCOMES: Adding ezetimibe to statin therapy safely and consistently reduced the risk of CV events in survivors of ACS across baseline LDL-C levels of 50-125 mg/dL.

TRANSLATIONAL OUTLOOK: Future research should aim to establish whether patients with ACS and baseline LDL-C <50 mg/dL and lower-risk patients with LDL-C below current guideline-recommended treatment thresholds benefit from intensification of LLT.

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KEY WORDS acute coronary syndrome, ezetimibe, low-density lipoprotein cholesterol, statin

APPENDIX For supplemental tables and figures, please see the online version of this paper.