Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18,144 patients after acute coronary syndromes: Final baseline characteristics of the IMPROVE-IT study population

Michael A. Blazing, MD,[a] Robert P. Giugliano, MD, SM,[b] Christopher P. Cannon, MD,[b] Thomas A. Musliner, MD,[c] Andrew M. Tershakovec, MD, MPH,[c] Jennifer A. White, MS,[a] Craig Reist, PhD,[a] Amy McCagg, BS,[b] Eugene Braunwald, MD,[b] and Robert M. Califf, MD[a] ***Durham, NC; Boston, MA; and Rahway, NJ***

Background The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is evaluating the potential benefit for reduction in major cardiovascular (CV) events from the addition of ezetimibe versus placebo to 40 mg/d of simvastatin therapy in patients who present with acute coronary syndromes and have low-density lipoprotein cholesterol (LDL-C) ≤125 mg/dL.

Methods The primary composite end point is CV death, nonfatal myocardial infarction (MI), nonfatal stroke, rehospitalization for unstable angina (UA), and coronary revascularization (≥30 days postrandomization). The simvastatin monotherapy arm's LDL-C target is <70 mg/dL. Ezetimibe was assumed to further lower LDL-C by 15 mg/dL and produce an estimated ~8% to 9% treatment effect. The targeted number of events is 5,250.

Results We enrolled 18,144 patients with either ST-segment elevation MI (STEMI, n = 5,192) or UA/non–ST-segment elevation MI (UA/NSTEMI, n = 12,952) from October 2005 to July 2010. Western Europe (40%) and North America (38%) were the leading enrolling regions. The STEMI cohort was younger and had a higher percentage of patients naive to lipid-lowering treatment compared with the UA/NSTEMI cohort. The UA/NSTEMI group had a higher prevalence of diabetes, hypertension, and prior MI. Median LDL-C at entry was 100 mg/dL for STEMI and 93 mg/dL for UA/NSTEMI patients.

Conclusions This trial is evaluating LDL-C lowering beyond previously targeted LDL-C levels. The results depend on achieving the desired separation of LDL-C with ezetimibe and on the assumption that ezetimibe's lowering of LDL-C will have similar event reduction efficacy as the LDL-C lowering from a statin. The results could affect future therapies and guidelines. (Am Heart J 2014;168:205-212.e1.)

Individual trials and meta-analyses have demonstrated that more aggressive treatment with statins, using either more potent drugs or higher doses, results in decreased low-density lipoprotein cholesterol (LDL-C) levels and a further lowering of cardiovascular (CV) event rates when compared with less potent or lower dose statin therapies.[1-6] Niacin, fibrates, and cholesteryl ester transfer protein inhibitors also alter serum lipid profiles in directions that have been presumed beneficial. When evaluated as adjuncts to aggressive statin therapy in trials designed to assess effects on CV outcomes, these nonstatin agents produced their expected complementary or additive lipid effects but failed to achieve their predicted effects on CV event reduction.[7-9]

Ezetimibe is a nonstatin agent commonly used as an adjunctive therapy in combination with statins to further lower LDL-C. It inhibits the intestinal absorption of cholesterol, leading to an upregulation of LDL receptors in the liver, which results in lowering of LDL-C in the serum.[10] This LDL-C lowering is independent and additive to that of a statin.[11] A large, pooled analysis found that adding ezetimibe to ongoing statin therapy resulted in an average 23.4% further reduction in LDL-C relative to the LDL-C level attained with statin monotherapy before addition of ezetimibe.[12] Furthermore, unlike niacin, fibrates, or cholesteryl ester transfer protein

From the [a]Duke Clinical Research Institute, Durham, NC, [b]Thrombolysis in Myocardial Infarction [TIMI] Study Group, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, and [c]Merck & Co., Rahway, NJ.

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Reprint requests: Michael A. Blazing, MD, Duke University Medical Center, Box 3126, Durham, NC 27710.
E-mail: michael.blazing@dm.duke.edu

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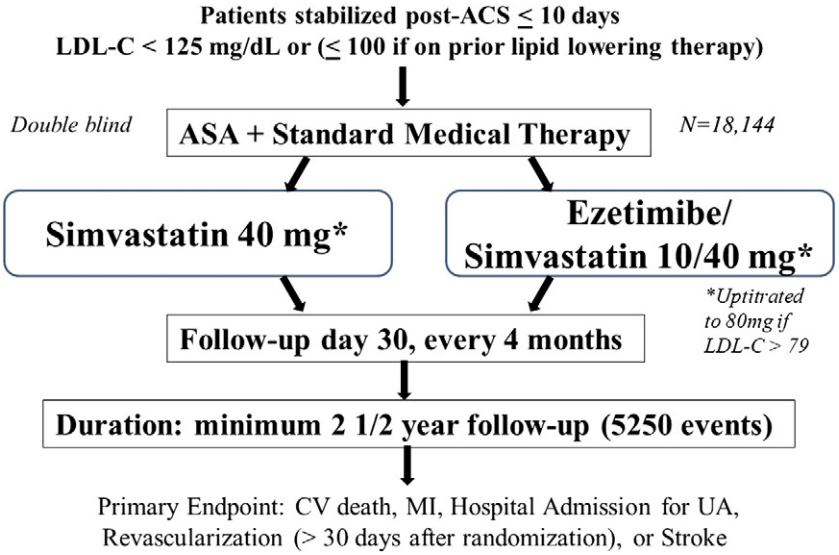
Figure 1



IMPROVE-IT study design. *ASA*, aspirin. Adapted from Cannon et al, Am Heart J 2008;156:826-832.

inhibitors when used as an adjunctive therapy, ezetimibe has been shown to augment the effect of statins on lowering of high-sensitivity C-reactive protein.[12] Clinically, the combination of ezetimibe with simvastatin compared with placebo has been shown to reduce first clinical cardiovascular event in patients with aortic stenosis who had no known coronary disease[13,14] and to reduce a primary composite end point of first major atherosclerotic event (nonfatal myocardial infarction [MI] or coronary death, nonhemorrhagic stroke, or any arterial revascularization procedure) in persons with moderate chronic kidney disease.[15]

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was designed to determine whether adding ezetimibe to simvastatin in patients presenting with acute coronary syndromes (ACS) adds clinical benefit by further reducing major CV events compared with simvastatin monotherapy.[16] The trial design and characteristics of the first 10,000 enrolled patients have been described previously.[16] This article describes the baseline characteristics of the complete cohort enrolled in IMPROVE-IT and discusses the implications of nonstatin-mediated LDL-C reduction and CV risk reduction relating to recent clinical outcomes data.

Methods

Study design and objectives

The design of IMPROVE-IT (ClinicalTrials.gov, NCT00202878) is outlined in Figure 1.[16] The study enrolled patients within 10 days of ACS hospitalization who had sufficient risk as defined in the protocol (outlined below) and who had an initial LDL-C of ≤125 mg/dL if lipid-lowering naive or <100 mg/dL if on a prior prescription lipid-lowering therapy identified as no more potent than simvastatin 40 mg/d. All patients received simvastatin at a starting daily dose of 40 mg and either placebo or 10 mg of ezetimibe added to the baseline simvastatin therapy. The LDL-C entry limitations were set to achieve a mean LDL-C of <70 mg/dL in the simvastatin/placebo cohort, which was the optional recommended target set in the last update of the Adult Treatment Panel III guidelines.[17] The primary end point is CV death, nonfatal MI, nonfatal stroke, rehospitalization for unstable angina (UA), and coronary revascularization (occurring at least 30 days after randomization).

Study population

Initially, the trial enrolled high-risk patients with ST-segment elevation MI (STEMI), non–ST-segment elevation MI (NSTEMI), or documented UA who had stable hemodynamics, arrhythmias, and ischemic symptoms and did not require medications known at the time of protocol development in 2004 to interact with simvastatin (see online Appendix). The protocol-specified high-risk characteristics for STEMI were anterior MI or age ≥50 years. The high-risk characteristics for UA/NSTEMI were age ≥50 years and one of the following: ST-segment changes of at least 1 mm, positive cardiac biomarkers, diabetes mellitus, a history of previous MI, a history of coronary artery bypass grafting at least 3 years earlier, or demonstration of at least 2 major coronary arteries with

≥50% luminal narrowing. Patients enrolled in the Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation ACS (EARLY ACS) trial[18] were eligible to be enrolled as well.

Enrollment of STEMI patients was phased out beginning in September 2007 with a second protocol amendment. The STEMI enrollment was limited to minimize any potential effects of lower long-term risk of this population on trial duration (Figure 2).

Treatment protocol

The original protocol outlined monitoring of patients' LDL-C levels during the trial and called for their dose of simvastatin to be raised to 80 mg/d if 2 successive LDL-C values exceeded 79 mg/dL. Minimum follow-up was specified to be 2.5 years after the last enrolled patient.

In September 2008, an association between ezetimibe and increased risk for cancer was reported in a trial evaluating the use of simvastatin with ezetimibe on the progress of aortic stenosis (Simvastatin and Ezetimibe in Aortic Stenosis [SEAS][14]). To address this concern, a specific cancer-related clinical events committee was formed to provide more detailed cancer-specific data regarding all prevalent and incident cancer cases within IMPROVE-IT to the independent data and safety monitoring board (DSMB) monitoring the trial. The data from this clinical events committee were reviewed by the trial DSMB a total of 7 times between 2008 and the end of the trial with no new safety concerns.

Overall, the protocol has undergone 5 amendments (Table I). The first 3 of these have been previously described and (1) were related to refinements of the inclusion/exclusion criteria, (2) set the cap on enrollment of STEMI patients, and (3) described the rationale of increasing sample size from an original value of 10,000 to the final value of approximately 18,000.[16] Modeling was used to arrive at this number of patients, which was found to be optimal for preserving study power while minimizing potential issues concerning duration of study follow-up and enrollment. Since 2009, the protocol has undergone 2 additional amendments to accommodate changes to the simvastatin product label and to add a second interim analysis. In June 2011, a Food and Drug Administration (FDA) safety communication restricted the use of 80 mg/d of simvastatin to patients who had been on that dose and stable for 12 months, contraindicated any new starts of simvastatin 80 mg/d, and identified amlodipine and ranolazine as new drugs requiring simvastatin dosage limitations.[19] This communication led to the discontinuation of protocol-directed use of 80 mg/d of simvastatin for (1) patients who had an LDL-C of >79 mg/dL on simvastatin 40 mg/d, (2) patients who had been on simvastatin 80 mg/d for <1 year, or (3) patients who needed to continue either amlodipine or ranolazine. In these 3 groups, the simvastatin dose was restricted or reduced to 40 mg/d. The 40-mg dose was continued rather than reducing it to the FDA-recommended limitation of 20 mg/d for patients taking amlodipine or ranolazine based on safety data from this trial. An independent events committee unaware of treatment assignment adjudicated and classified all muscle-related events identified on adverse event and serious adverse event reports using prespecifed criteria described in the protocol. The data from this committee, stratified by treatment assignment, were evaluated in the safety reviews of the DSMB. Patients stable on simvastatin 80 mg/d for ≥1 year were left at that dose per the FDA advisory. These protocol changes and a second interim analysis at 75% of accumulated target events resulted in a combined fourth and fifth amendment to the protocol.

Table I. Protocol amendments

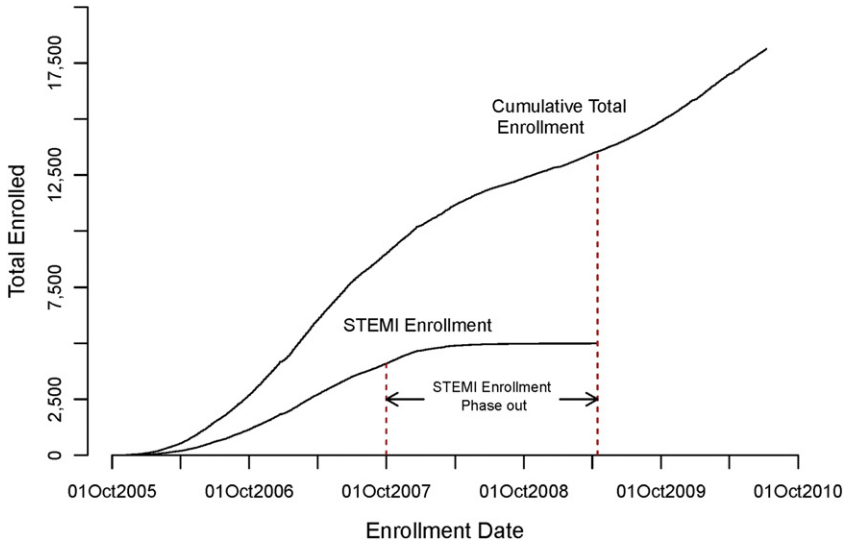
Amendment number	Date	Major focus
1	April 2007	Changes to inclusion and exclusion criteria[16]
2	September 2007	Capped enrollment of STEMI[16]
3	March 2008	Rationale and plan for sample size readjustment[16]
4 and 5	June 2011	Response to restrictions on simvastatin 80 mg/d use and a second interim analysis at 75% of events

Statistical design and analysis

Key assumptions about sample size and targeted expectations about events included an estimated 1% clinical benefit for every 1.6 mg/dL difference in LDL-C,[1] a 15 mg/dL incremental reduction in LDL-C with ezetimibe treatment, and a 25% discounting of treatment effect in the first 6 months.[16] These assumptions yielded an estimated treatment effect of 9.375% for the primary end point. An independent lipid monitoring committee reviewed on-treatment LDL-C values in the context of the study power assumptions. The committee did not recommend any changes in sample size or trial duration.

There were 3 interim analyses for efficacy during the trial. The original protocol-specified interim analysis at 50% of targeted end points was performed in March 2010 and recommended continuation of the trial. The second DSMB interim analysis at 75% of targeted end points included in the fifth protocol amendment was performed in March 2012. At that time, the DSMB recommended continuation of the trial but requested a third analysis for efficacy, which took place in March 2013 with the same recommendations as after the 2012 analysis. Stopping guidelines for "overwhelming efficacy" were in place from the outset and were based on findings for the primary end point in conjunction with a directionally consistent reduction in total mortality. There were no stopping rules for futility provided to the DSMB for any of

Figure 2



Enrollment into IMPROVE-IT.

the interim analyses. Using East Software (Version 5.3; Cytel, Cambridge, MA), the nominal alpha level for the final primary end point analysis was adjusted to 0.0394 to account for the 3 interim analyses.

The trial was initially funded by Schering-Plough and Merck and then by Merck & Co alone after their merger in November 2009.

Results

Enrollment began in October 2005 and completed in July 2010 (Figure 2). The shape of the overall enrollment pace reflects the change in sample size to 18,000 patients, made 2.5 years into enrollment and implemented in March 2008, and the closeout of STEMI enrollment that started in September 2007. Median enrollment was reached in October 2007. The target was met with 18,144 patients enrolled at 1,148 sites in 39 countries. The 2 highest enrolling regions were Western Europe (40%) and North America (38%). The prespecified minimum trial duration was reached in January 2013. The targeted number of 5,250 events is projected to be reached in late spring of 2014.

Baseline demographic and medical history characteristics are shown in Table II. The median age at randomization was 63 years, with an interquartile range of 56 to 71 years. Most of the patients are male (76%). At randomization, 27% of patients had diabetes, and 21% had experienced a previous MI. The initial event was STEMI in 5,192 (29%), NSTEMI in 8,567 (47%), and UA in 4,385 (24%) patients. Compared with the UA/NSTEMI cohort, the STEMI cohort was younger (median of 60 years vs 64 years) and had lower prevalence of hypertension, diabetes mellitus, and previous MI. Substantially more STEMI patients were not on lipid-lowering therapy at entry (83%) compared with the UA/NSTEMI cohort (60%). Forty-nine percent of the STEMI patients had anterior infarction as a high-risk feature (data not shown). Diabetes (30%) was the most common high-risk feature qualifying patients with UA/NSTEMI, followed by previous MI (26%).

Baseline laboratory findings are also shown in Table II. The trial enrolled patients in the target LDL-C range, and the median high-density lipoprotein cholesterol (HDL-C) level was 40 mg/dL. The median LDL-C level was lower in the UA/NSTEMI cohort compared with the STEMI cohort (93 mg/dL vs 100 mg/dL, $P < .001$). Renal function was well preserved, with a median serum creatinine of 1.0 mg/dL, and 75% of patients had a calculated creatinine clearance of ≥65 mL/min.

The distributions of baseline lipid levels are shown in Figure 3. They demonstrate a narrow range of LDL-C levels, as anticipated from the eligibility criteria. Approximately two-thirds of the patients enrolled were naive to lipid-lowering therapy. The lipid-lowering–naive patients had a median LDL-C level that was higher (104 mg/dL) compared with the median LDL-C (80 mg/dL) of those on prior lipid-lowering therapy (data not shown).

Discussion

The IMPROVE-IT trial enrolled patients with selected high-risk criteria after stabilization of a qualifying ACS event who presented with an LDL-C level ≤125 mg/dL. The patients are from countries with different clinical

Table II. Baseline characteristics

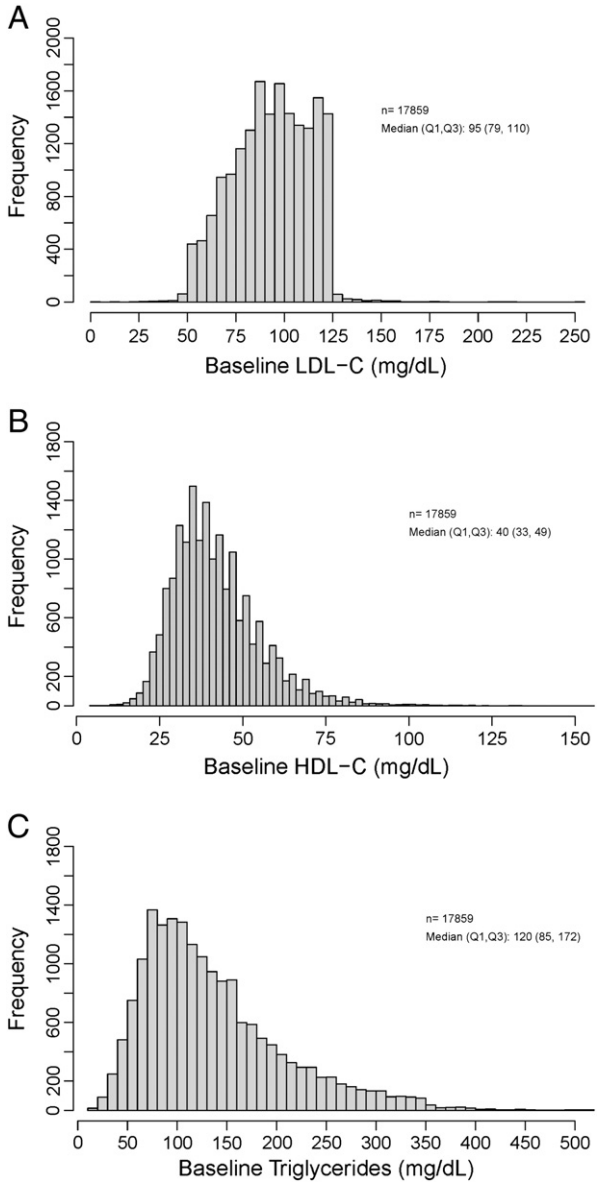
	STEMI	UA/NSTEMI	All subjects
Age at randomization (y)			
n	5192	12952	18144
Median (IQR)	60 (54-68)	64 (57-72)	63 (56-71)
Male	4155 (80.0%)	9573 (74%)	13728 (76%)
Race			
American Indian or Alaskan Native	14 (0.3%)	38 (0.3%)	52/18141 (0.3%)
Asian	157 (3%)	616 (5%)	773/18141 (4%)
Black	106 (2%)	392 (3%)	498/18141 (3%)
Spanish descent	270 (5%)	538 (4%)	808/18141 (5%)
Native Hawaiian or Pacific Islander	9 (0.2%)	10 (0.1%)	19/18141 (0.1%)
Caucasian	4458 (86%)	10745 (83%)	15203/18141 (84%)
Other	174 (3%)	597 (5%)	771/18141 (4%)
Collection prohibited	3 (0.1%)	14 (0.1%)	17/18141 (0.1%)
Region			
United States	1928 (37%)	3938 (30%)	5866 (32%)
Canada	434 (8%)	673 (5%)	1107 (6%)
Western Europe	2071 (40%)	5203 (40%)	7274 (40%)
Eastern Europe	224 (4%)	1192 (9%)	1416 (8%)
Malaysia/Singapore/Hong Kong	89(2%)	527 (4%)	616 (3%)
South America	393 (8%)	1192 (9%)	1585 (9%)
Australia/New Zealand	53 (1%)	227 (2%)	280 (2%)
Hypertension	2498 (48%)	8640 (67%)	11138 (61%)
Diabetes	1005 (19%)	3911 (30%)	4916 (27%)
Previous MI	486 (9%)	3320 (26%)	3806 (21%)
Lipid-lowering naive	4321 (83%)	7742 (60%)	12063 (67%)
LDL-C (mg/dL)			
n	5156	12843	17999
Median (IQR)	100 (85-113)	93 (77-108)	95 (79-110)
HDL-C (mg/dL)			
n	5142	12717	17859
Median (IQR)	40 (33-49)	40 (33-49)	40 (33-49)
Triglycerides (mg/dL)			
n	5142	12762	17904
Median (IQR)	114 (79-165)	124 (88-175)	120 (85-172)
Creatinine (mg/dL)			
n	5159	12872	18031
Median (IQR)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	1.0 (0.8-1.2)
Creatinine clearance (mL/min)			
n	5136	12836	17972
Median (IQR)	87 (69-110)	83 (64-105)	84 (65-106)

Abbreviation: *IQR,* interquartile range.

practice patterns and varying social and economic backgrounds, which should make the findings from the trial widely applicable. As expected, the STEMI and UA/NSTEMI ACS populations differ with respect to age and risk factors. The median lipid values for the study population were within expected ranges (LDL-C 95 mg/dL, HDL-C 40 mg/dL, triglycerides 120 mg/dL) given the LDL-C entry criteria. The lower LDL-C and higher triglyceride levels in the UA/NSTEMI population possibly result from differences in previous statin use and in prevalence of diabetes between the 2 populations. The results should provide an evaluation of whether ezetimibe, with its modest estimated incremental reduction in LDL-C of 15 mg/dL in this trial, produces further reduction in CV events in comparison with a simvastatin monotherapy control population targeted to achieve (on average) the Adult Treatment Panel III/European guideline–based goal of <70 mg/dL.[17,20]

The outcome depends on ezetimibe producing the targeted LDL-C difference between treatment arms and this difference having proportionally the same effect on outcomes as would be expected with a statin. Using ezetimibe in addition to a statin produces an average incremental LDL-C reduction of 23% to 24% relative to on-statin LDL-C, an effect similar to that achieved by an 8-fold increase in simvastatin statin dose (ie, 3 dose doublings from 10 to 80 mg).[21] Thus, for the IMPROVE-IT population, where simvastatin monotherapy was designed to achieve a median LDL-C of slightly <70 mg/dL, the addition of ezetimibe should produce the targeted 15 mg/dL difference in LDL-C between the treatment groups. This delta for LDL-C lies at the lower limit of the range of other more

Figure 3



Distribution of LDL-C **A**, HDL-C **B**, and triglycerides **C** at entry. *Q1, Q3,* first and third quartiles.

Table III. Comparison of more intensive statin therapy trials

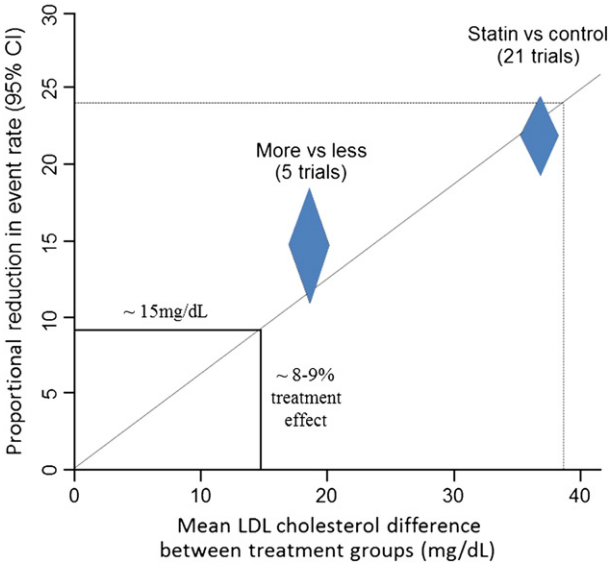
Trial	n	LDL-C control	LDL-C aggressive	Delta LDL-C
A to Z[3] phase Z	4496	77 mg/dL	63 mg/dL	14 mg/dL
PROVE IT[4]	4162	95 mg/dL	62 mg/dL	33 mg/dL
TNT[6]	10001	100 mg/dL	77 mg/dL	23 mg/dL
IDEAL[5]	8888	104 mg/dL	81 mg/dL	23 mg/dL
IMPROVE-IT	18154	<70 mg/dL	<55 mg/dL	~15 mg/dL

Abbreviations: *A to Z,* Aggrastat to Zocor; *TNT,* Treating to New Targets; *IDEAL,* Incremental Decrease in Endpoints through Aggressive Lipid Lowering.

intensive statin therapy trials[3-6] (Table III). The IMPROVE-IT trial is larger than these previous trials, with longer follow-up (~6 years vs 2-5 years), and will have substantially more primary end points (5,250) than all of these other studies combined. Based on data derived from these and other statin trials included in the Cholesterol Treatment Trialists' meta-analysis[2] (Figure 4), the incremental outcomes reduction attributable to the between-group difference of 15 mg/dL in LDL-C due to ezetimibe is estimated to fall in the range of 8% to 9%.

A variety of factors could potentially influence the treatment effect of ezetimibe in IMPROVE-IT. First is the assumption that the relationship between LDL-C lowering and CV event lowering with statins will be the same for ezetimibe. The 2 drugs work through final pathways that lead to upregulation of LDL receptors that mediate a complementary reduction in serum LDL-C, and the combination of ezetimibe with ongoing statin augments lowering of C-reactive protein[11,12]; however, the incremental efficacy of adding ezetimibe on biomarkers such as carotid intimal thickening and vascular reactivity has been inconsistent, with studies showing beneficial, neutral, and possibly detrimental effects of the drug despite its consistent lowering of LDL-C in those studies.[22-24] Second, there is question whether the relationship between LDL-C lowering and reduction in CV risk (based on meta-analyses of statin trials[2]) will remain linear over the entire comparison range of LDL-C being evaluated in IMPROVE-IT.[25] In a post hoc analysis of a similar post-ACS population enrolled in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial (n = 4,162),[4] an examination of statin-naive patients (n = 2,986) stratified by quartiles of entry LDL-C found the benefit of intensive therapy progressively declined as untreated baseline entry LDL-C decreased.[25] This study suggests that the lower LDL-C entry criteria in IMPROVE-IT compared with PROVE IT (LDL-C limited to ≤125 mg/dL vs no limit, respectively) could make the IMPROVE-IT results more susceptible to any effects of flattening of the relationship between efficacy and LDL-C that may occur at lower LDL-C levels. Interpretation of a separate analysis from PROVE IT, in which cohorts of patients who achieved LDL-C of ≤60 mg/dL were found to have fewer major CV events than cohorts not reaching these levels,[26] suggests that the ezetimibe arm of IMPROVE-IT (with its projected mean achieved LDL-C <55 mg/dL) could have fairly low event rates. These lower rates could help preserve a linear relationship between LDL-C and efficacy at lower levels of achieved LDL-C. Although it is unclear which marker—

Figure 4



Projected positioning of IMPROVE-IT in comparison with the relationship of LDL-C difference and proportional event reduction for intensive versus less-intensive statin therapy trials. Adapted from a slide available on the SHARP trial website (http://www.sharpinfo.org/) and presented at the FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting in November 2011 (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM279296.pdf) (From www.fda.gov: "Unless otherwise noted, the contents of the FDA website (www.fda.gov)—both text and graphics—are not copyrighted. They are in the public domain and may be republished, reprinted and otherwise used freely by anyone without the need to obtain permission from FDA. Credit to the U.S. Food and Drug Administration as the source is appreciated but not required.").

statin-naive LDL-C at entry or achieved LDL-C—is more important or a better predictor of outcomes, it is certain that the data from IMPROVE-IT will add further insight into the markers' relative importance and that the outcome of IMPROVE-IT could be affected by either. Finally, any relationship between the measured LDL-C difference and measured treatment effect will have to account for possible effects of potential trial-related issues such as withdrawn consent and patient drug discontinuation. For example, in IMPROVE-IT, the median trial duration of almost 6 years, new FDA regulations[19] that required changes in the dosing of simvastatin during the trial, and the 2 negative episodes of publicity surrounding other ezetimibe trials that closed during IMPROVE-IT (re. drug efficacy concerns in the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression [ENHANCE] trial[27] and drug safety concerns of a cancer risk in SEAS[14]) are all factors that could produce issues with patient drug discontinuation or withdrawal of consent.

The implications of the results from IMPROVE-IT go beyond the specific circumstances of the trial. Although some may question the clinical utility of small treatment effects at low achieved LDL-C levels, the practical value of a positive trial will serve as a definitive proof of concept that LDL-C lowering with compounds other than statins can affect outcomes. The trial may provide support for driving LDL-C to levels below those previously recommended and will raise the issue of whether other molecules—such as PCSK9 antibodies—could have similar proportional benefit as an adjunct to statins. A positive result will also support the concept that ezetimibe can be effective in patients who are unable to tolerate high-dose statins, those who may better tolerate a combination of low-dose statin plus ezetimibe, and those who do not achieve adequate LDL-C lowering despite high-dose statin use. A positive result could also lead to an early re-evaluation of the new American College of Cardiology/American Heart Association cholesterol guidelines that endorse statins as the only recommended drugs for treating cholesterol-related CV risk.[28] If IMPROVE-IT does not meet its primary end point, subsequent analyses evaluating the trial population, drug discontinuations, and assumptions made regarding treatment effects will provide insight into possible trial design issues or mechanistic revelations that could certainly affect beliefs about the "lower is better" hypothesis. Regardless of the outcome with respect to ezetimibe, a trial with 18,144 patients that accumulated 5,250 events and had a mean follow-up time approaching 6 years will add to our understanding of post-ACS and long-term care of atherosclerotic CV disease in current practice.

Disclosures

Dr Blazing has served as an advisory board member for Merck, has consulted for AstraZeneca and Novartis, and has received grant support from Merck (to the Duke Clinical Research Institute). Dr Giugliano has received grant support from Amgen, Daiichi-Sankyo, and Merck (to the Thrombolysis in Myocardial Infarction [TIMI] Study Group) and honoraria from Amgen, Beckman-Coulter, Bristol-Myers Squibb, Daiichi-Sankyo, Janssen, Lexicon, Merck, Regeneron, and Sanofi. Dr Cannon has received research grants and support from Accumetrics, Arisaph, AstraZeneca, Boehringer-Ingelheim, CSL Behring, Essentialis, GlaxoSmithKline, Janssen, Merck, Regeneron, Sanofi, and Takeda and has served on an advisory board for Bristol-Myers Squibb, Lipimedix, and Pfizer. Drs Musliner and Tershakovec are employees and stockholders of Merck. Dr Braunwald has received grant support from AstraZeneca, Johnson & Johnson, Beckman-Coulter, Daiichi-Sankyo, Merck, Roche Diagnostics, Sanofi-Aventis, GlaxoSmithKline, and Bristol-Myers Squibb (to the TIMI Study Group) and honoraria

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Appendix. Prohibited medications at trial inception

Medication
Probucol
Amiodarone
Cyclosporine
Fibric acid derivatives (fibrates)
Resins
Niacin >100 mg/d
Danazol
Antifungal azoles via oral and parenteral administration (itraconazole, fluconazole, and ketoconazole)
Macrolide/ketolide antibiotics via oral and parenteral administration (eg, clarithromycin, erythromycin, telithromycin)
Protease inhibitors
Nefazodone
Any investigational drugs
Diltiazem
Verapamil
Statins
Ezetimibe
Fusidic acid
Torcetrapib, within 1 y before screening/randomization

Short-term use of these medications, except for investigational drugs, and-lipid lowering agents was permitted provided the study drug could be stopped during administration and restarted after completion of the course of therapy.