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ORIGINAL INVESTIGATIONS

Reduction in Total Cardiovascular Events With Ezetimibe/Simvastatin Post-Acute Coronary Syndrome

The IMPROVE-IT Trial

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ABSTRACT

BACKGROUND Intensive low-density lipoprotein cholesterol therapy with ezetimibe/simvastatin in IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) significantly reduced the first primary endpoint (PEP) in patients post-acute coronary syndrome (ACS) compared to placebo/simvastatin.

OBJECTIVES This analysis tested the hypothesis that total events, including those beyond the first event, would also be reduced with ezetimibe/simvastatin therapy.

METHODS All PEP events (cardiovascular [CV] death, myocardial infarction [MI], stroke, unstable angina [UA] leading to hospitalization, coronary revascularization ≥30 days post-randomization) during a median 6-year follow-up were analyzed in patients randomized to receive ezetimibe/simvastatin or placebo/simvastatin in IMPROVE-IT. Negative binomial regression was used for the primary analysis.

RESULTS Among 18,144 patients, there were 9,545 total PEP events (56% were first events and 44% subsequent events). Total PEP events were significantly reduced by 9% with ezetimibe/simvastatin vs placebo/simvastatin (incidence-rate ratio [RR]: 0.91; 95% confidence interval [CI]: 0.85 to 0.97; p = 0.007), as were the 3 pre-specified secondary composite endpoints and the exploratory composite endpoint of CV death, MI, or stroke (RR: 0.88; 95% CI: 0.81 to 0.96; p = 0.002). The reduction in total events was driven by decreases in total nonfatal MI (RR: 0.87; 95% CI: 0.79 to 0.96; p = 0.004) and total NF stroke (RR: 0.77; 95% CI: 0.65 to 0.93; p = 0.005).

CONCLUSIONS Lipid-lowering therapy with ezetimibe plus simvastatin improved clinical outcomes. Reductions in total PEP events, driven by reductions in MI and stroke, more than doubled the number of events prevented compared with examining only the first event. These data support continuation of intensive combination lipid-lowering therapy after an initial CV event. (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial [IMPROVE-IT]; NCT00202878) (J Am Coll Cardiol 2016;67:353–61) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CV = cardiovascular

LDL-C = low-density lipoprotein cholesterol

MI = myocardial infarction

PCI = percutaneous coronary intervention

PEP = primary endpoint

PWP = Prentice, Williams, and Peterson

UA = unstable angina

WLW = Wei, Lin, and Weissfeld

Most long-term acute coronary syndrome (ACS) trials use survival analysis methods that take into account only the first event that a patient experiences during the trial to evaluate efficacy, even if the primary endpoint (PEP) is a composite made up of multiple component events. This is a somewhat limited evaluation of efficacy, as subjects with a nonfatal event continue to be followed during the trial, and can experience additional events during the course of follow-up. In clinical practice, a first event usually does not reflect the complete cardiovascular clinical experience of a patient over time. Indeed, previous trials have examined total events for comparing high-intensity versus moderate-intensity statins. In both the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) and the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trials, analyses demonstrated that lower low-density lipoprotein cholesterol (LDL-C) achieved with high-intensity statins reduced both the first cardiovascular event as well as the total number of cardiovascular events post-ACS compared with moderate-intensity statins (1,2).

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As previously reported (3), IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) showed an overall reduction in the primary composite endpoint of time to first cardiovascular (CV) death, nonfatal MI, unstable angina requiring hospitalization, coronary revascularization (≥30 days post-randomization), or nonfatal stroke over a median 6 years of follow-up with the combination therapy of simvastatin and ezetimibe (a non-statin lipid-lowering agent) compared to simvastatin and placebo in patients with recent ACS and LDL-C of 50 to 125 mg/dl. We tested the pre-specified hypothesis in IMPROVE-IT that, in addition to reducing first events in patients after an ACS, combination therapy with ezetimibe plus simvastatin would also reduce total events compared with simvastatin alone.

METHODS

The study design and primary results of IMPROVE-IT have been published previously (3–6). Patients who were ≥50 years of age were eligible for inclusion if they were hospitalized for an ACS within the preceding 10 days, with either acute myocardial infarction (MI) with or without electrocardiographic ST-segment elevation, or high-risk unstable angina (UA). Eligible patients had an LDL-C concentration of ≥50 mg/dl (1.3 mM/l), with a maximum of 125 mg/dl (3.2 mM/l) if not receiving chronic lipid-lowering therapy, or ≤100 mg/dl (2.6 mM/l) if chronically treated. A total of 18,144 patients were randomized in a double-blind manner to either placebo plus simvastatin, 40 mg, or the combination of ezetimibe, 10 mg, plus simvastatin, 40 mg once daily, in addition to standard ACS therapy. Simvastatin dose was increased in each group to 80 mg if LDL-C was >79 mg/dl (2.0 mM/l).

Patients had follow-up visits at 30 days, 4 months, and every 4 months thereafter. The primary composite endpoint was time to first CV death, nonfatal MI, UA requiring hospitalization, coronary revascularization (≥30 days post-randomization), or nonfatal stroke. Study medication and follow-up were to be continued until trial end even if a patient experienced a nonfatal component of the PEP. All endpoints (excluding revascularization) used in the analyses in the initial as well as this report were adjudicated by members of an independent clinical events committee who were blinded to the treatment assignment.

STATISTICAL ANALYSIS. Baseline clinical characteristics are presented as frequencies for categorical variables and medians and interquartile ranges for continuous variables. Comparisons between baseline characteristics for patients with no events, a single event, or multiple events, as well as

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for the comparison of ezetimibe/simvastatin with placebo/simvastatin in the cohort of patients with at least 1 event (Online Table 1), were made using the chi-square test for categorical variables and Wilcoxon rank test for continuous variables. Negative binomial regression analysis, a type of modified Poisson model, was performed to compare the total number of PEPs and other endpoints between all patients in the ezetimibe/simvastatin and placebo/simvastatin groups. This model included an exposure variable for duration of follow-up as this could vary by subject. Incidence-rate ratio (RR) and corresponding 95% confidence intervals (CI) are reported from the negative binomial regression model. In addition, we performed a pre-specified analysis using the Wei, Lin, and Weissfeld (WLW) method (7), which is a marginal model and an extension of survival models based on the Cox proportional hazard; the first 4 events that could have occurred in a subject were evaluated in the model. An additional sensitivity analysis was performed using a Prentice, Williams, and Peterson (PWP) model (8), which is a conditional model and also an extension of survival models based on the Cox proportional hazard. An Andersen Gill model was also performed as a sensitivity analysis using up to the first 4 events in a subject.

Efficacy comparisons were performed according to the intention-to-treat principle. All tests were 2-sided with a p value <0.05 considered to be significant. Analyses were performed using Stata/IC version 13.1 software (College Station, Texas) and SAS version 9.3 software (Cary, North Carolina).

RESULTS

The median length of follow-up was 6 years (25th, 75th percentiles: 4.3 and 7.1 years). Compared to patients with only 1 event, patients with multiple events had more comorbidities at study entry, including hypertension and diabetes; were more often on prior statin therapy; and more frequently had previously experienced MI, angina, and revascularization (**Table 1**). The 1-month LDL-C levels were lowest in those without a subsequent PEP event and highest in those with more than 1 PEP event (mean 58.3 mg/dl if no event vs. 59.6 mg/dl if 1 event and 60.1 mg/dl if >1 event, $p<0.001$ for 3-way comparison). However, there were no further differences when LDL-C levels in subjects with 1 PEP event were compared with those who had >1 PEP event ($p = 0.54$). The frequency of reaching a target of LDL-C concentration of <70 mg/dl at 1 month was also analyzed. An LDL-C of <70 mg/dl at 1 month was most common among subjects without a PEP event during the trial (74.2%) compared with subjects with 1 event (71.0%) or >1 event (69.0%; $p < 0.001$ for 3-way comparison), but again, there was no statistically significant difference when we compared subjects with 1 PEP event with those who had >1 PEP event ($p = 0.16$). Baseline characteristics among patients who experienced at least 1 event were similar for those randomized to ezetimibe/simvastatin compared to those randomized to placebo/simvastatin (Online Table 1).

EVENTS. During the course of the trial, a total of 9,545 PEP events occurred. Of these, 5,314 (56%) were first events, which were included in the primary IMPROVE-IT study analysis (3), and there were an additional 4,231 (44%) events that occurred after the first PEP event during the course of the trial, and were thus not included in the primary analysis. Overall, a similar proportion of first and additional events were stroke, UA, and CV death (**Figure 1**). In contrast, there were proportionately fewer MIs (24.0% vs. 31.7%) and proportionately more revascularizations (58.4% vs. 43.8%) among the additional events compared to the distribution of first events. There were a total of 48 peri-percutaneous coronary intervention (PCI) MI events, of which only 4 were the first PEP event that occurred in a subject; no subject had more than 1 peri-PCI MI during the trial.

When we considered the total number of events of the 18,144 subjects, 70.7% (n = 12,830) had no events, 16.6% (n = 3,017) had a single event, 7.3% (n = 1,325) had 2 PEP events, and 5.4% (n = 972) had 3 or more such events (Online Table 2). The maximum number of events experienced was 14 events each in 2 patients.

EFFICACY. As previously reported (3), the PEP of first occurrence of CV death, nonfatal MI, UA requiring hospitalization, coronary revascularization, or nonfatal stroke was significantly reduced by 170 events in the ezetimibe/simvastatin group compared with the placebo/simvastatin group (7-year Kaplan-Meier rate = 32.7% [n = 2,572] vs. 34.7%, respectively [n = 2,742]; hazard ratio [HR]: 0.936; 95% CI: 0.887 to 0.988; $p = 0.016$). In addition to this reduction in first primary events, there were 251 fewer subsequent events in the ezetimibe/simvastatin group (n = 1,990 in the ezetimibe/simvastatin group vs. n = 2,241 in the placebo/simvastatin group) (**Central Illustration**, Online Table 3), resulting in 421 fewer total primary events during follow-up (total events n = 4,562 vs. n = 4,983, respectively; RR: 0.91; 95% CI: 0.85 to 0.97; $p = 0.007$). When comparing ezetimibe/simvastatin versus placebo/simvastatin, there was a 13% reduction in the total number of MIs

TABLE 1 Baseline Characteristics in Patients With No Events, a Single Event, or Multiple Events*

	No Events (n = 12,830)	1 Event (n = 3,017)	Multiple Events (n = 2,297)	p Value for 1 vs. ≥2 Events
Male	75.1	76.4	78.1	0.162
Caucasian	83.3	84.5	86.2	0.070
Age, yrs	62 (56-70)	64 (58-73)	64 (57-72)	0.006
LDL-C >95 mg/dl (median) at qualifying event	51.0	47.0	42.6	0.001
Qualifying event				0.173
STEMI	27.7	27.8	26.2	
NSTEACS	72.3	72.2	73.8	
Prior MI	18.1	25.7	31.4	<0.001
History of angina	37.5	46.9	53.5	<0.001
History of diabetes	24.6	31.9	35.3	0.009
History of hypertension	59.1	65.7	68.7	0.024
Current smoker	33.5	31.4	32.3	0.489
History of CHF	3.4	6.6	6.6	0.972
History of PAD	4.5	7.7	8.7	0.164
History of cerebrovascular disease	6.0	9.2	9.7	0.549
Family history of coronary artery disease	27.4	28.7	30.2	0.239
Prior CABG	7.1	12.0	18.1	<0.001
History of PCI	16.3	24.0	32.5	<0.001
Catheterization for qualifying event	88.4	85.5	87.5	0.035
PCI for treatment of qualifying event	70.0	68.0	73.4	<0.001
BMI group, kg/m^2				0.023
BMI ≤25	26.8	25.9	24.9	
BMI >25 to 30	43.5	43.4	40.8	
BMI >30	29.8	30.7	34.2	
Creatinine clearance group at qualifying event, ml/min				0.158
CrCl <60	16.6	22.2	21.5	
CrCl 60 to <90	39.2	39.6	37.7	
CrCl ≥90	44.2	38.2	40.8	
Medications prior to qualifying event				
Aspirin	38.6	48.6	54.2	<0.001
Beta-blocker	31.5	40.2	45.7	<0.001
Statin	31.2	39.5	46.0	<0.001
Thienopyridine	9.0	13.1	17.9	<0.001

Values are % or median (interquartile range). *Pooled randomization groups. For 3-way comparison, all p < 0.001 except sex (p = 0.005), qualifying event (p = 0.289), current smoker (p = 0.076), and family history CAD (p = 0.017).

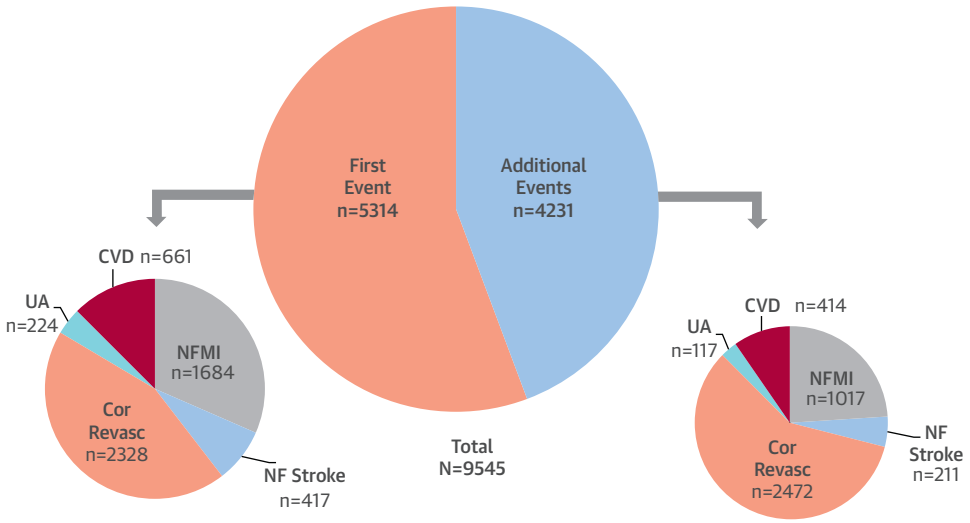
BMI = body mass index; CABG = coronary artery bypass graft; CHF = congestive heart failure; CrCl = creatinine clearance; LDL = low-density lipoprotein; MI = myocardial infarction; NSTEACS = non-ST-segment elevation acute coronary syndrome; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

(RR: 0.87; 95% CI: 0.79 to 0.96; p = 0.004), a 23% reduction in the total number of strokes (RR: 0.77; 95% CI: 0.65 to 0.93; p = 0.005), and a nonsignificant 6% reduction in coronary revascularizations (RR: 0.94; 95% CI: 0.88 to 1.01; p = 0.095) (Figure 2). Among the total 48 peri-PCI MI events, 20 occurred in the ezetimibe/simvastatin group, and 28 occurred in the placebo/simvastatin group. Among the stroke events, total ischemic stroke was reduced with ezetimibe/simvastatin (RR: 0.76; 95% CI: 0.63-0.91; p = 0.002). Recurrent hemorrhagic strokes were uncommon, with only 5 subjects having an additional hemorrhagic stroke (3 subjects in the placebo/simvastatin group and 2 subjects in the ezetimibe/simvastatin group), and no difference was observed between randomized groups in total hemorrhagic stroke (RR: 1.32; 95% CI: 0.86 to 2.03; p = 0.20). Total urgent revascularization was also reduced with ezetimibe/simvastatin (RR: 0.79; 95% CI: 0.70 to 0.90; p <0.001). The number of total unstable angina events was similar between treatment groups, as was the number of CV deaths.

Total events were also consistently lower in the ezetimibe/simvastatin group for the 3 pre-specified secondary endpoints (Figure 3), as well as for the exploratory endpoint of CV death, MI, or stroke (RR: 0.88; 95% CI: 0.81 to 0.96; p = 0.002).

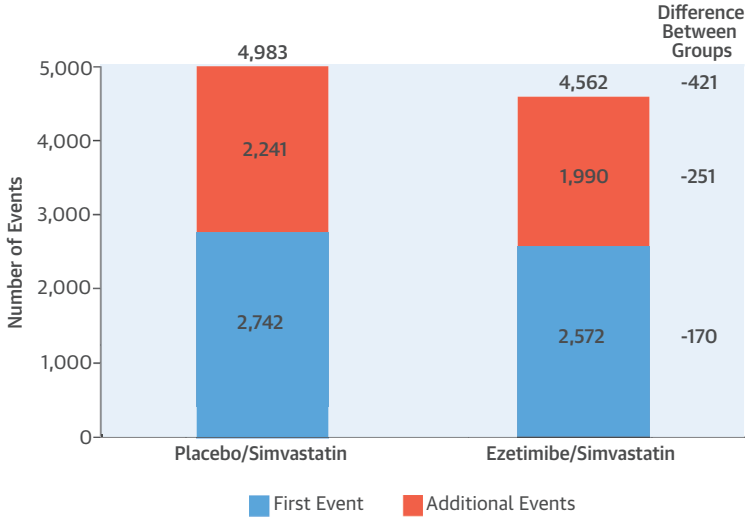
In the WLW Cox model of the PEP, results were similar, with a reduction in primary endpoint events associated with the ezetimibe/simvastatin group (HR: 0.93; 95% CI: 0.89 to 0.99; p = 0.01) (Figure 4).

FIGURE 1 **Number of First and Subsequent Primary Endpoint Events, Overall and by Component**



Overall, a similar proportion of first and additional events were stroke (7.8% vs. 5.0%, respectively), unstable angina (4.2% vs. 2.8%, respectively), and cardiovascular death (12.4% vs. 9.8%, respectively). There were proportionately fewer MIs (24.0% vs. 31.7%, respectively) and proportionately more revascularizations (58.4% vs. 43.8%, respectively) among the additional events than among the first events. CVD = cardiovascular death; Revasc = revascularization; MI = myocardial infarction; NF = nonfatal; UA = unstable angina.

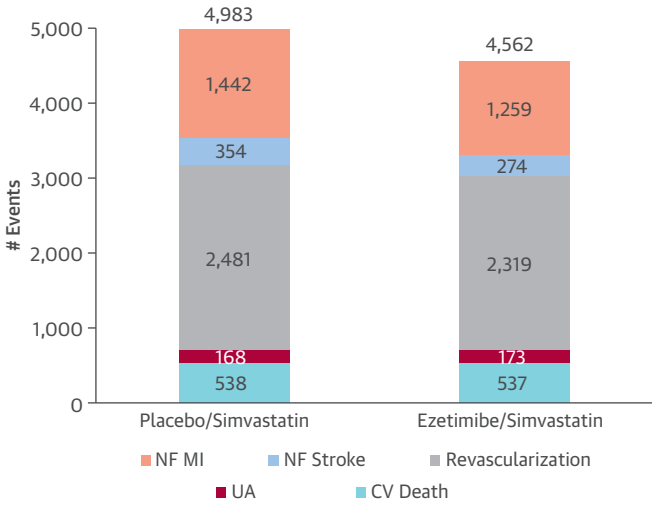
CENTRAL ILLUSTRATION **First, Additional, and Total Primary Endpoint Events During Follow-Up by Randomization Group**



Murphy, S.A. et al. J Am Coll Cardiol. 2016; 67(4):353–61.

The first occurrence of the primary endpoint was significantly reduced in the ezetimibe/simvastatin group compared to that in the placebo/simvastatin group (HR: 0.936; 95% CI: 0.887 to 0.988; p = 0.016), as were additional events (RR: 0.88; 95% CI: 0.79 to 0.98) and total events (RR: 0.91; 95% CI: 0.85 to 0.97; p = 0.007).

FIGURE 2 Total Events During Follow-Up by Randomization Group for Components of the Primary Endpoint



Total events were significantly reduced with ezetimibe/simvastatin versus placebo/simvastatin for the component of nonfatal MI (RR: 0.87; 95% CI: 0.79 to 0.96; p = 0.004) and nonfatal stroke (RR: 0.77; 95% CI: 0.65 to 0.93; p = 0.005), and there was a nonsignificant reduction in coronary revascularizations (RR: 0.94; 95% CI: 0.88 to 1.01; p = 0.095). There were no differences between treatment groups in total unstable angina events or in CV deaths. CV = cardiovascular; other abbreviations as in Figure 1.

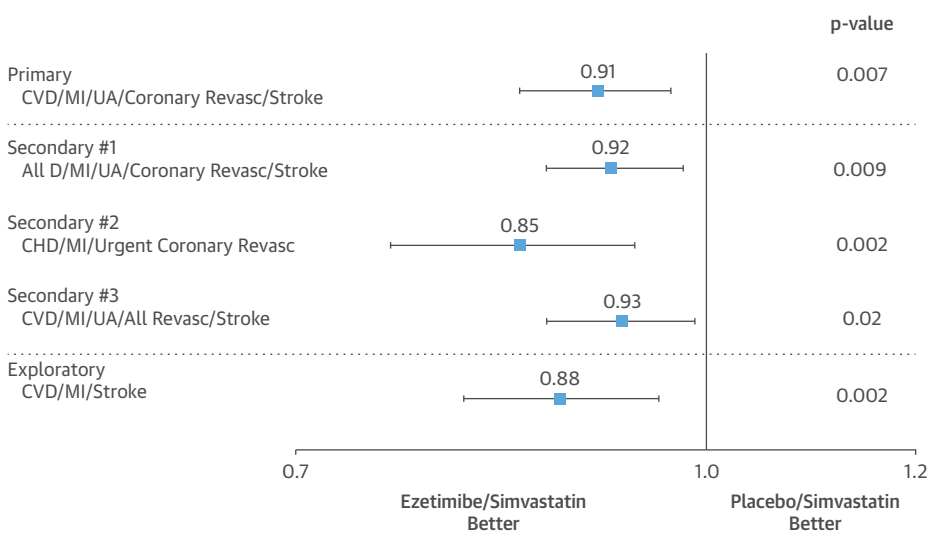
Likewise, when we evaluated outcomes using the PWP model, the overall PEP findings were consistent (HR: 0.94; 95% CI: 0.90 to 0.98; p = 0.002), as were the findings with the Andersen Gill model (HR: 0.93; 95% CI: 0.88 to 0.98; p = 0.01).

In an on-treatment analysis that included events between first dose of study drug and 30 days of discontinuation, results were consistent with the intent to treat analysis, with a reduction in the total number of PEP events in the ezetimibe/simvastatin group compared with the placebo/simvastatin group (n = 3,246 vs. n = 3,539, respectively; RR: 0.89; 95% CI: 0.82 to 0.96; p = 0.003).

DISCUSSION

CLINICAL BENEFIT BEYOND THE FIRST EVENT. Previous trials have consistently demonstrated a reduction in first and total cardiovascular events associated with more aggressive lipid lowering with intensive statin therapy compared with moderate-dose statin among post-ACS patients (9–16). Although lower LDL-C levels are attributed as the principal basis of the benefit, it was not known if additional persistent reductions in LDL-C with a nonstatin agent could further prevent recurrent cardiovascular events. Several previously studied lipid modifying nonstatin agents, when added to background statin, did not show a reduction in clinical outcomes, such as niacin

FIGURE 3 Total Events During Follow-Up by Randomization Group for the Primary and 3 Pre-Specified Secondary Endpoints



Total events were consistently lower in the ezetimibe/simvastatin group for the 3 pre-specified secondary endpoints, as well as for the exploratory endpoint of CV death, MI, or stroke. CHD = coronary heart disease death; CV = cardiovascular; other abbreviations as in Figure 1.

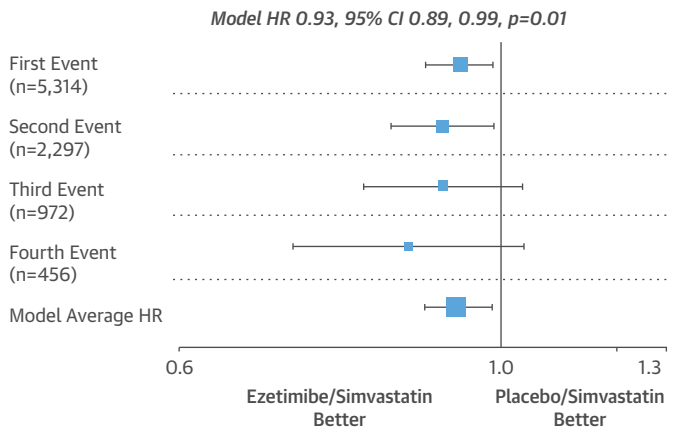
(17,18), torcetrapib (19), and dalcetrapib (20). The IMPROVE-IT trial demonstrated that the addition of the nonstatin lipid-lowering agent ezetimibe when added to simvastatin reduced LDL-C by approximately an additional 24% and resulted in a significantly lower risk of first cardiovascular events compared with statin monotherapy (3). The present study extends these findings, demonstrating a reduction in not only first events but in total events over long-term follow-up with the addition of ezetimibe to statin therapy. Trials are currently underway studying other nonstatin therapies for LDL-C reduction, including PCSK9 inhibitors, which will also be evaluating clinical event reduction with greater LDL-C lowering (FOURIER trial, NCT01764633; and the ODYSSEY Outcomes trial, NCT01663402).

Although there were reductions in the total primary and 3 pre-specified secondary endpoints of the trial, it should be noted that much of the reduction associated with the ezetimibe/simvastatin combination was driven by the clinically important endpoints of MI and stroke. Specifically, the reduction was greatest for ischemic stroke. Although there was no mortality effect in IMPROVE-IT, additional ischemic events of stroke and MI have been associated with not only a higher mortality, but also an impaired quality of life (21) and higher costs (22), making these events especially critical for patients, clinicians, and the health care system. Multiple events in a subject consume more resources as a result of additional hospitalizations, tests, and physician visits. Health economic analyses relating to IMPROVE-IT are underway.

LONG-TERM FOLLOW-UP. The IMPROVE-IT study had a particularly long duration of follow-up among post-ACS trials, with a median 6-year follow-up. This resulted in 13% of the 18,144 subjects having more than 1 occurrence of the primary composite endpoint, making this trial particularly well suited to evaluate total events. The first event contributed 5,314 (56%) of all events; thus 4,231 (44%) events were not analyzed in the initial primary analysis of the trial (3) when performing traditional Cox survival analysis of time to first event.

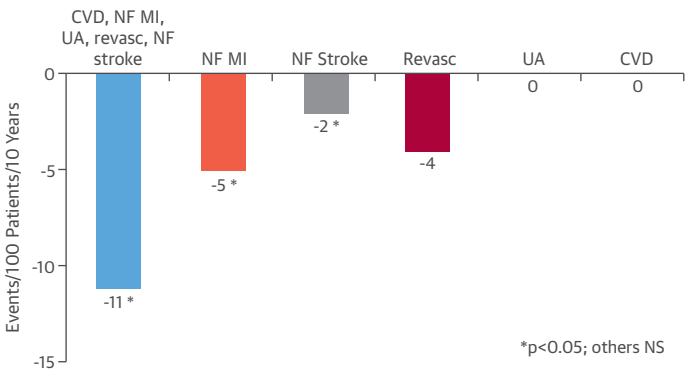
STATISTICAL CHALLENGES FOR ANALYSIS AND STUDY LIMITATIONS. Examining efficacy using total events can present statistical challenges for analysis. Standard survival analysis methods require the assumption of independence of failure times. However, with total events analysis, failure times are often correlated within a subject. The present analysis used a negative binomial model, which evaluates the number of occurrences of an event over a period of time. In addition, a marginal model was used for analysis as described by the WLW method (7). This technique uses survival methods that consider the occurrence of each event separately from the time of randomization without specifically considering the occurrence of the first event or the order of events, but does take into account the correlation between observations within each subject. Other statistical methods include the use of conditional models, in which each additional event is conditional on having had a prior event. An example of a conditional model includes the PWP (8). With the PWP model, it is assumed that a subject is not at risk of a second

FIGURE 4 Primary Endpoint by Randomization Group as Assessed Using the Wei, Lin, Weissfeld Model



Primary endpoint events were reduced with ezetimibe/simvastatin compared with placebo/simvastatin (HR: 0.93; 95% CI: 0.89 to 0.99; p = 0.01).

FIGURE 5 Risk Differences for 100 Patients Treated for 10 Years With Ezetimibe/Simvastatin for the Components of the Primary Endpoint



For every 100 patients treated for 10 years, 11 total primary endpoint events were prevented with ezetimibe plus simvastatin. Abbreviations as in Figure 1.

event until the first event has occurred. Other novel methods for analyzing additional events including the win ratio (23) and weighted composite endpoints (24). As demonstrated by Bakal et al. (25), model selection can impact the results and conclusion of events analysis (25). In the present analysis, the results from both the WLW (7), Andersen Gill, and PWP (8) models were consistent with the main negative binomial analysis, showing a reduction in PEP events with ezetimibe/simvastatin compared with placebo/simvastatin.

Several limitations of total events analyses must be acknowledged. Recurrent events within patients are often correlated and thus may violate the assumption of independence of events. In addition, after a first nonfatal event, many subjects discontinue blinded study drug, which may result in a higher proportion of subsequent events occurring off study drug. To address this limitation, an on-treatment analysis was performed which showed findings consistent with the intent to treat analysis. Although some components of the PEP can occur multiple times, the component of CV death precludes the occurrence of subsequent events. This is particularly critical when there is an imbalance between treatment arms in the number of CV deaths. In the present study, the number of CV deaths was nearly identical between randomization groups (n = 537 for ezetimibe/simvastatin and n = 538 for placebo/simvastatin). Given the balanced number of CV deaths, we did not incorporate additional modifications in our analysis.

CONCLUSIONS

Lipid-lowering therapy with ezetimibe plus simvastatin improved clinical efficacy with reductions in total PEP events compared with simvastatin alone. Translated into a risk difference, for every 100 patients treated for 10 years, 11 total PEP events were prevented with ezetimibe plus simvastatin (**Figure 5**). As there were no differences in cardiovascular death or unstable angina, these 11 total events prevented were due to a reduction of 5 MIs, 2 strokes, and 4 revascularizations. Evaluating total events more than doubled the number of events prevented compared with examining only the first event (first PEP [n = 170] vs. total PEPs [n = 421]) (**Central Illustration**). These data provide further support for the benefit of continuation of intensive combination lipid-lowering therapy after a recurrent cardiovascular event.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among survivors of acute coronary syndromes, lipid-lowering therapy combined with the nonstatin agent ezetimibe plus simvastatin significantly reduced the total number of cardiovascular events (both first and subsequent) during follow-up compared with simvastatin alone.

TRANSITIONAL OUTLOOK: Additional trials of other intensive lipid-lowering strategies should compare the effects on total cardiovascular events during long-term therapy in high-risk patient populations.

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KEY WORDS ezetimibe, low-density lipoprotein cholesterol, simvastatin, total events

APPENDIX For supplemental tables as well as endpoint definitions, please see the online version of this article.