The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)

Journal club

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- I have no disclosures…

What is IMPROVE-IT?

- A multicenter, double-blind, randomized study to establish the clinical benefit and safety of vytorin (ezetimibe/simvastatin tablet) vs simvastatin monotherapy in high risk subjects presenting with acute coronary syndrome

- 1158 sites, 39 countries

Background:

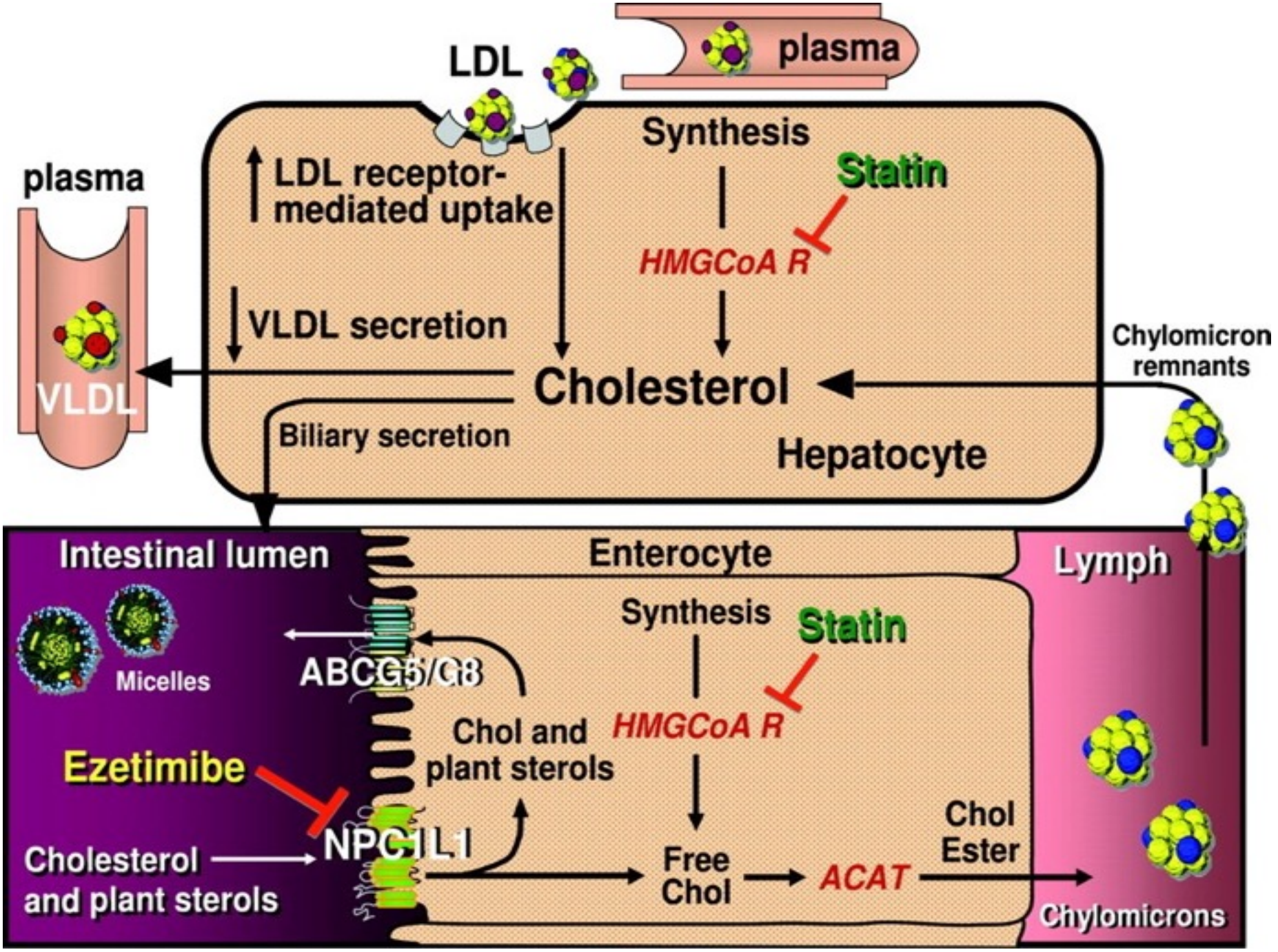
- Lowering LDL-C a mainstay of cardiovascular prevention
- Evidence from statin trials show reduction in morbidity and mortality
- High-dose statins further reduce non fatal CV events

- To date, no lipid-modifying therapy added to statins has been demonstrated to provide a clinical benefit- Fibrates, niacin, CETP inh.
- Recent ACC/AHA Guidelines have emphasized use of statin thx
- Despite current thx, patients remain at high risk

Ezetimibe: Background

- Ezetimibe inhibits Niemann Pick C1 like 1–located primarily on the epithelial brush border of the GI tract, resulting in reduced cholesterol absorption
- When added to statin, produces ~20% further reduction in LDL C
- 2 recent human genetic analyses have correlated polymorphisms in NPC1L1 with lower levels of LDL C and lower risk of CV events

MI Genetics Consortium Investigators NEJM 2014; online Nov 12; Ference BA et al AHA 2014


LDL
plasma
plasma
LDL receptor-mediated uptake
Synthesis
Statin
HMGCoA R
VLDL secretion
VLDL
Chylomicron remnants
Cholesterol
Biliary secretion
Hepatocyte
Intestinal lumen
Enterocyte
Lymph
Synthesis
Statin
Micelles
ABCG5/G8
Chol and plant sterols
HMGCoA R
Ezetimibe
NPC1L1
Cholesterol and plant sterols
Free Chol
ACAT
Chol Ester
Chylomicrons

Context

- Previous cholesterol treatment trials
- Previous work on ezetimibe;
  - ENHANCE- Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression- in pts with familial hypercholesterolaemia
  - SEAS- Simvastatin and Ezetimibe in Aortic Stenosis
  - SHARP –Study of Heart and Renal Protection
- (?cancer causation)

Study hypothesis

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

Research Questions

- Does lowering LDL C with the non-statin agent ezetimibe reduce cardiac events?
- Is (Even) Lower (Even) Better? (estimated mean LDL C ~50 vs. 65mg/dL)
- Safety of ezetimibe

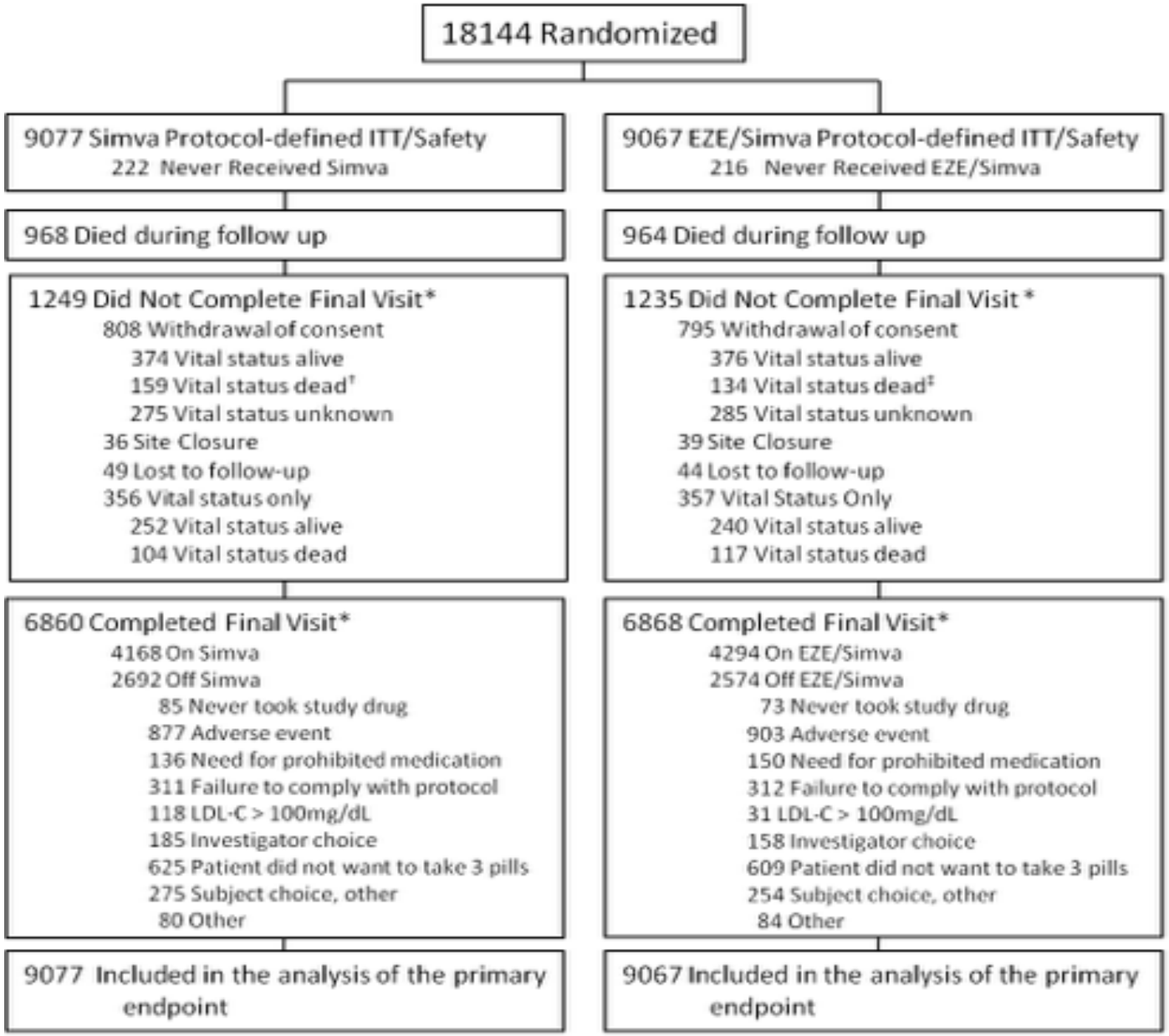
Subjects

Inclusion criteria

- Hospitalization for STEMI, NSTEMI/UA < 10 days
- Age ≥ 50 years, and ≥ 1 high risk feature:
  - New ST chg, + troponin, DM, prior MI, PAD, cerebrovasc,
  - prior CABG > 3 years, multivessel CAD,
- LDLC 50-125 mg/dL (50–100 mg/dL (if prior lipid-lowering Rx)

Exclusion criteria

- CABG for treatment of qualifying ACS
- Current statin Rx more potent than simva 40mg
- Creat Cl < 30mL/min, active liver disease



*Final visits occurred on or after May 1, 2014; Vital status recorded in 2014.

†Includes 28 CV deaths, 16 non-CV deaths during follow up and 115 deaths > 4 months after last contact (30 non-CV death, 85 unknown deaths); ‡Includes 14 CV deaths, 14 non-CV deaths during follow up and 106 deaths > 4 months after last contact (27 non-CV death, 79 unknown deaths)

Follow up

- Visit Day 30, every 4 months
- Duration -Minimum 2 ½ year follow-up (at least 5250 events)

Endpoints

- Primary endpoint :
  - CV death, MI, hospital admission for UA, coronary revascularization (≥30 days after randomization), or stroke
- Secondary efficacy endpoint:
  - All deaths, MI, coronary revascularization, CVA
  - CHD, MI, Urgent coronary revascularization
  - CVD, MI, UA, All revascularization, CVA

Analysis

- All efficacy and safety analyses performed in the intention-to-treat population.
- 5250 events required to give the study 90% power to detect a 9.375% lower relative risk for the primary end point with simvastatin–ezetimibe than with simvastatin monotherapy.

Analysis…..cont.

- DSMB-10 safety reviews
- 3 interim efficacy analyses were performed, after 45.7%, 76.1%, and 86.9% of the required events had occurred.
- Adjustment of the level of significance to account for this determined by the Lan–DeMets Approximation of the O'Brien–Fleming boundaries for group sequential testing, with a final two-sided P value for significance of 0.0394 or less.
- The false positive error rate for the three secondary end points controlled with the use of the Hochberg method.

Analysis….cont.

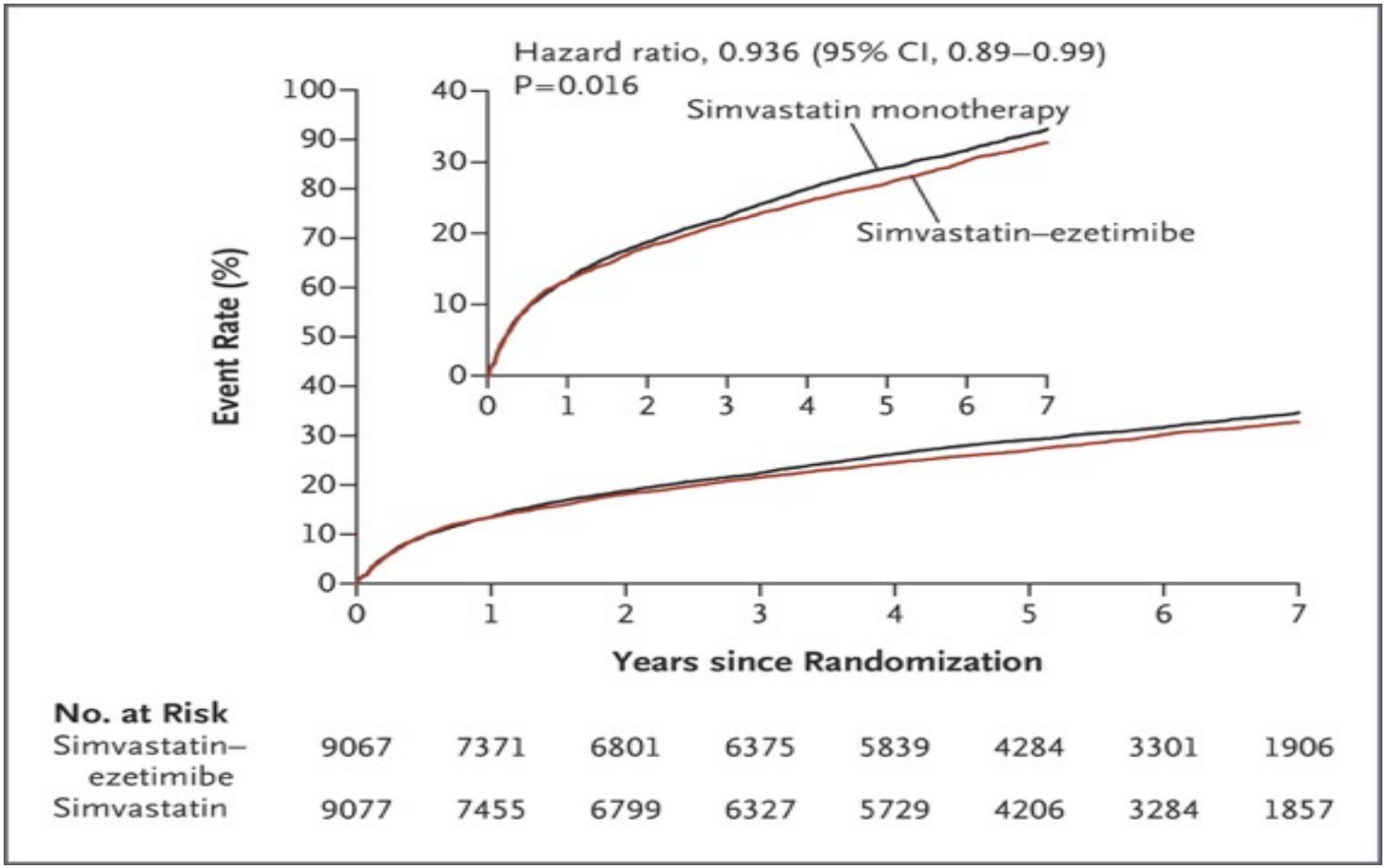
- A nominal P value of 0.05 or less without adjustment for multiple testing was used for other end points.
- Estimates of the hazard ratios and associated 95% confidence intervals for the comparison of simvastatin–ezetimibe with simvastatin monotherapy were obtained with the use of a Cox proportional-hazards model, with study group and stratification factors as covariates.
- Event rates are Kaplan–Meier failure rates at 7 years.

KEY RESULTS

Table 1. Baseline Characteristics.

Variable	Simvastatin Monotherapy (N = 9077)	Simvastatin–Ezetimibe (N = 9067)
Demographic characteristic		
Age — yr	63.6±9.8	63.6±9.7
Male — no. (%)	6886 (75.9)	6842 (75.5)
White race — no. (%)†	7624 (84.0)	7578 (83.6)
Weight — kg	83.0±17.4	82.9±17.4
Body-mass index‡	28.3±5.2	28.3±5.2
Region — no. (%)		
North America	3487 (38.4)	3486 (38.4)
Western Europe	3641 (40.1)	3633 (40.1)
Eastern Europe	707 (7.8)	709 (7.8)
Asia Pacific	448 (4.9)	448 (4.9)
South America	794 (8.7)	791 (8.7)
Coexisting conditions — no./total no. (%)		
Diabetes	2474/9077 (27.3)	2459/9067 (27.1)
Hypertension	5557/9072 (61.3)	5580/9063 (61.6)
Congestive heart failure	371/9077 (4.1)	419/9067 (4.6)
Peripheral arterial disease	518/9077 (5.7)	487/9067 (5.4)
Current smoker — no./total no. (%)	3035/9072 (33.5)	2943/9067 (32.5)
Previous MI — no./total no. (%)	1881/9077 (20.7)	1925/9054 (21.3)
Previous PCI — no. (%)	1796 (19.8)	1766 (19.5)
Previous CABG — no. (%)	842 (9.3)	842 (9.3)
Before index ACS		
Medications — no./total no. (%)		
Lipid-lowering agent	3207/9063 (35.4)	3227/9067 (35.6)
Statin	3111/9077 (34.3)	3135/9067 (34.6)
Aspirin	3855/9077 (42.5)	3799/9067 (41.9)
Creatinine clearance — ml/min		
Median	84.7	84.4

Primary Endpoint — ITT



Primary Endpoint in Pre-specified Subgroups

Characteristic	Total Patients	KM % at 7 years SIMVA/EZE	KM % at 7 years SIMVA	Hazard Ratio (95% CI)	Interaction *P*-Value
Overall	5314	32.73	34.67	0.936 (0.887, 0.988)	
Gender					
Male	13728	33.26	34.87	0.952 (0.895, 1.012)	0.267
Female	4416	31.01	34.02	0.885 (0.791, 0.991)	
Age Group 1 (years)					
<65	10173	29.94	30.79	0.975 (0.904, 1.051)	0.098
≥65	7971	36.35	39.94	0.890 (0.824, 0.961)	
Age Group 2 (years)					
<75	15346	31.67	32.46	0.971 (0.915, 1.031)	0.005
≥75	2798	38.95	47.60	0.797 (0.704, 0.902)	
Race					
Caucasian	15202	33.06	35.02	0.939 (0.885, 0.995)	0.790
Non-Caucasian	2923	31.15	32.90	0.919 (0.799, 1.058)	
Region					
United States	5866	34.41	35.41	0.969 (0.883, 1.064)	0.575
Canada	1107	22.15	25.54	0.894 (0.698, 1.145)	
Western Europe	7274	33.92	35.87	0.923 (0.849, 1.002)	
Eastern Europe	1416	33.43	32.94	1.071 (0.878, 1.307)	
Malaysia/Singapore/Hong Kong	616	25.90	28.29	0.845 (0.602, 1.187)	
South America	1585	32.05	37.68	0.859 (0.714, 1.034)	
Australia/New Zealand	280	24.06	32.12	0.734 (0.460, 1.170)	

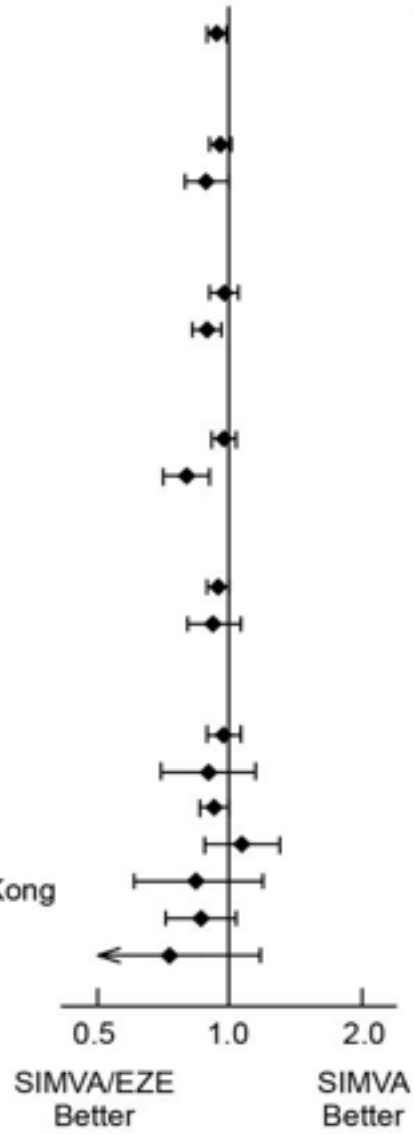


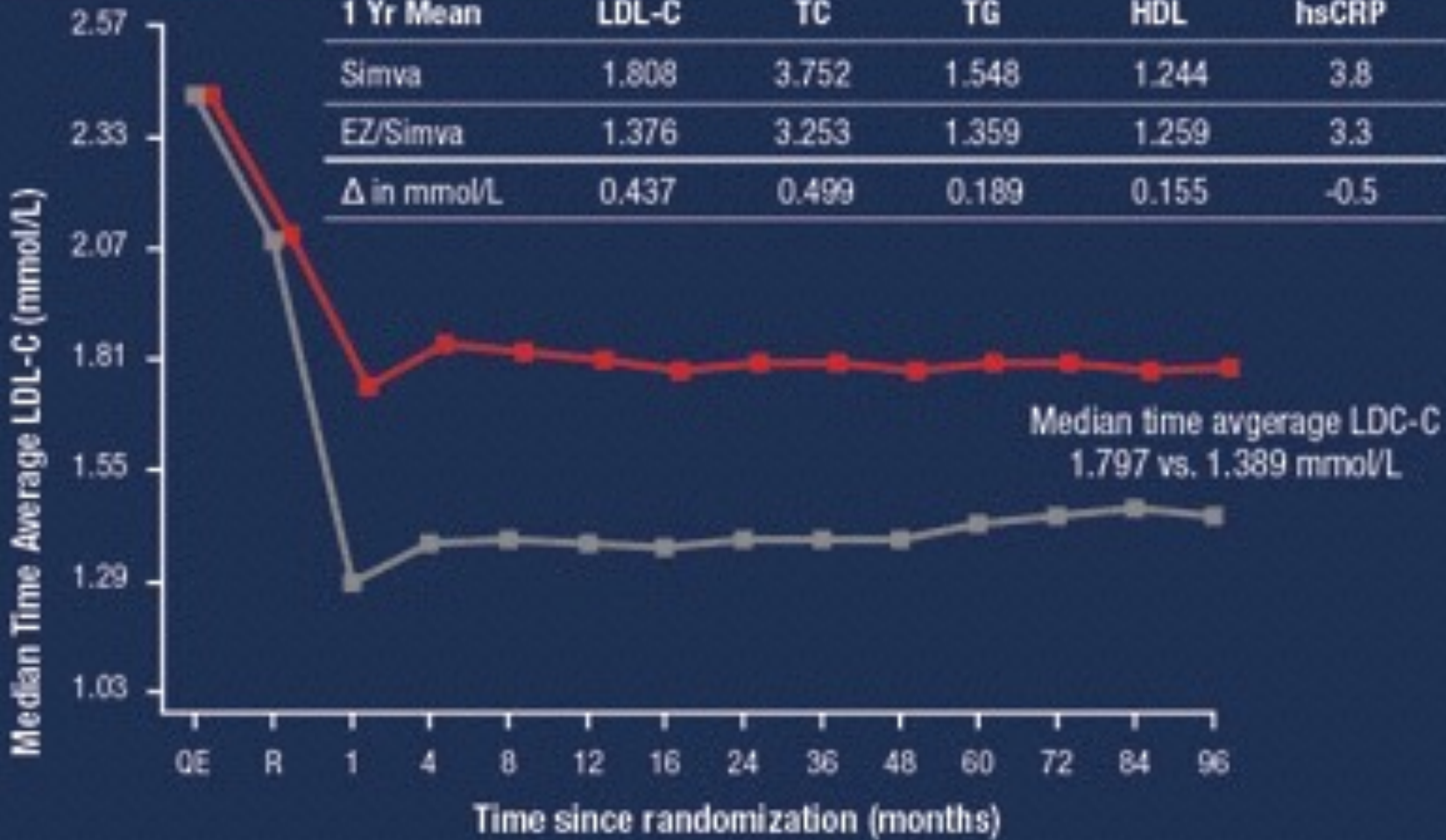
Table 2. Primary, Secondary, and Individual End Points.*

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

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

LDL-C and Lipid Changes

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	1.808	3.752	1.548	1.244	3.8
EZ/Simva	1.376	3.253	1.359	1.259	3.3
Δ in mmol/L	0.437	0.499	0.189	0.155	-0.5



EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4326	3387	2569	1168

Adapted from Cannon *et al.* AHA 2014 Late-breaker IMPROVE-IT trial.

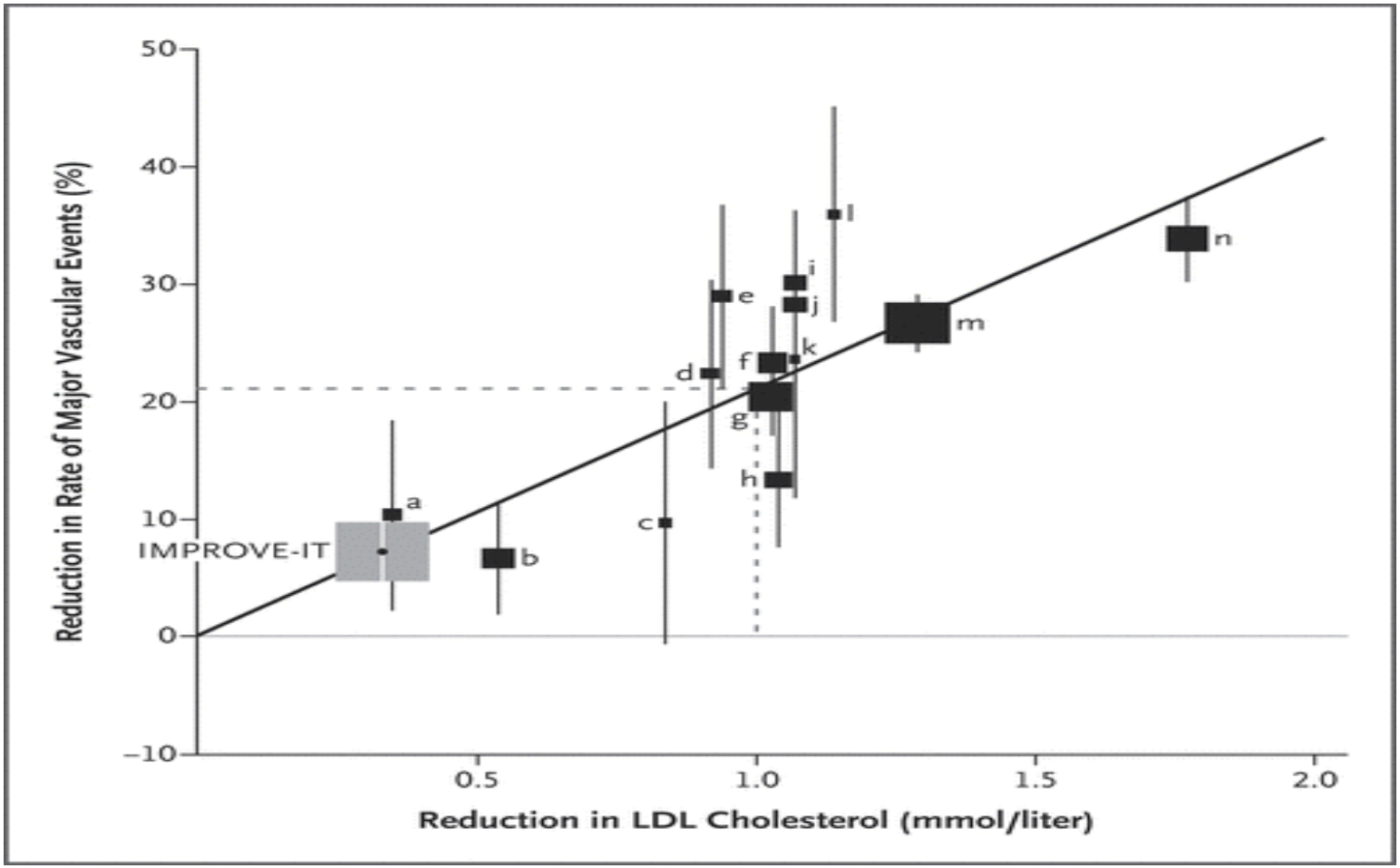
Table 3. Prespecified Safety End Points.*

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

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

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

In comparison to CTT Trials…



DISCUSSION

- **Validity of the study**
  - Double-blinding
  - Randomized assignment of patients to each arm
  - Groups were similar at the start of the trial
  - Patients all accounted for
  - Groups treated equally during trial

- ?Unblinding of the study due to safety issues

- Results-**positive**
  - Allows use of non-statin medication for lowering lipids, supports even lower LDL levels
- **Very small** treatment effect after a very long treatment exposure
  - 50 people would have to be treated for 7 years to prevent 1 event
  - No optimal target of LDL-C

- Results **may not** be applicable presently to patient care
  - Study done in a specific population of patients- post-ACS- very high risk, 2 prevention
  - All clinically important outcomes not considered-use of other potent statins
  - Are the likely treatment benefits worth potential harms and costs?
  - Compliance- 42% of the participants regardless of treatment assignment, discontinued the study medication prematurely, lifelong thx