IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

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

Background: Cholesterol Lowering

- Lowering LDL cholesterol (LDL-C) has been a mainstay of cardiovascular prevention
- Evidence mostly from statin trials which 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 inhibitors
- Recent ACC/AHA Guidelines have emphasized use of statin therapy
- Despite current therapies, patients remain at high risk

Ezetimibe: Background

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- Ezetimibe inhibits Niemann-Pick C_1-like 1 (NPC_1L_1) protein
  - 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
- Two recent human genetic analyses have correlated polymorphisms in NPC_1L_1 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*

Goals

IMPROVE-IT: First large trial evaluating clinical efficacy of combination EZ/Simva vs. simvastatin (i.e., the addition of ezetimibe to statin therapy):

- **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**

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

Patient Population

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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
- LDL-C 50-125 mg/dL (50–100 mg/dL if prior lipid-lowering Rx)

Major Exclusion Criteria:

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

Study Design

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Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM
**2.6mM

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

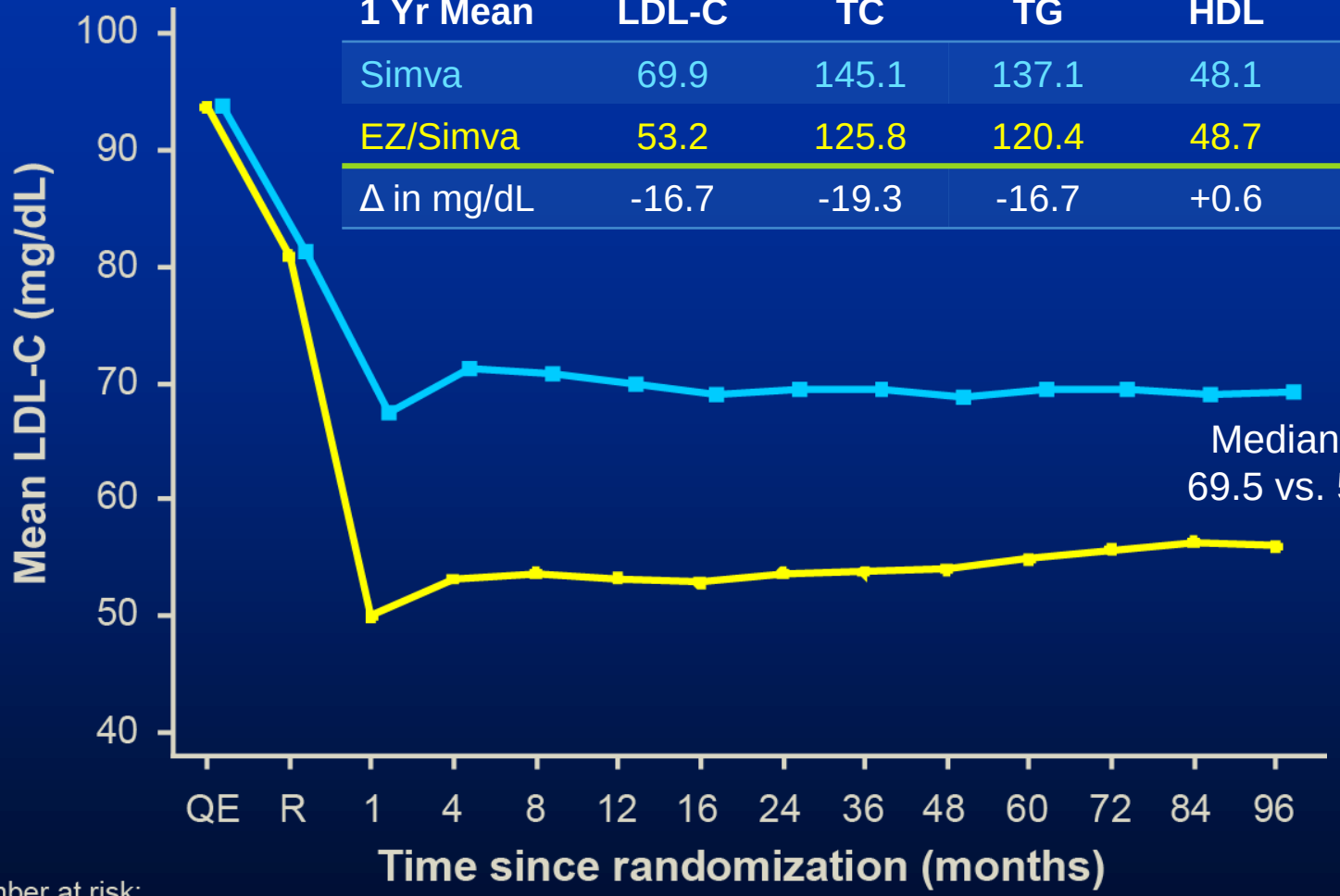
Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

Baseline Characteristics

	Simvastatin (N=9077) %	EZ/Simva (N=9067) %
Age (years)	64	64
Female	24	25
Diabetes	27	27
MI prior to index ACS	21	21
STEMI / NSTEMI / UA	29 / 47 / 24	29 / 47 / 24
Days post ACS to rand (IQR)	5 (3, 8)	5 (3, 8)
Cath / PCI for ACS event	88 / 70	88 / 70
Prior lipid Rx	35	36
LDL-C at ACS event (mg/dL, IQR)	95 (79, 110)	95 (79,110)

LDL-C and Lipid Changes

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



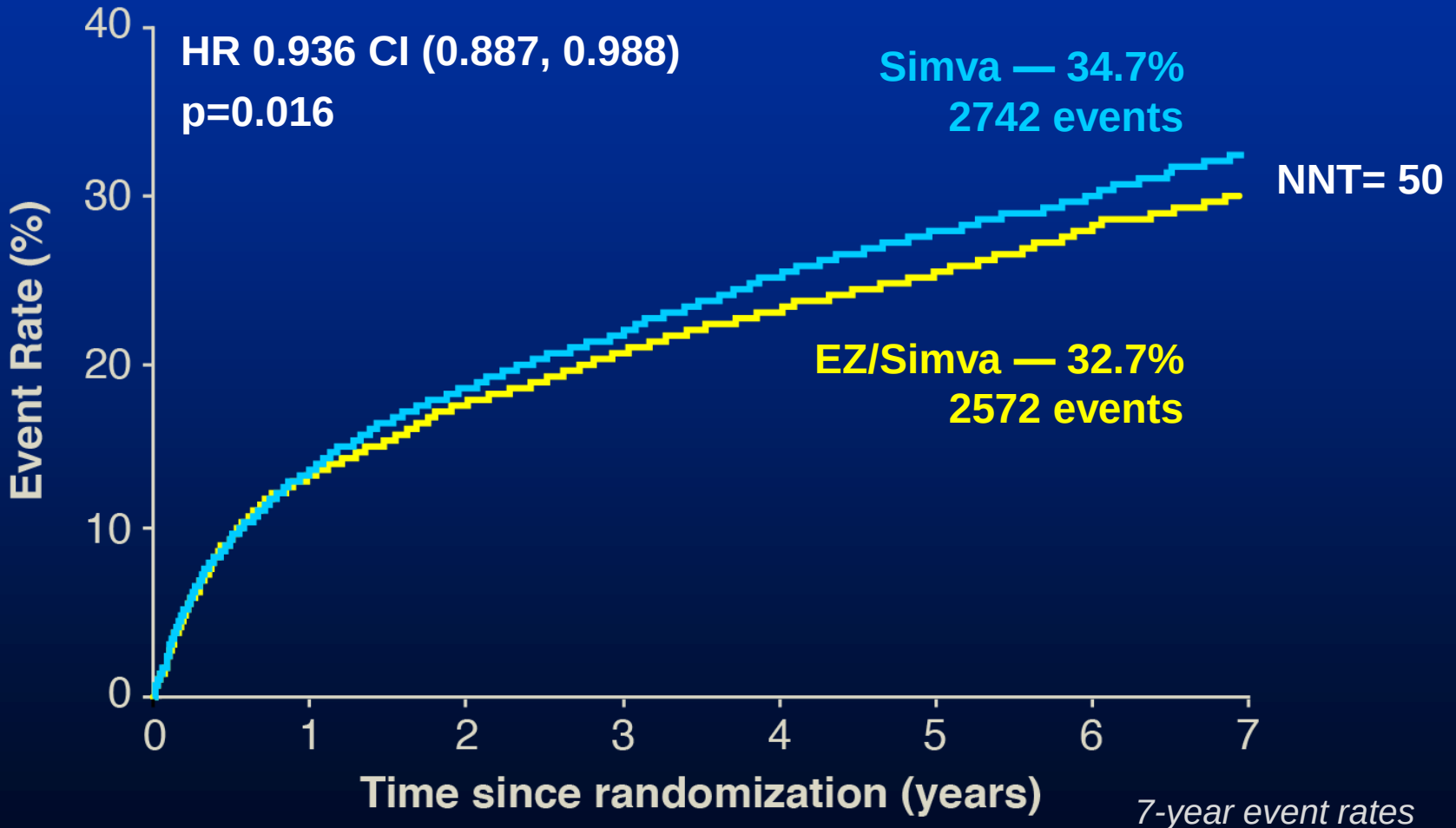
Median Time avg
69.5 vs. 53.7 mg/dL

Number at risk:

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	4395	3387	2569	1068

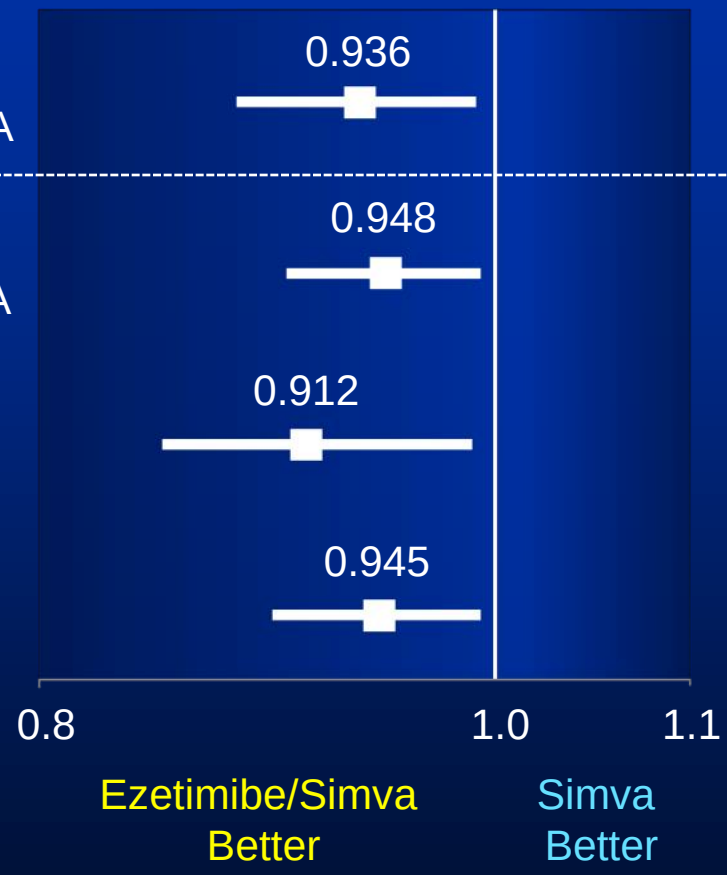
Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



7-year event rates

Primary and 3 Prespecified Secondary Endpoints — ITT



	Simva*	EZ/Simva*	p-value
Primary CVD/MI/UA/Cor Revasc/CVA	34.7	32.7	0.016
Secondary #1 All D/MI/UA/Cor Revasc/CVA	40.3	38.7	0.034
Secondary #2 CHD/MI/Urgent Cor Revasc	18.9	17.5	0.016
Secondary #3 CVD/MI/UA/All Revasc/CVA	36.2	34.5	0.035

**7-year event rates (%)*

UA, documented unstable angina requiring rehospitalization; Cor Revasc, coronary revascularization (≥30 days after randomization); All D, all-cause death; CHD, coronary heart disease death; All Revasc, coronary and non-coronary revascularization (≥30 days)

Individual Cardiovascular Endpoints and CVD/MI/Stroke

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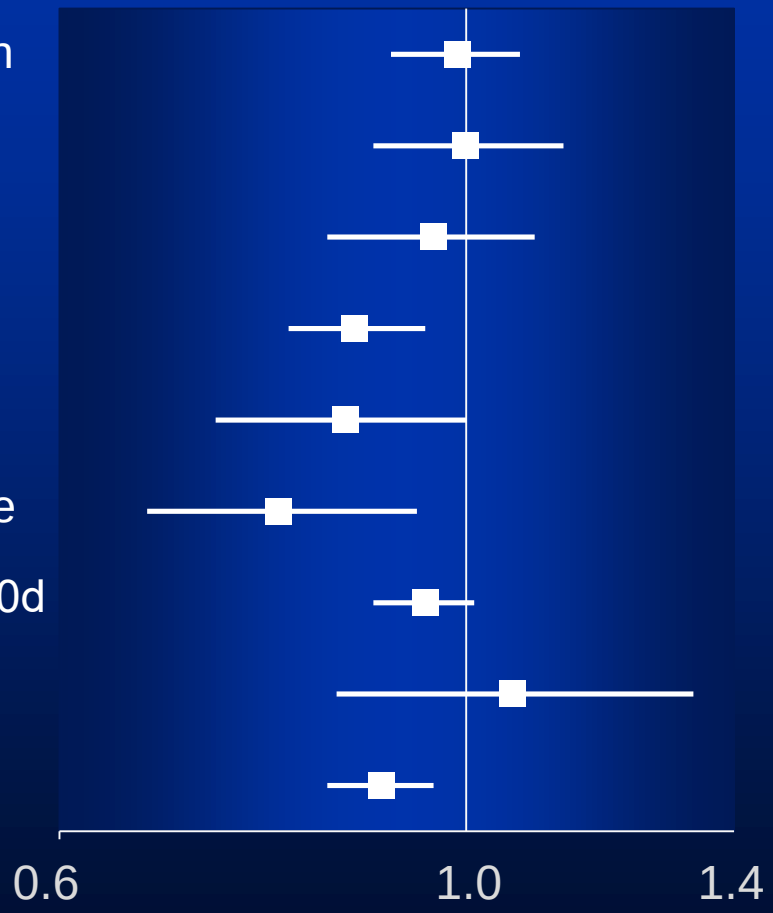
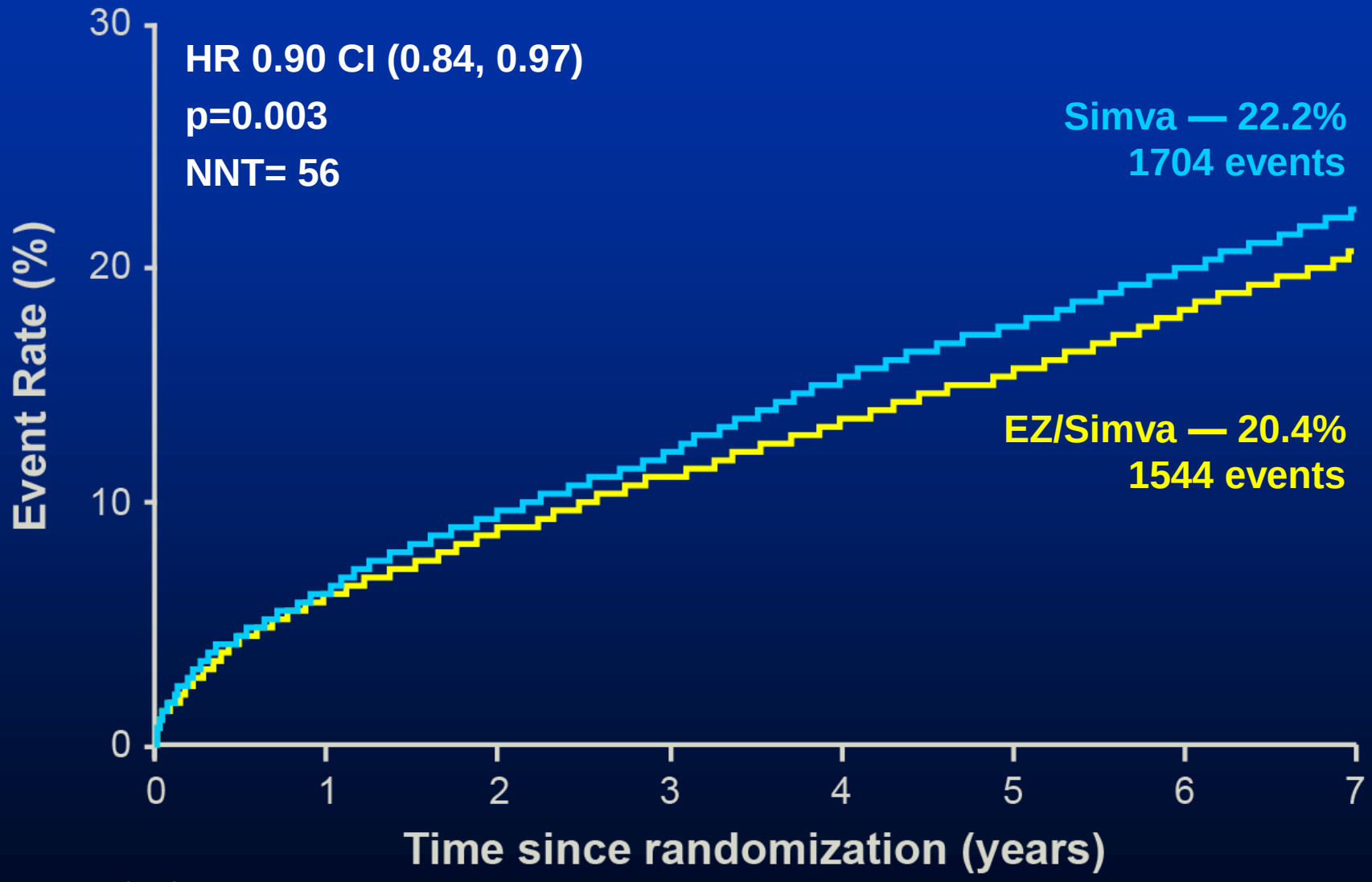


	HR	Simva*	EZ/Simva*	p-value
All-cause death	0.99	15.3	15.4	0.782
CVD	1.00	6.8	6.9	0.997
CHD	0.96	5.8	5.7	0.499
MI	0.87	14.8	13.1	0.002
Stroke	0.86	4.8	4.2	0.052
Ischemic stroke	0.79	4.1	3.4	0.008
Cor revasc ≥ 30d	0.95	23.4	21.8	0.107
UA	1.06	1.9	2.1	0.618
CVD/MI/stroke	0.90	22.2	20.4	0.003

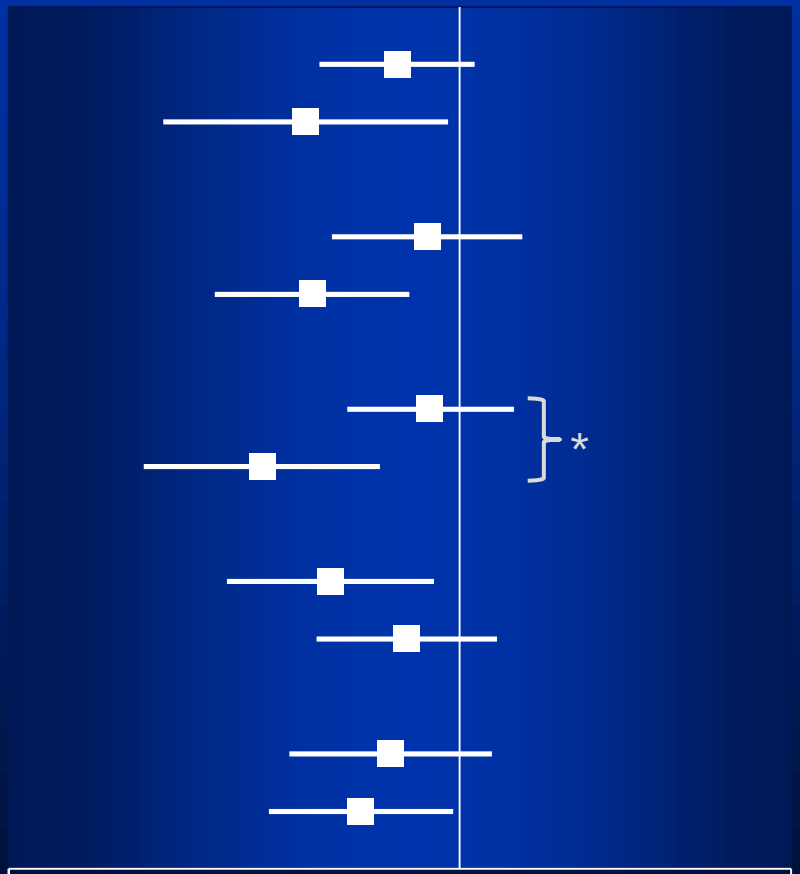
**7-year event rates (%)*

CV Death, Non-fatal MI, or Non-fatal Stroke



7-year event rates

Major Pre-specified Subgroups

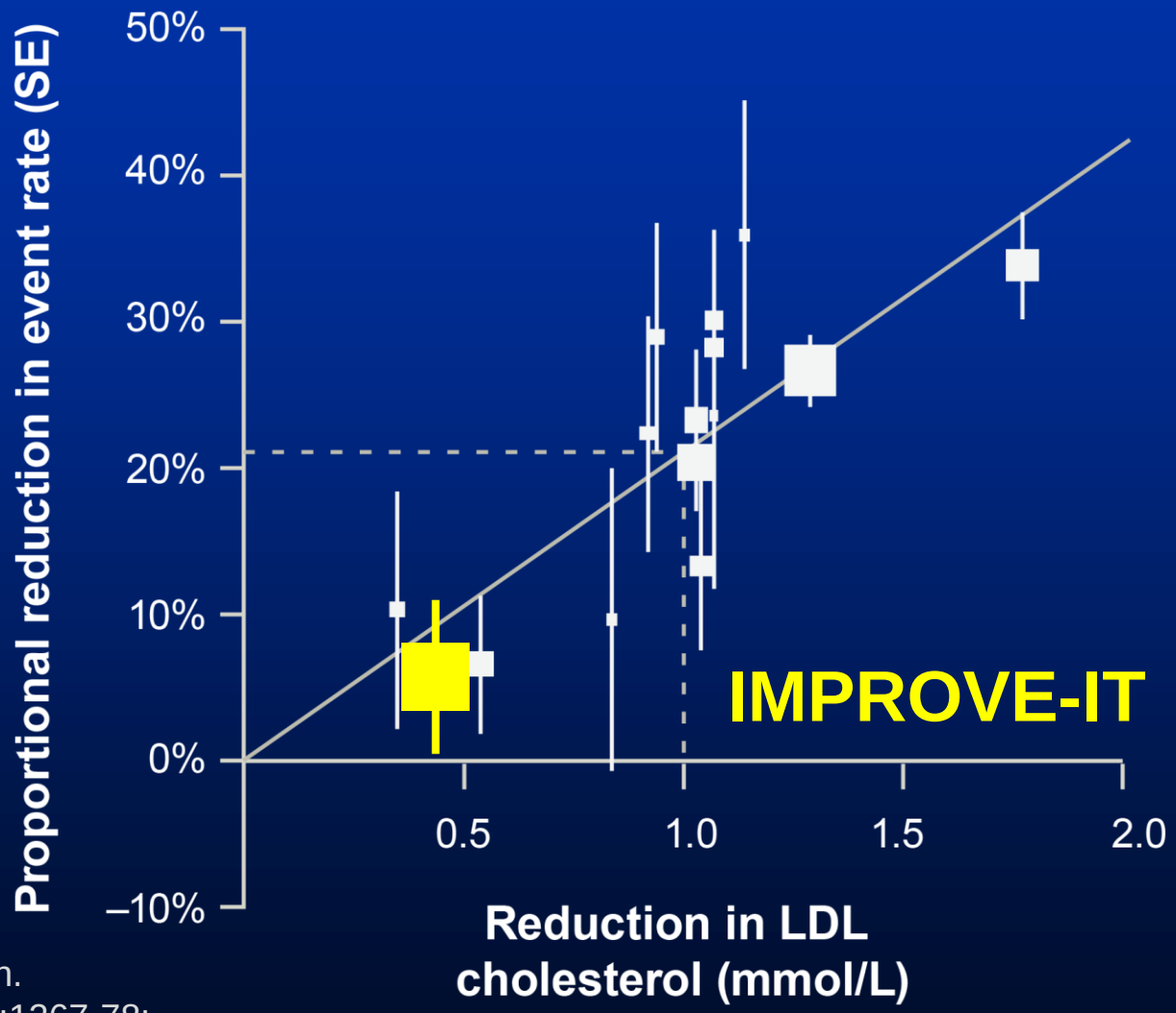


	Simva†	EZ/Simva†
Male	34.9	33.3
Female	34.0	31.0
Age < 65 years	30.8	29.9
Age ≥ 65 years	39.9	36.4
No diabetes	30.8	30.2
Diabetes	45.5	40.0
Prior LLT	43.4	40.7
No prior LLT	30.0	28.6
LDL-C > 95 mg/dl	31.2	29.6
LDL-C ≤ 95 mg/dl	38.4	36.0

†*7-year event rates*

**p-interaction = 0.023, otherwise > 0.05*

IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit



CTT Collaboration.
Lancet 2005; 366:1267-78;
Lancet 2010;376:1670-81.

Safety — ITT

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No statistically significant differences in cancer or muscle- or gallbladder-related events

	Simva n=9077 %	EZ/Simva n=9067 %	p
ALT and/or AST≥3x ULN	2.3	2.5	0.43
Cholecystectomy	1.5	1.5	0.96
Gallbladder-related AEs	3.5	3.1	0.10
Rhabdomyolysis*	0.2	0.1	0.37
Myopathy*	0.1	0.2	0.32
Rhabdo, myopathy, myalgia with CK elevation*	0.6	0.6	0.64
Cancer* (7-yr KM %)	10.2	10.2	0.57

** Adjudicated by Clinical Events Committee*

% = n/N for the trial duration

Conclusions

IMPROVE-IT: First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:

- **YES:** *Non-statin* lowering LDL-C with ezetimibe reduces cardiovascular events
- **YES:** Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
- **YES:** Confirms ezetimibe safety profile

Affirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events

Results could be considered for future guidelines

Effect of Simvastatin-Ezetimibe compared with Simvastatin monotherapy after ACS among patients 75 years or older - a secondary analysis

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

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

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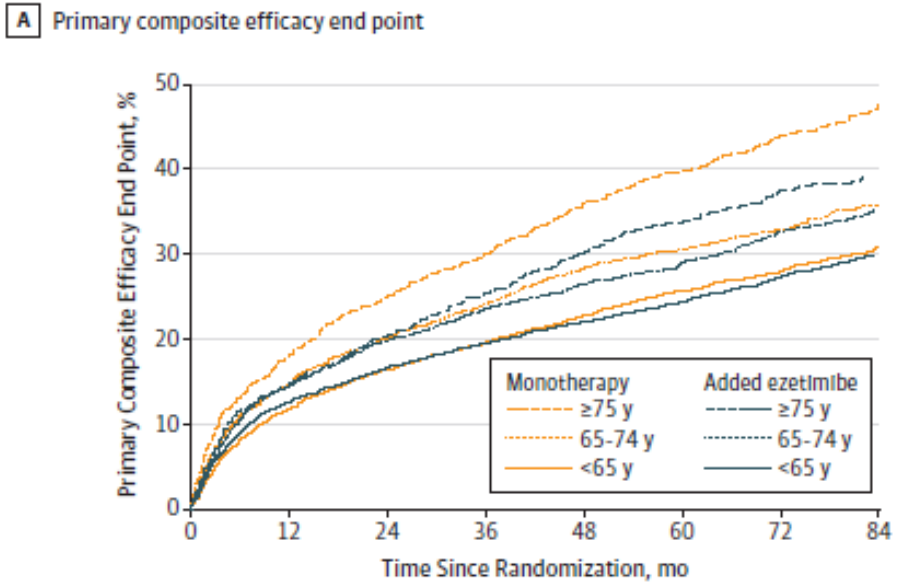

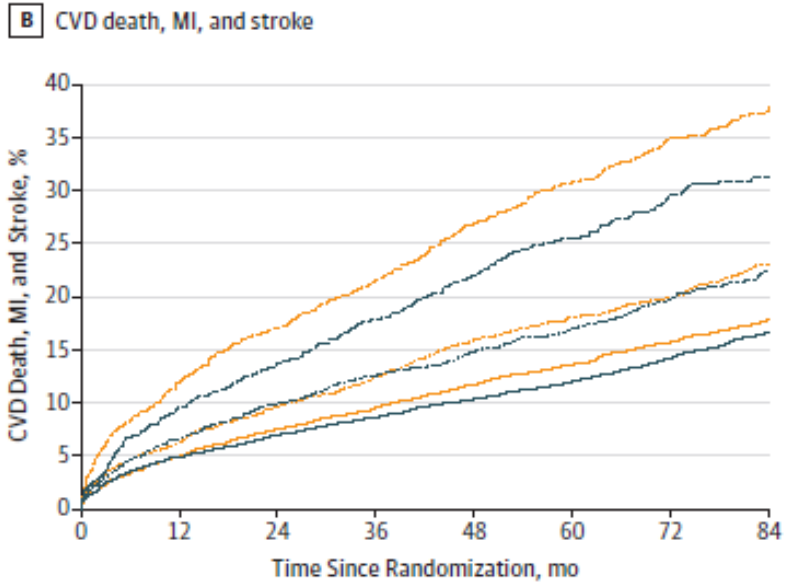

No. at risk

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

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

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Effect of Simvastatin-Ezetimibe compared with Simvastatin monotherapy after ACS among patients 75 years or older - a secondary analysis

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Figure 2. Forest Plot of Study Therapy and Event Rates

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

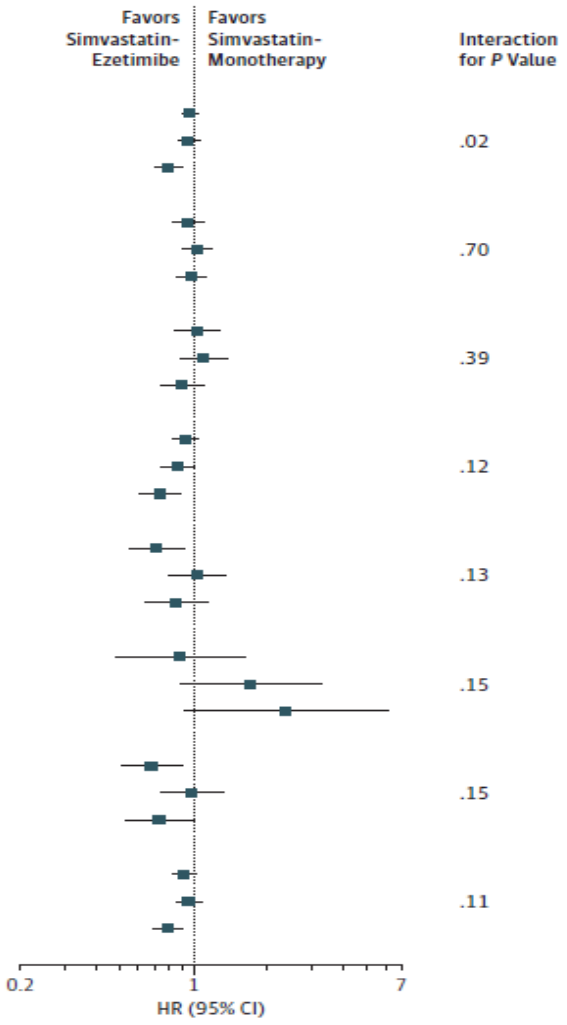

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Table 2. Safety End Points According to Age at Randomization and Treatment

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

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

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