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

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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

Study Metrics

	Simva (N=9077)	EZ/Simva (N=9067)
Uptitration to Simva 80mg, %	27	6
Premature study drug D/C, %	42	42
Median follow-up, yrs	6.0	5.9
Withdraw consent w/o vital status, %/yr	0.6	0.6
Lost to follow-up, %/yr	0.10	0.09
Follow up for primary endpoint, %	91	91
Follow up for survival, %	97	97

Total primary endpoint events = 5314
Total patient-years clinical follow-up = 97,822
Total patient-years follow-up for survival = 104,135

Baseline Characteristics

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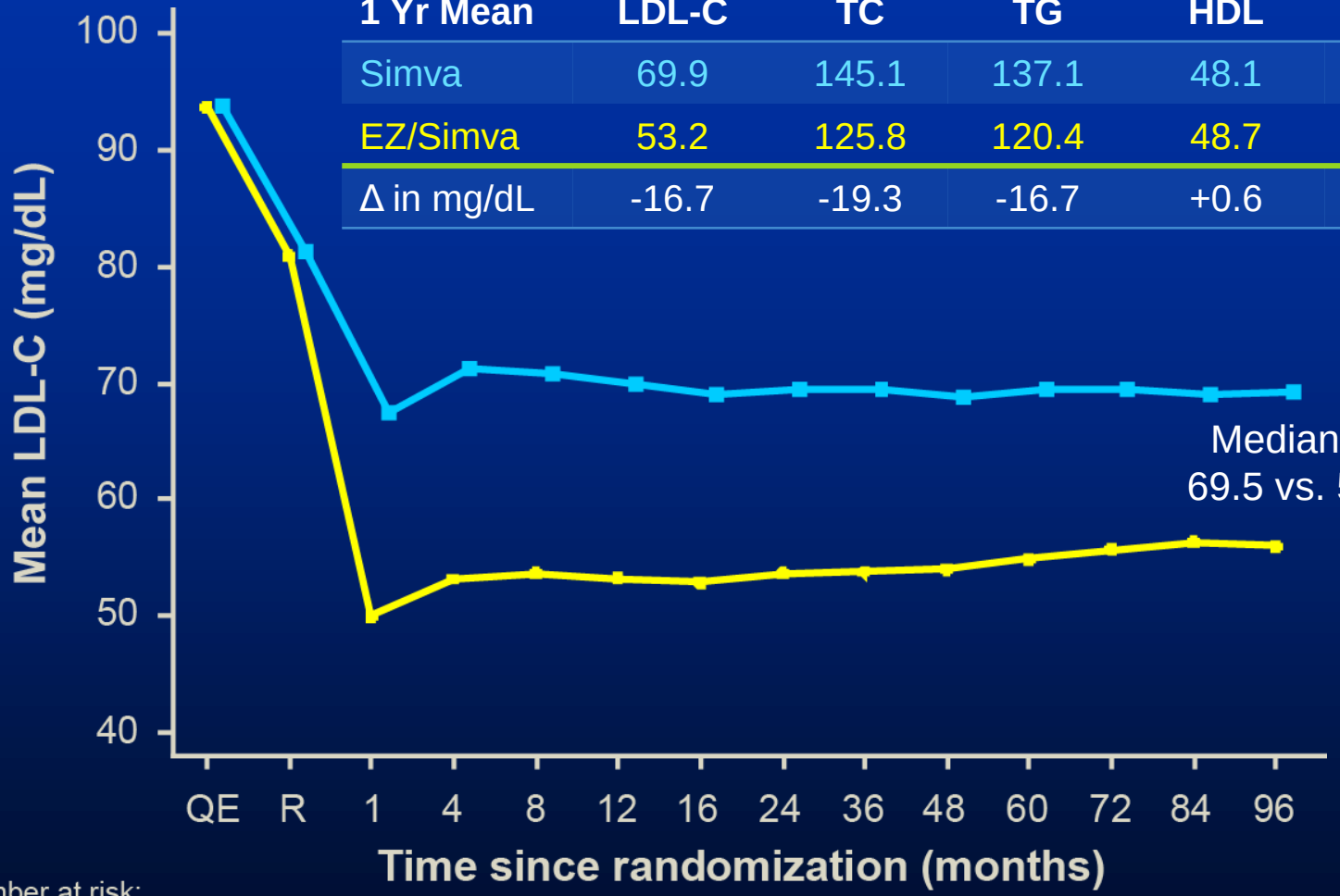
	Simvastatin (N=9077) %	EZ/Simva (N=9067) %
Age (years)	64	64
Female	24	25
Diabetes	27	27
MI prior to index ACS	21	21
STEMI / NSTEMI / UA	29 / 47 / 24	29 / 47 / 24
Days post ACS to rand (IQR)	5 (3, 8)	5 (3, 8)
Cath / PCI for ACS event	88 / 70	88 / 70
Prior lipid Rx	35	36
LDL-C at ACS event (mg/dL, IQR)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



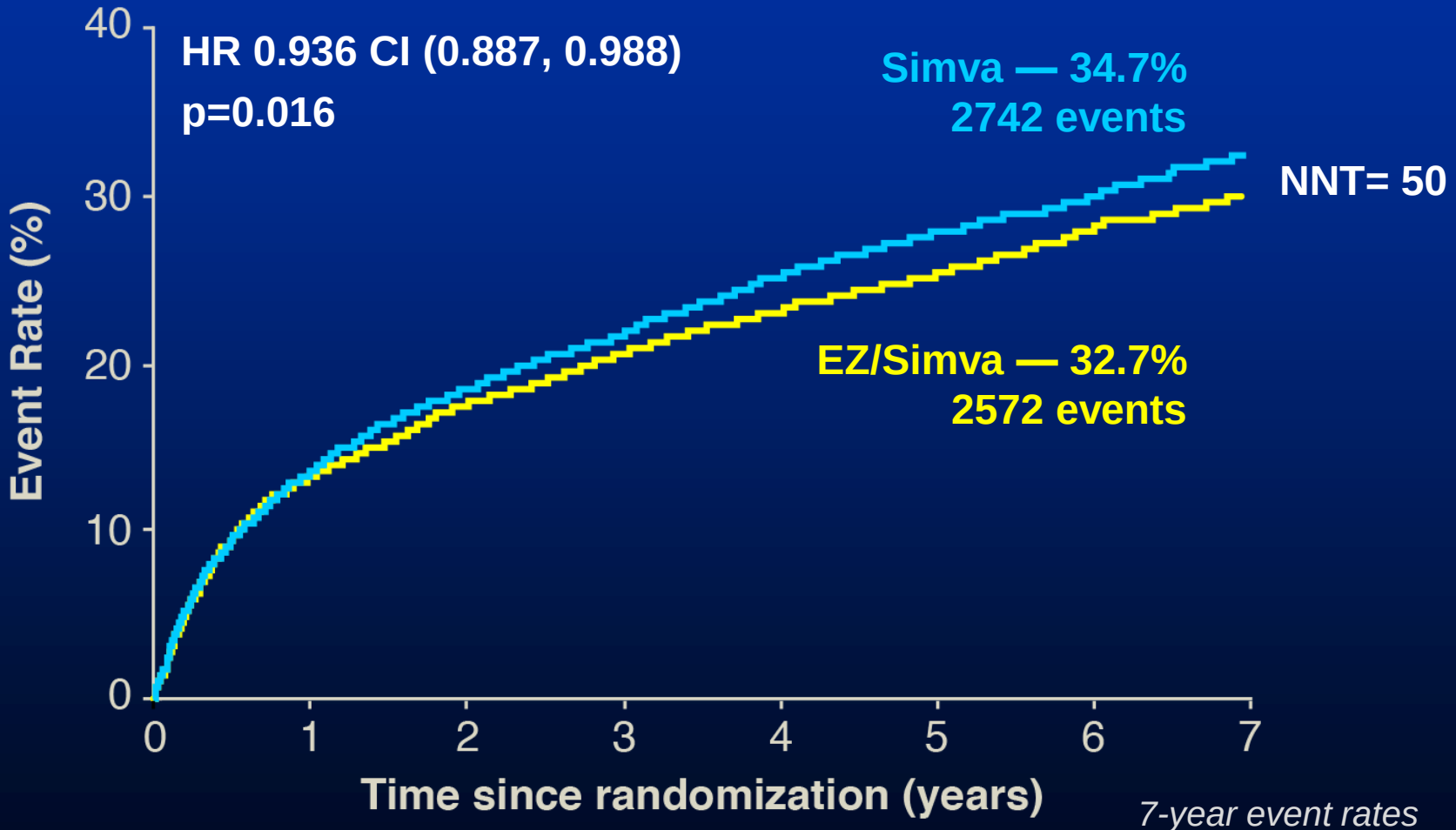
Median Time avg
69.5 vs. 53.7 mg/dL

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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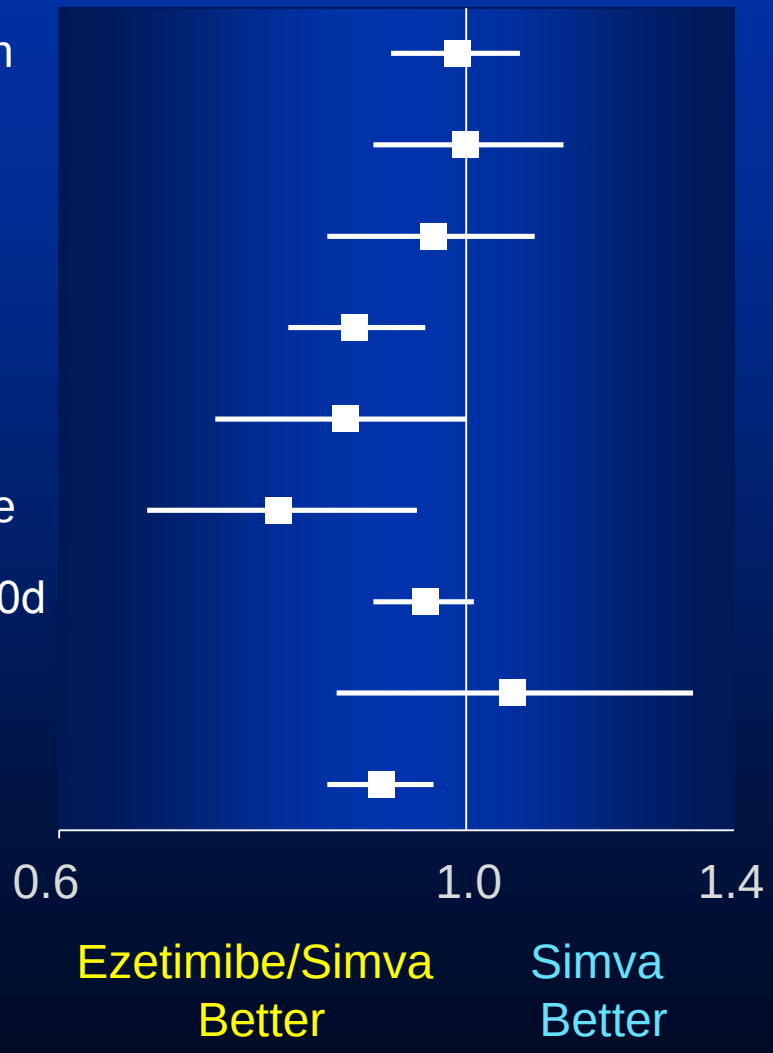
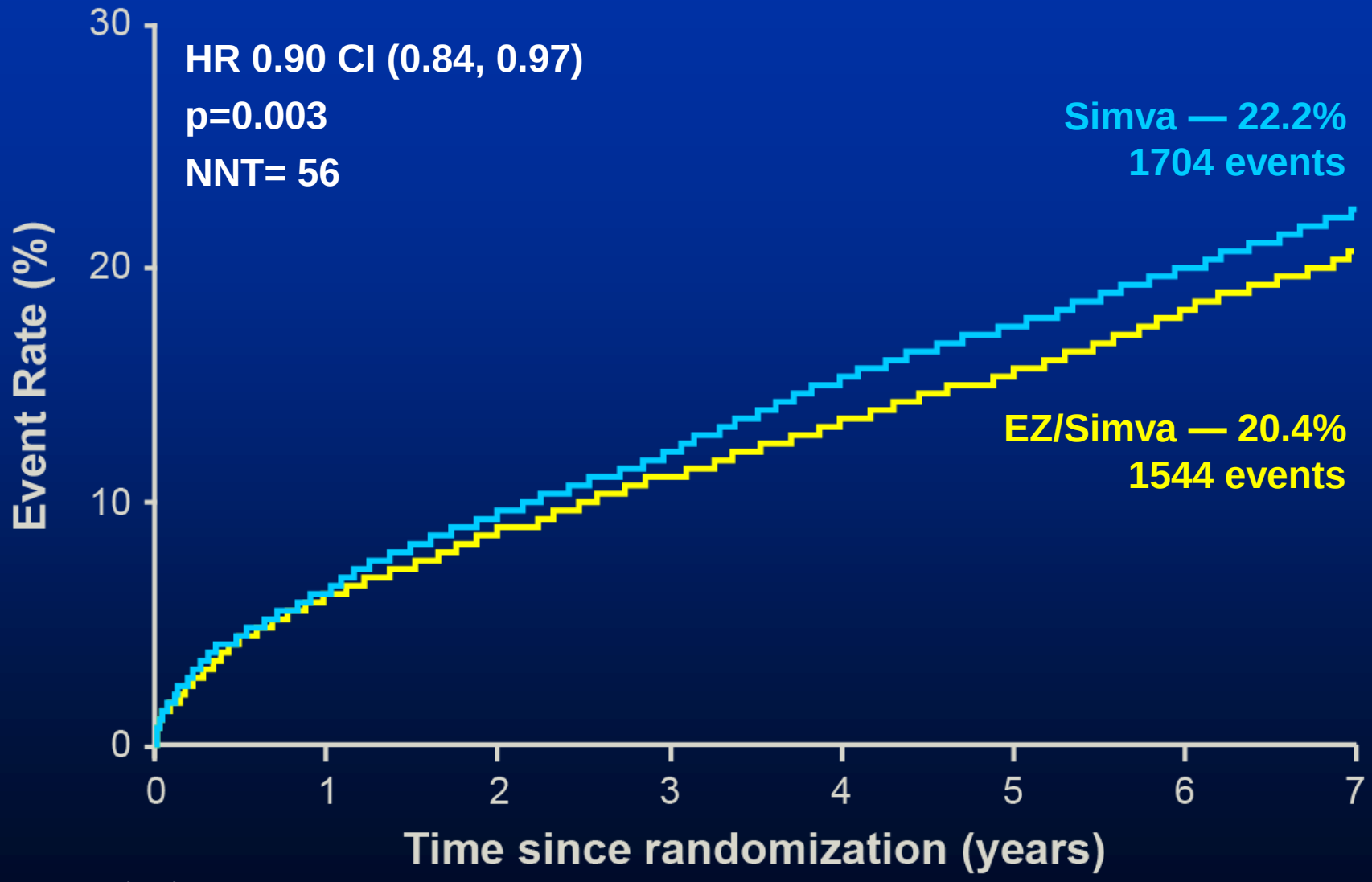


	HR	Simva*	EZ/Simva*	p-value
All-cause death	0.99	15.3	15.4	0.782
CVD	1.00	6.8	6.9	0.997
CHD	0.96	5.8	5.7	0.499
MI	0.87	14.8	13.1	0.002
Stroke	0.86	4.8	4.2	0.052
Ischemic stroke	0.79	4.1	3.4	0.008
Cor revasc ≥ 30d	0.95	23.4	21.8	0.107
UA	1.06	1.9	2.1	0.618
CVD/MI/stroke	0.90	22.2	20.4	0.003

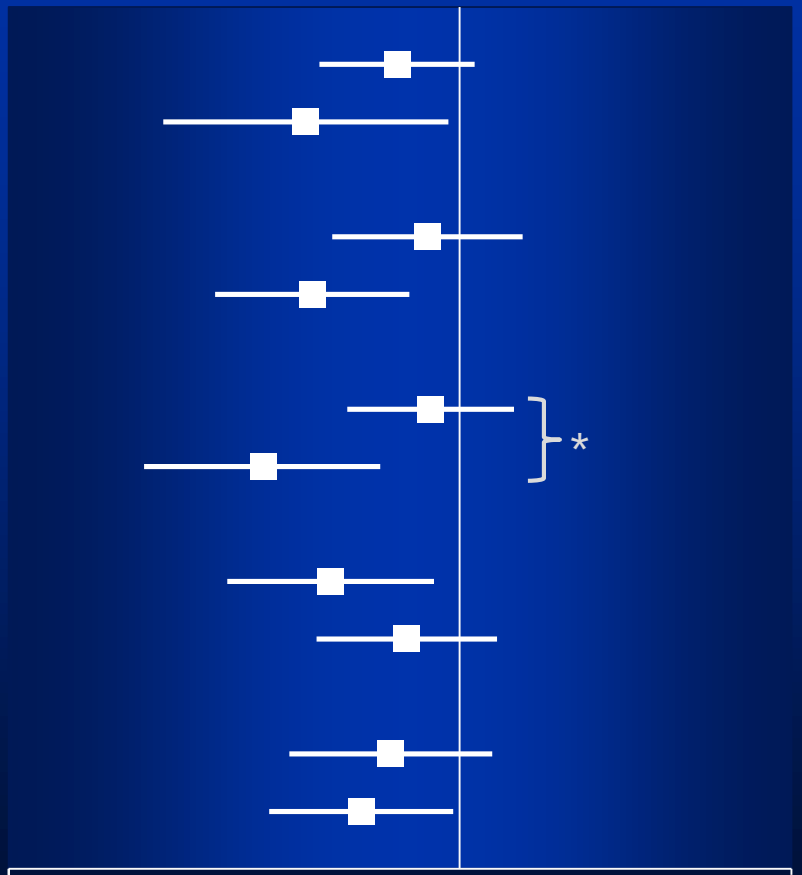
**7-year event rates (%)*

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



7-year event rates

Major Pre-specified Subgroups

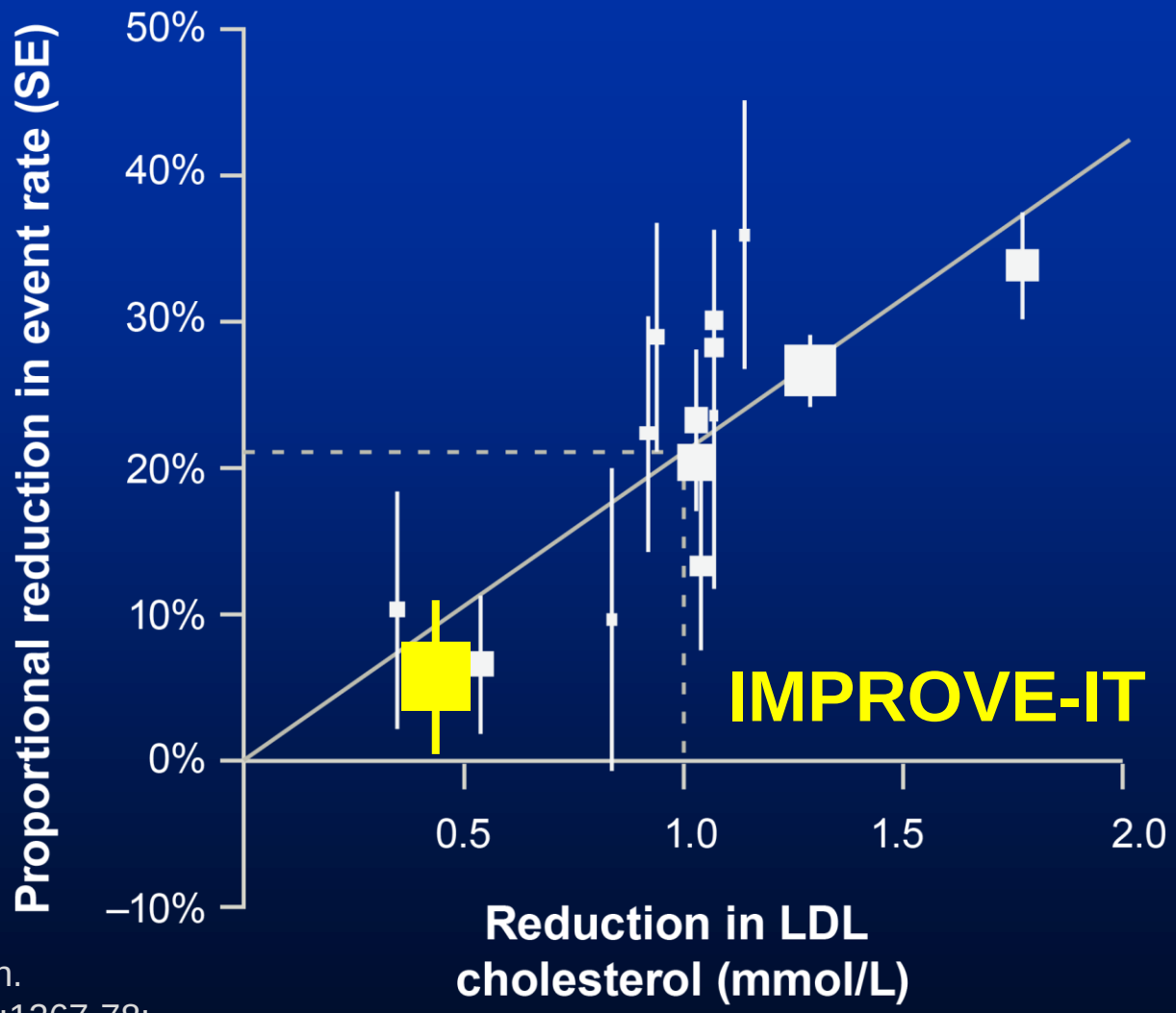


	Simva†	EZ/Simva†
Male	34.9	33.3
Female	34.0	31.0
Age < 65 years	30.8	29.9
Age ≥ 65 years	39.9	36.4
No diabetes	30.8	30.2
Diabetes	45.5	40.0
Prior LLT	43.4	40.7
No prior LLT	30.0	28.6
LDL-C > 95 mg/dl	31.2	29.6
LDL-C ≤ 95 mg/dl	38.4	36.0

†*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

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

→ **Reaffirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events**

→ **Results could be considered for future guidelines**