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

מטרות המחקר

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

מבנה המחקר

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

↓

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

↓

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

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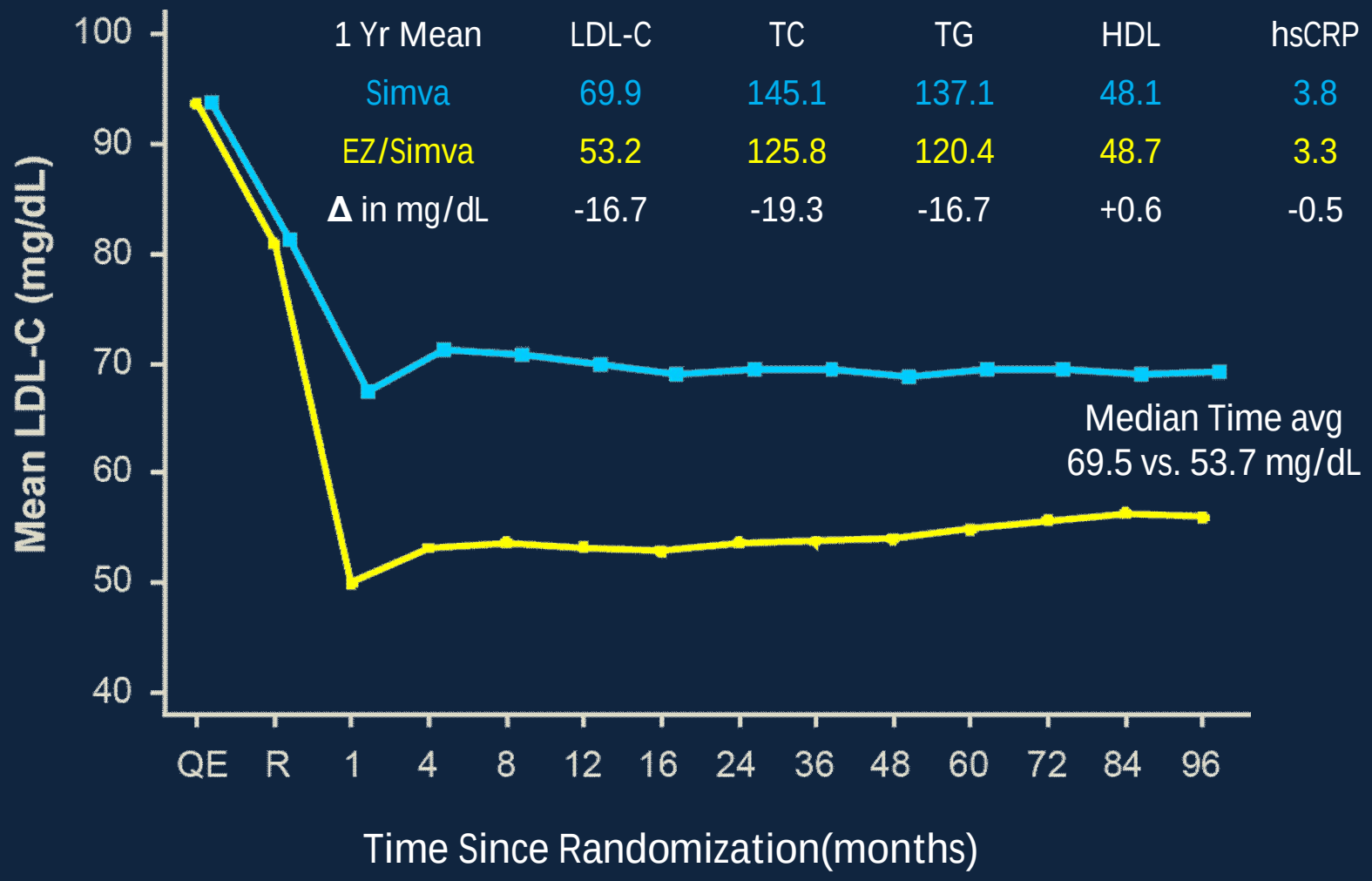
מאפייני אוכלוסיית המחקר

	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 randomisation	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)	95 (79, 110)	95 (79,110)

תוצאות: שינוי בערכי ליפידים

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



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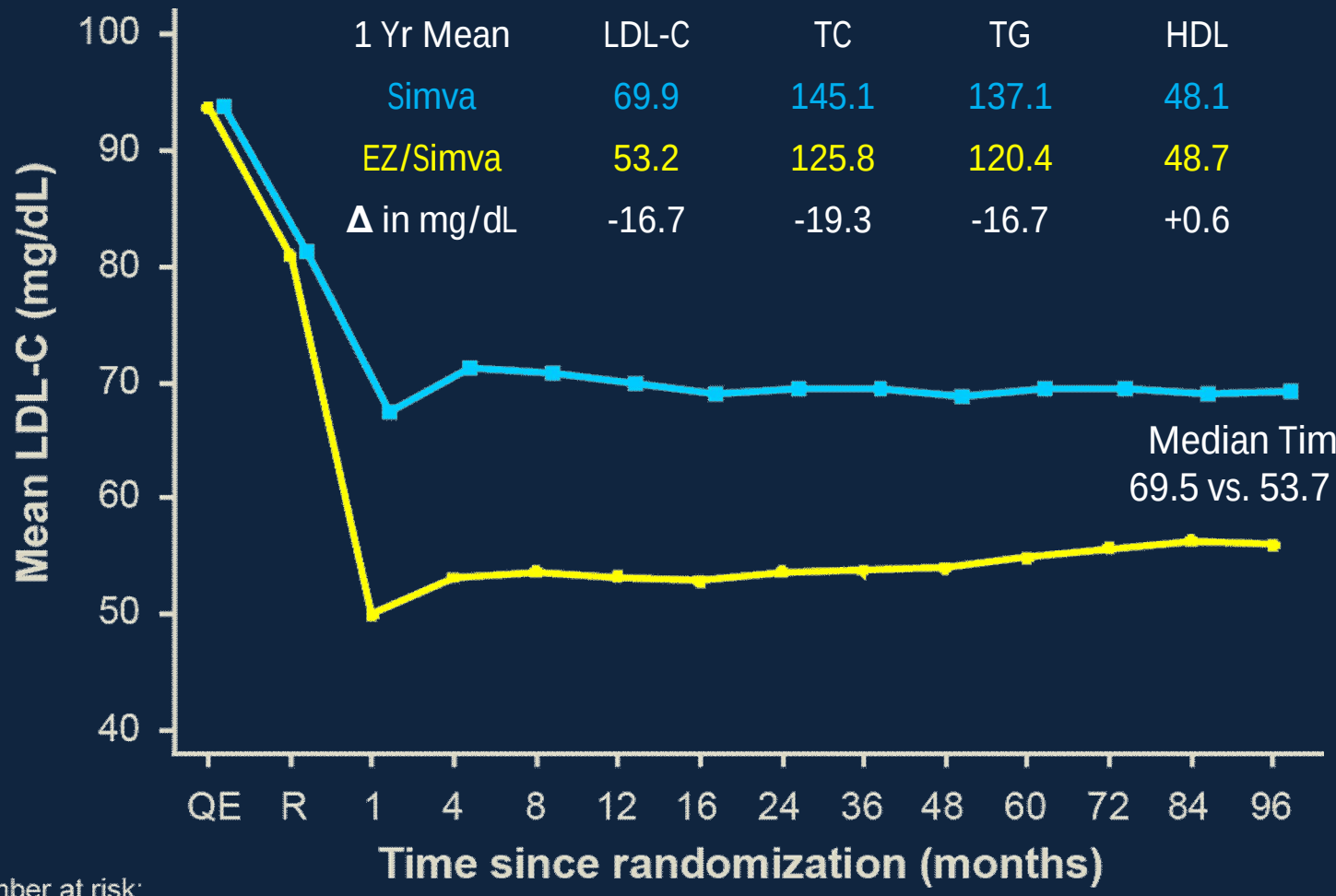
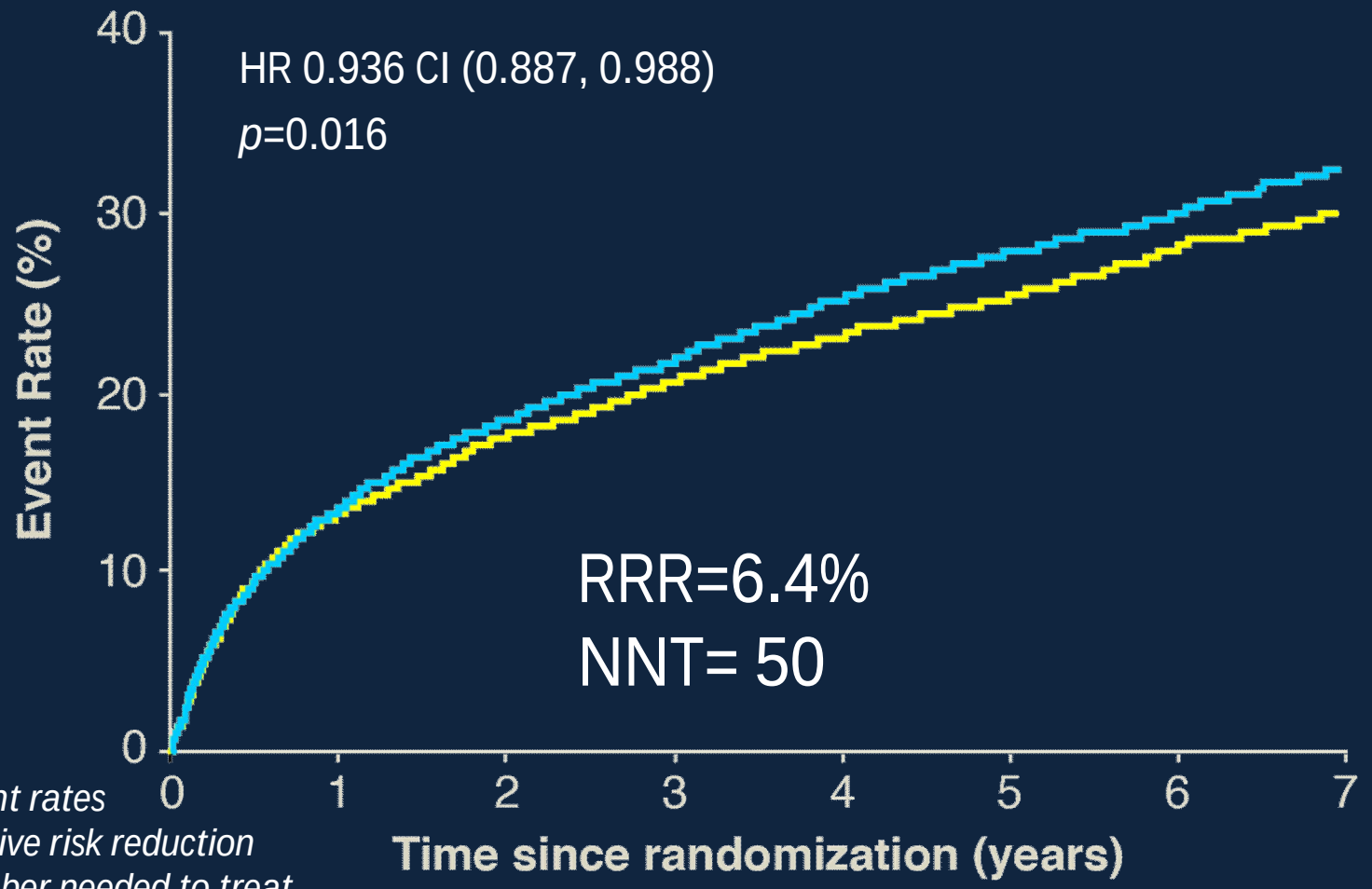


Number at risk:

	QE	R	1	4	8	12	16	24	36	48	60	72	84	96
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

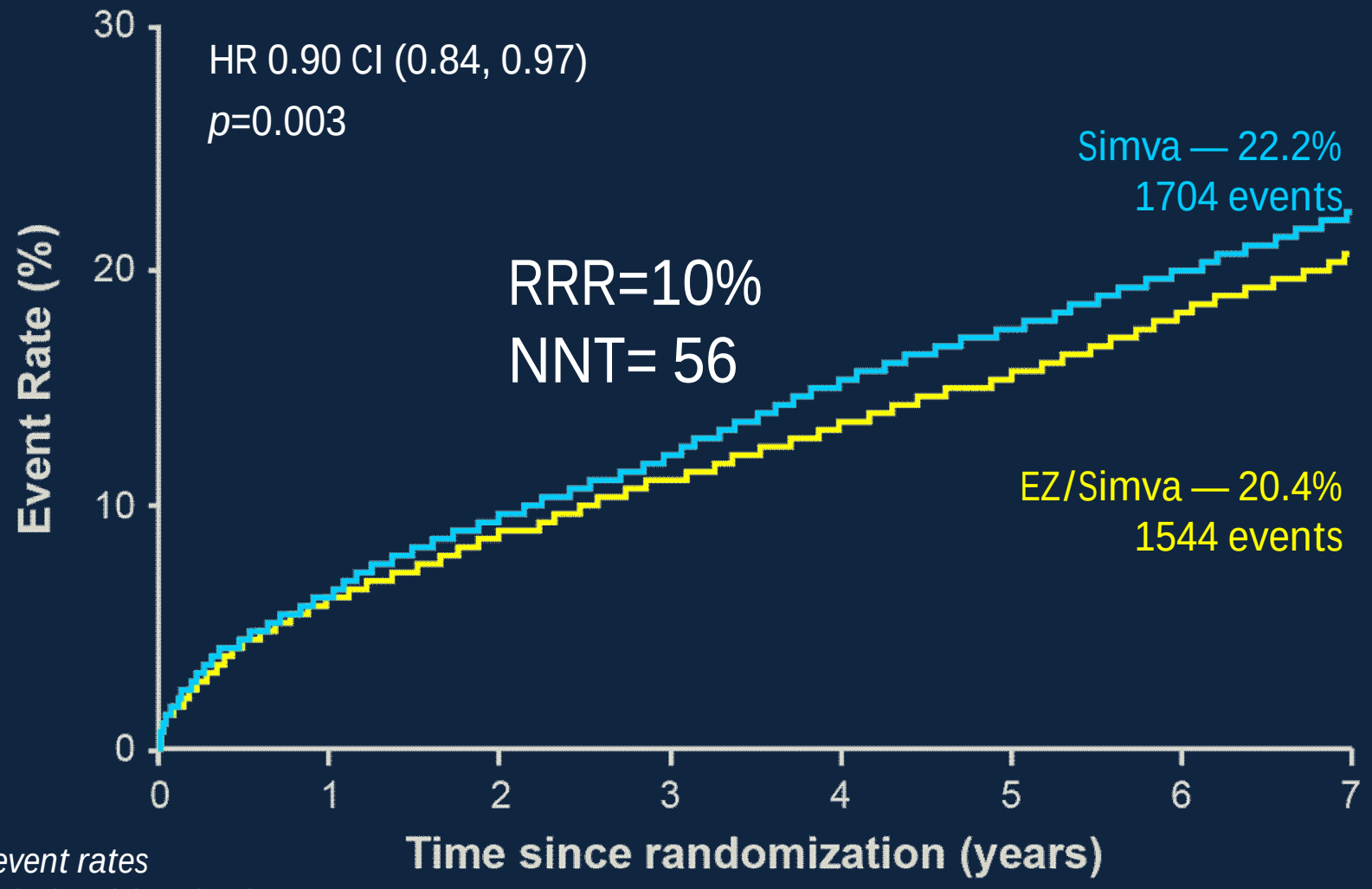
ITT (intention to treat)
Primary Endpoint

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



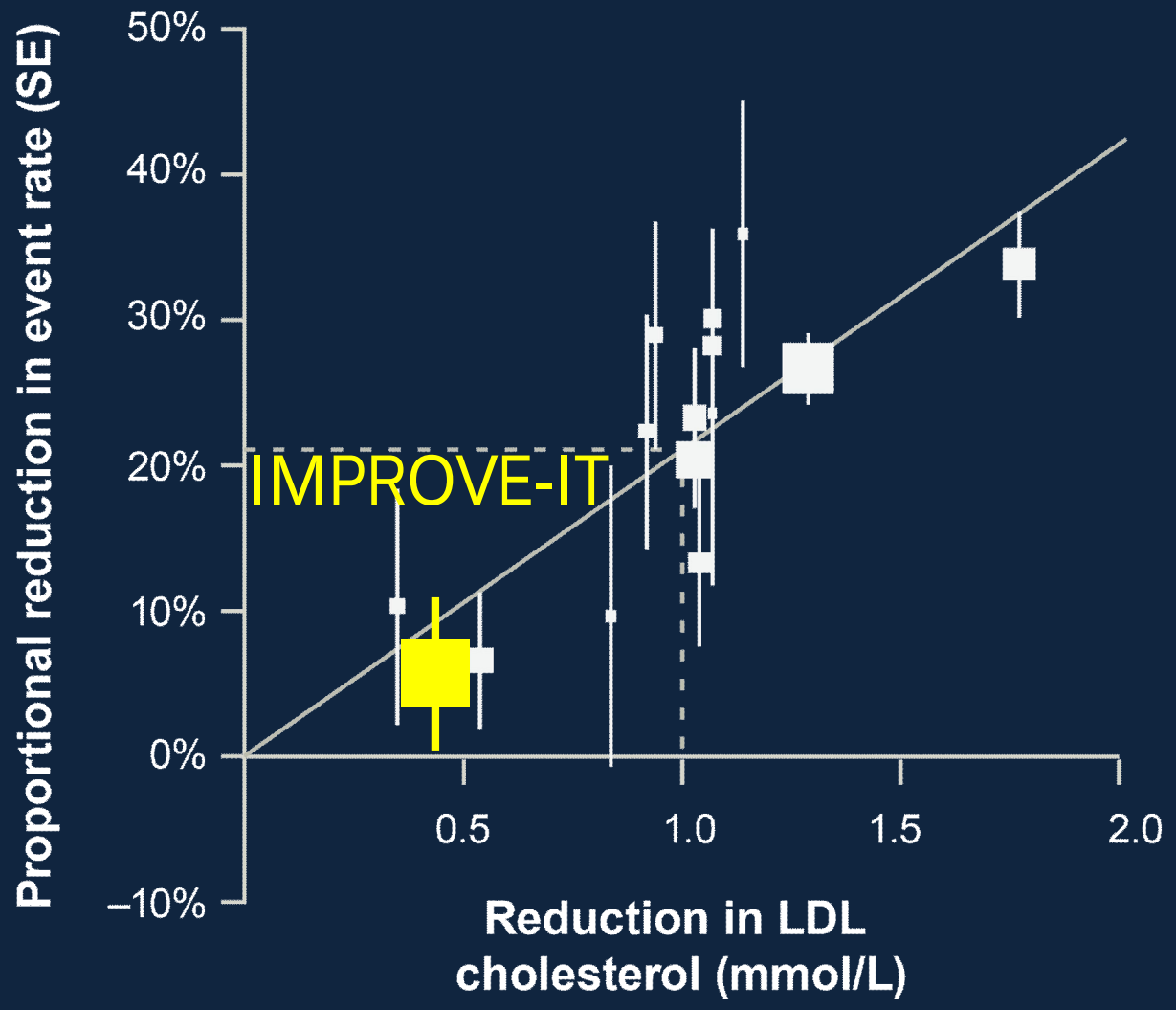
7-year event rates
RRR = relative risk reduction
NNT = number needed to treat

Composite Endpoint: CV Death, Non-fatal MI, or Non-fatal Stroke



7-year event rates
RRR – relative risk reduction
NNT- number needed to treat

תוצאות IMPROVE-IT בהשוואה למסקנות ה-CTT



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

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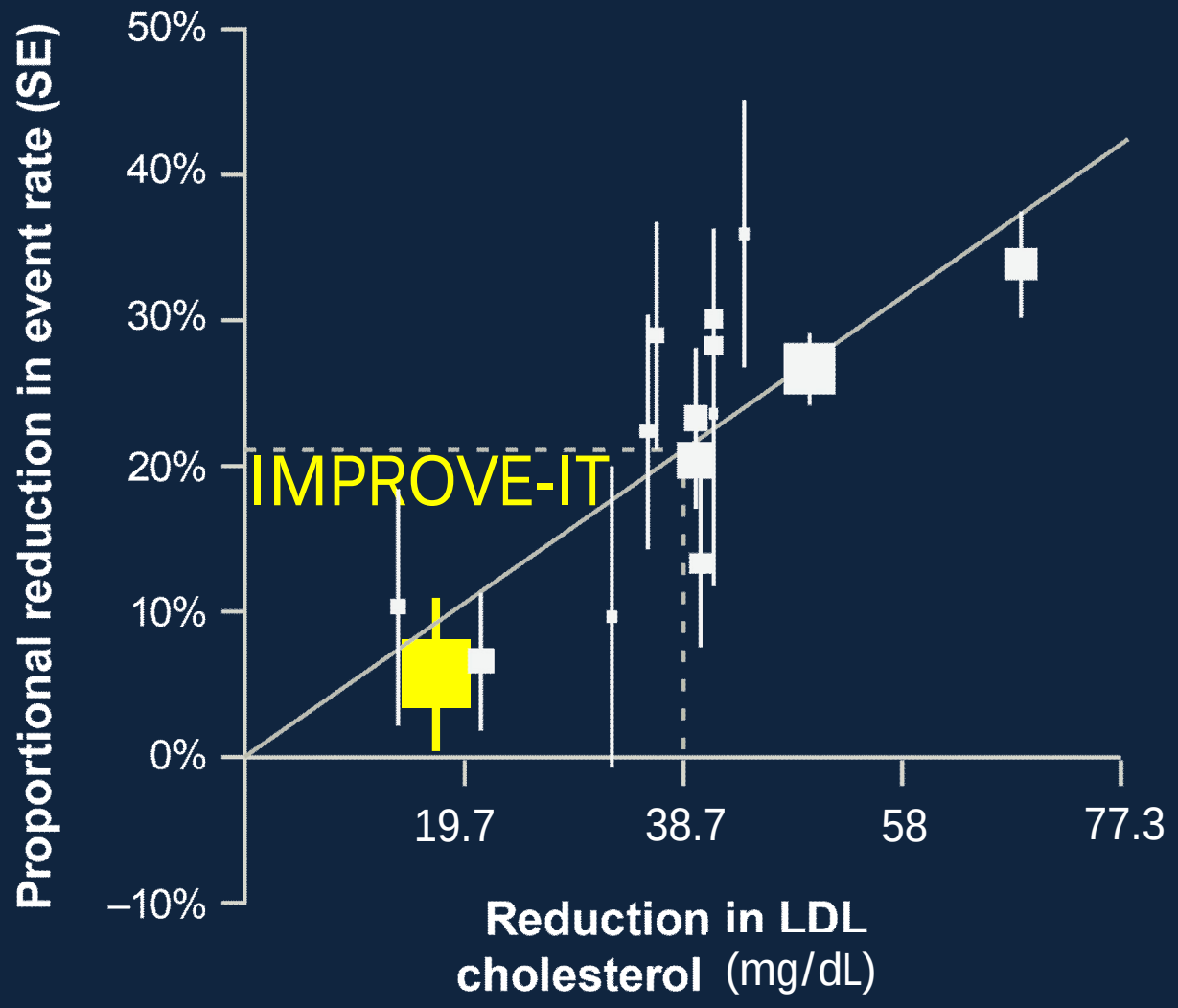

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בטיחות

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

מסקנות

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

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

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

➡ Results could be considered for future guidelines