Zürcher Herzkurs, 29.09.2017

New drugs and interactions
LDL - what else?

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Private Universität im Fürstentum Liechtenstein, Triesen, FL
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Vice-Chair ESC-Working Group "Cardiovascular Pharmacotherapy"
Swiss Cardiovascular Centre, University Hospital Bern, Bern, Switzerland

Outline

1. Ansätze zur Atheroskleroseprävention
2. LDL-Senkung
3. Interaktionen zur Diskussion

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1. Ansätze zur Atheroskleroseprävention
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Atheroskleroseprävention

Intervention	Evidenz
LDL-Senkung	Ja
HDL-Steigerung	Nein
Antibiotika	Nein
Antiphlogistika	Nein
Glukosesenkung	Nein
Blutdrucksenkung	Ja

Outline

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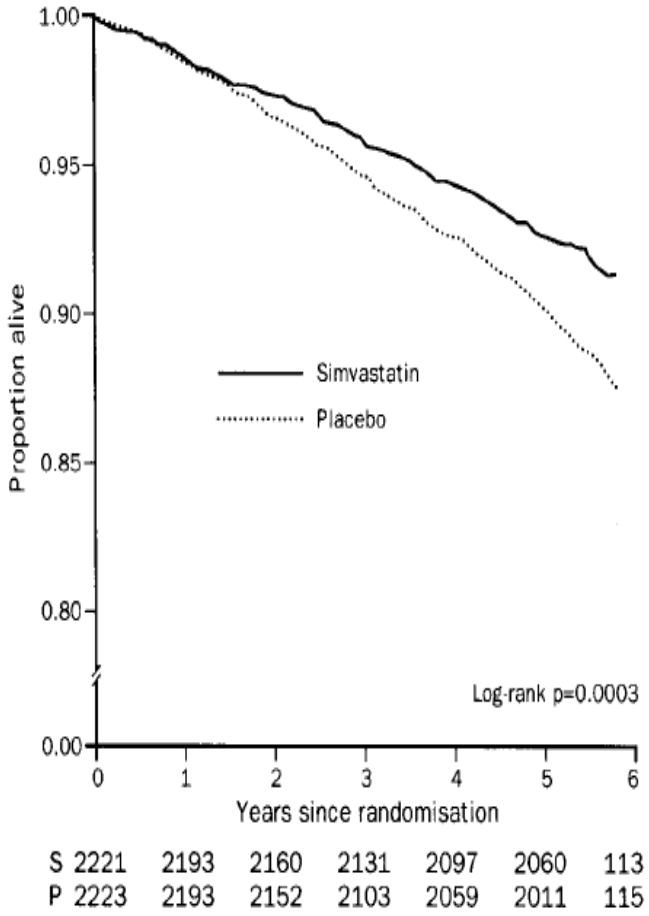
How it All Started: 4S – Total Mortality



Pedersen TR et al., Lancet 1994; 344: 1383-1389.

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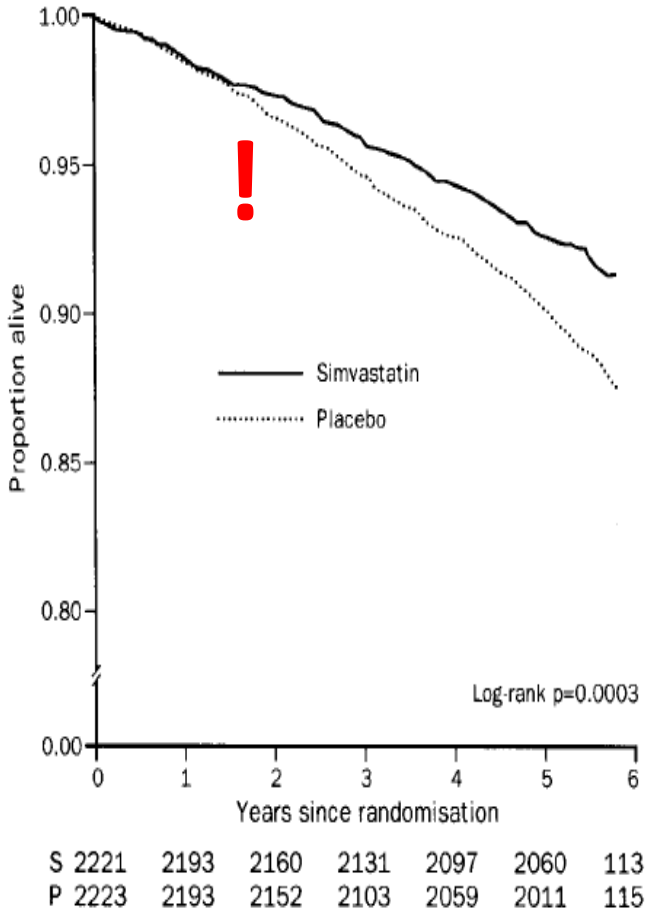


Pedersen TR et al., Lancet 1994; 344: 1383-1389.

The NEW ENGLAND JOURNAL of MEDICINE

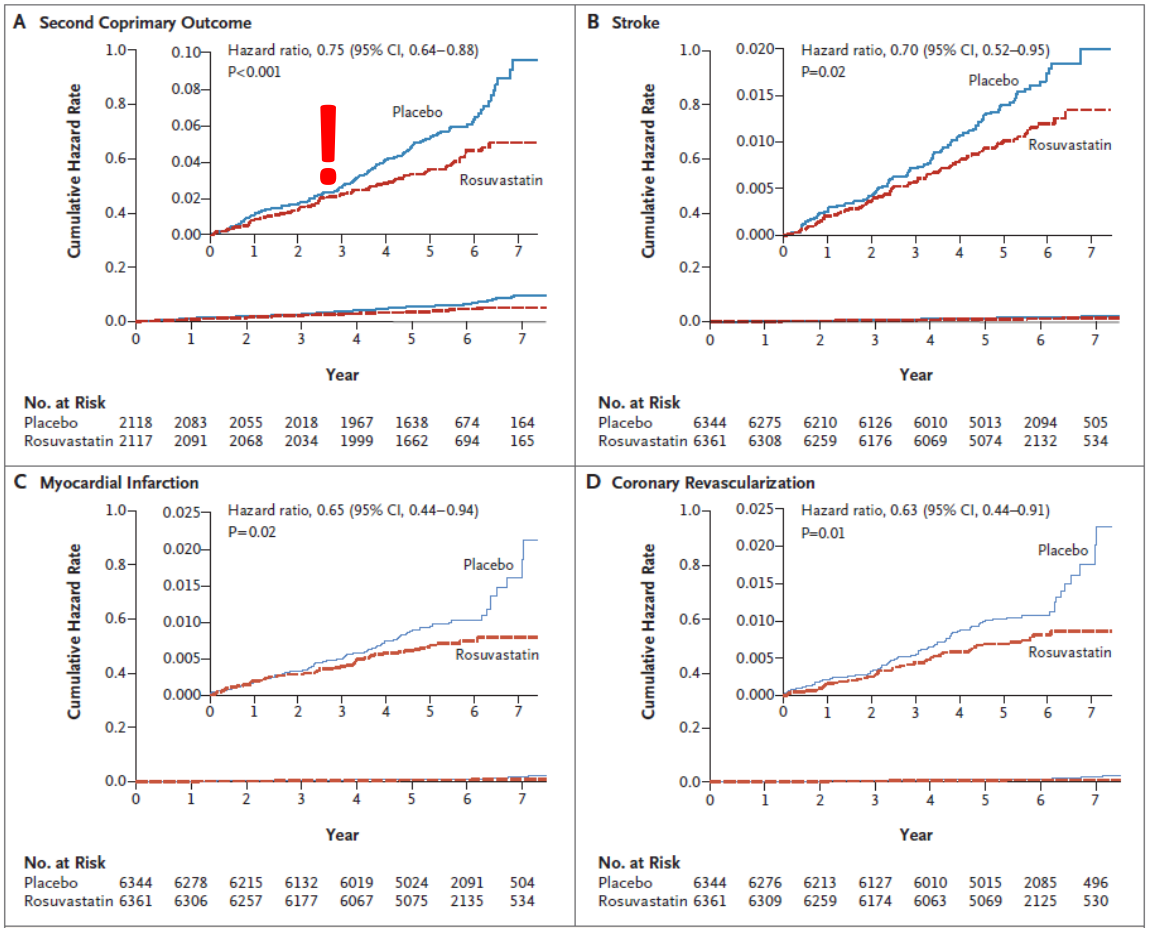
ORIGINAL ARTICLE

Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease

S. Yusuf, J. Bosch, G. Dagenais, J. Zhu, D. Xavier, L. Liu, P. Pais, P. López-Jaramillo, L.A. Leiter, A. Dans, A. Avezum, L.S. Piegas, A. Parkhomenko, K. Keltai, M. Keltai, K. Sliwa, R.J.G. Peters, C. Held, I. Chazova, K. Yusoff, B.S. Lewis, P. Jansky, K. Khunti, W.D. Toff, C.M. Reid, J. Varigos, G. Sanchez-Vallejo, R. McKelvie, J. Pogue,* H. Jung, P. Gao, R. Diaz, and E. Lonn, for the HOPE-3 Investigators†

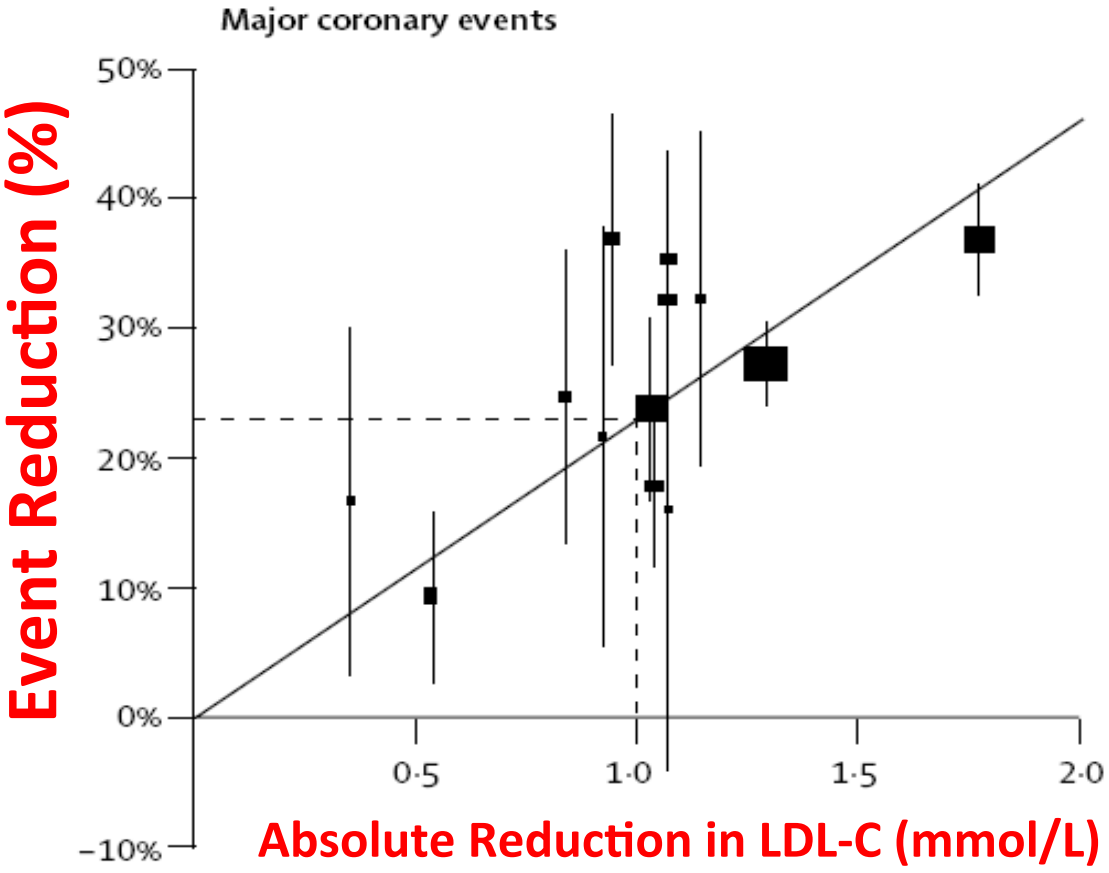
Yusuf S et al. NEJM 2016; 374: 2021-2031.

Cumulative Incidence of Cardiovascular Events



Yusuf S et al. NEJM 2016; 374: 2021-2031.

LDL-C Reduction and Coronary Events

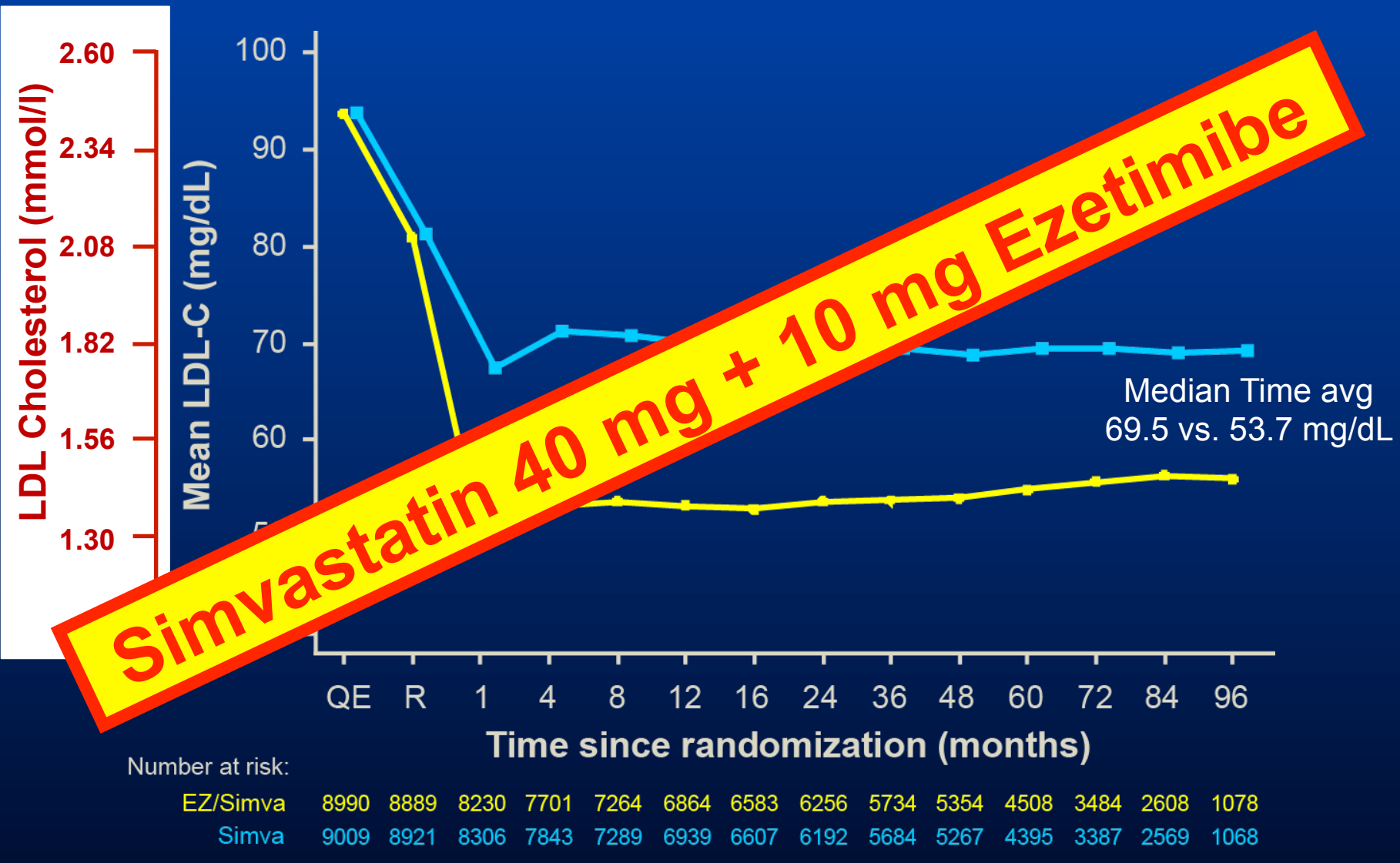


Cholesterol Treatment Trialists' (CTT) Collaborators Lancet 2005;366:1267-78.

IMPROVE-IT

LDL-C and Lipid Changes

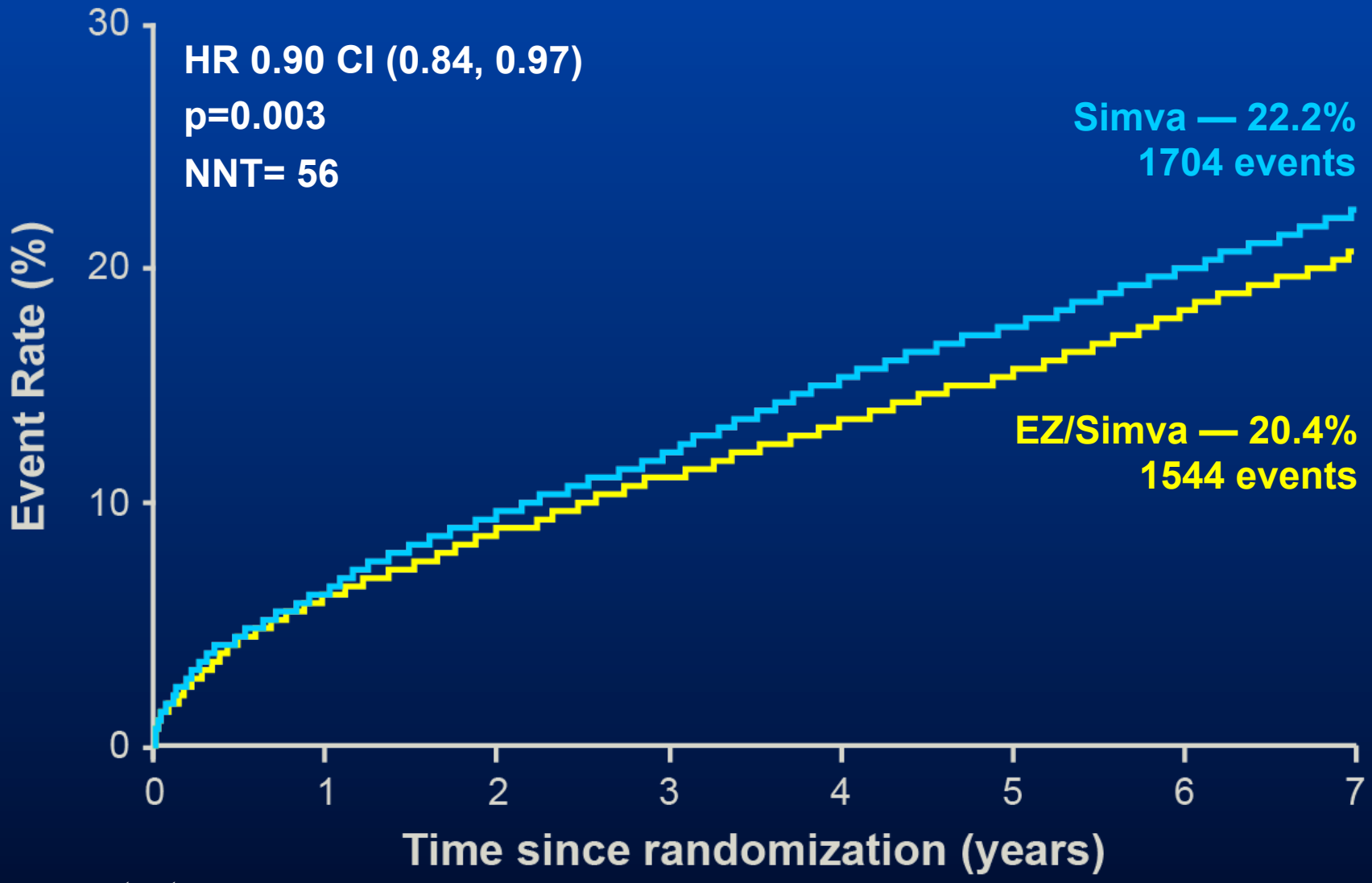
IMPROVE-IT



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

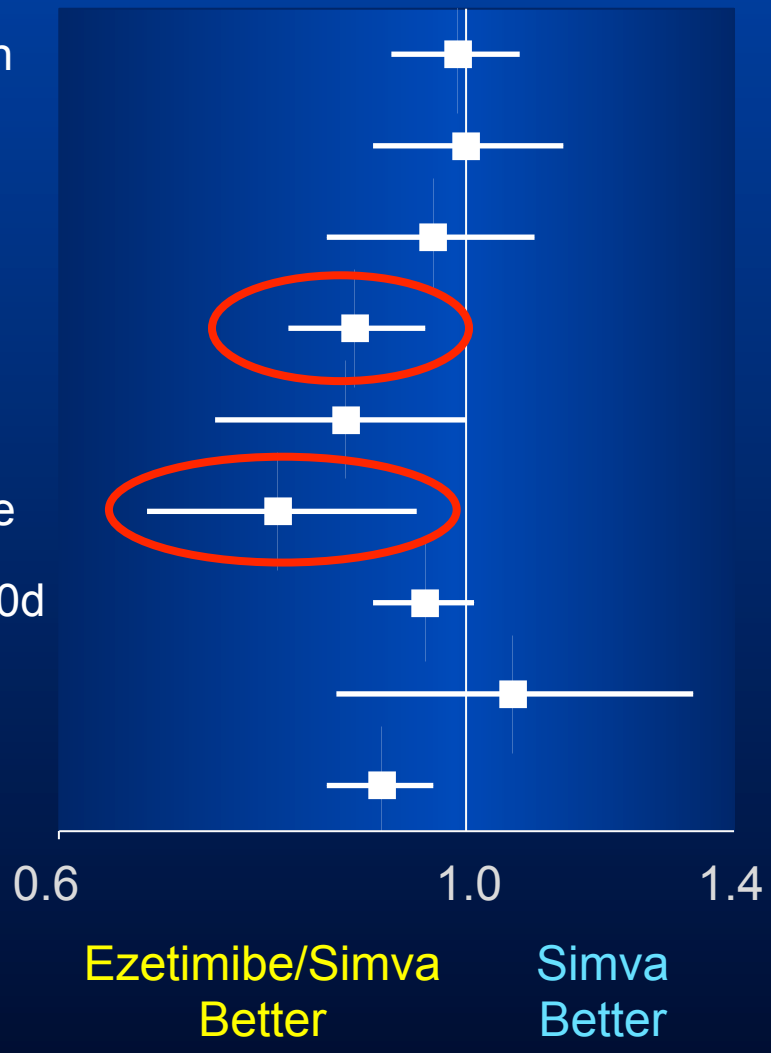
CV Death, Non-fatal MI, or Non-fatal Stroke



7-year event rates

Individual Cardiovascular Endpoints and CVD/MI/Stroke

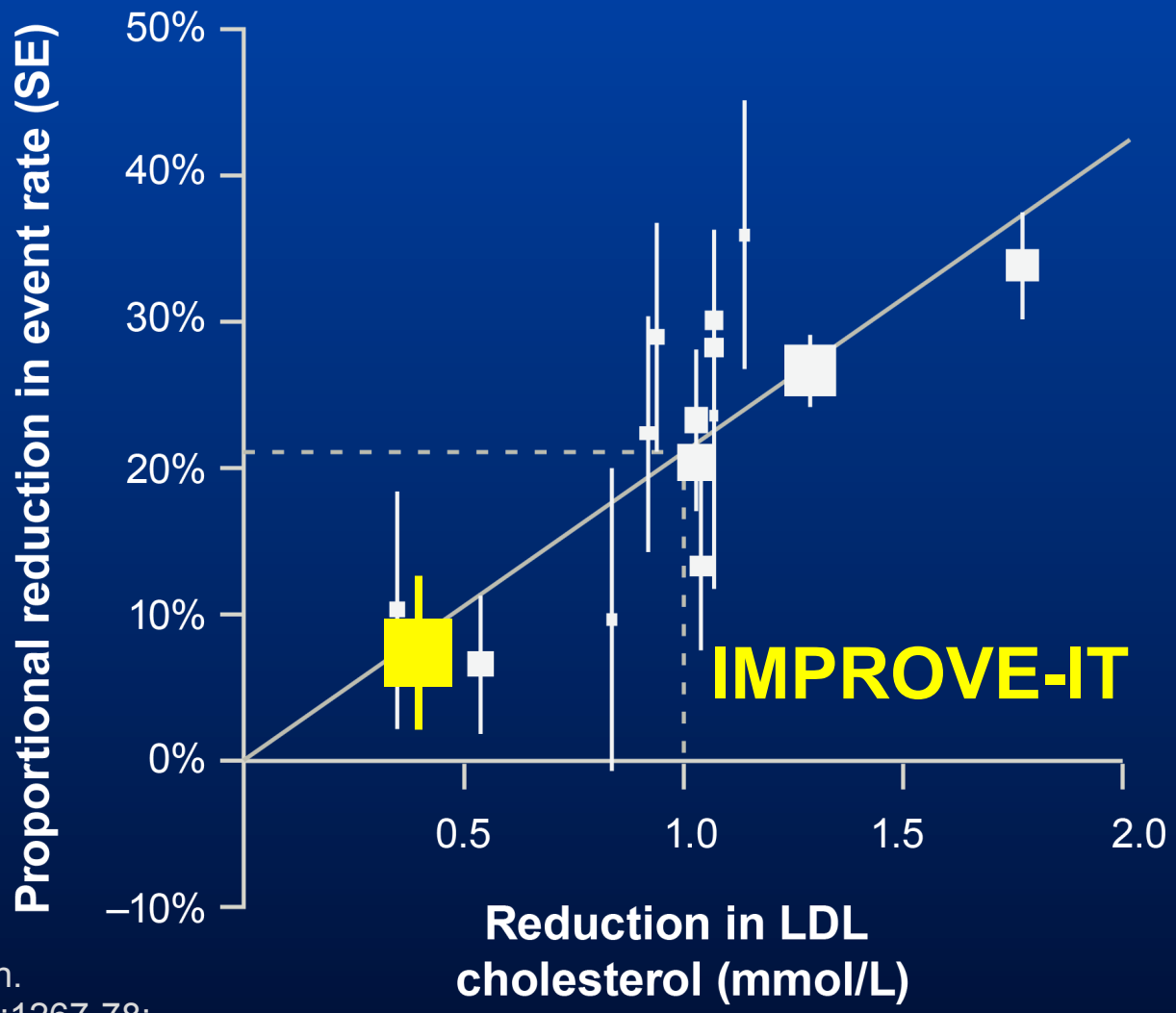
IMPROVE-IT



	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 (%)*

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



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

FOURIER

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

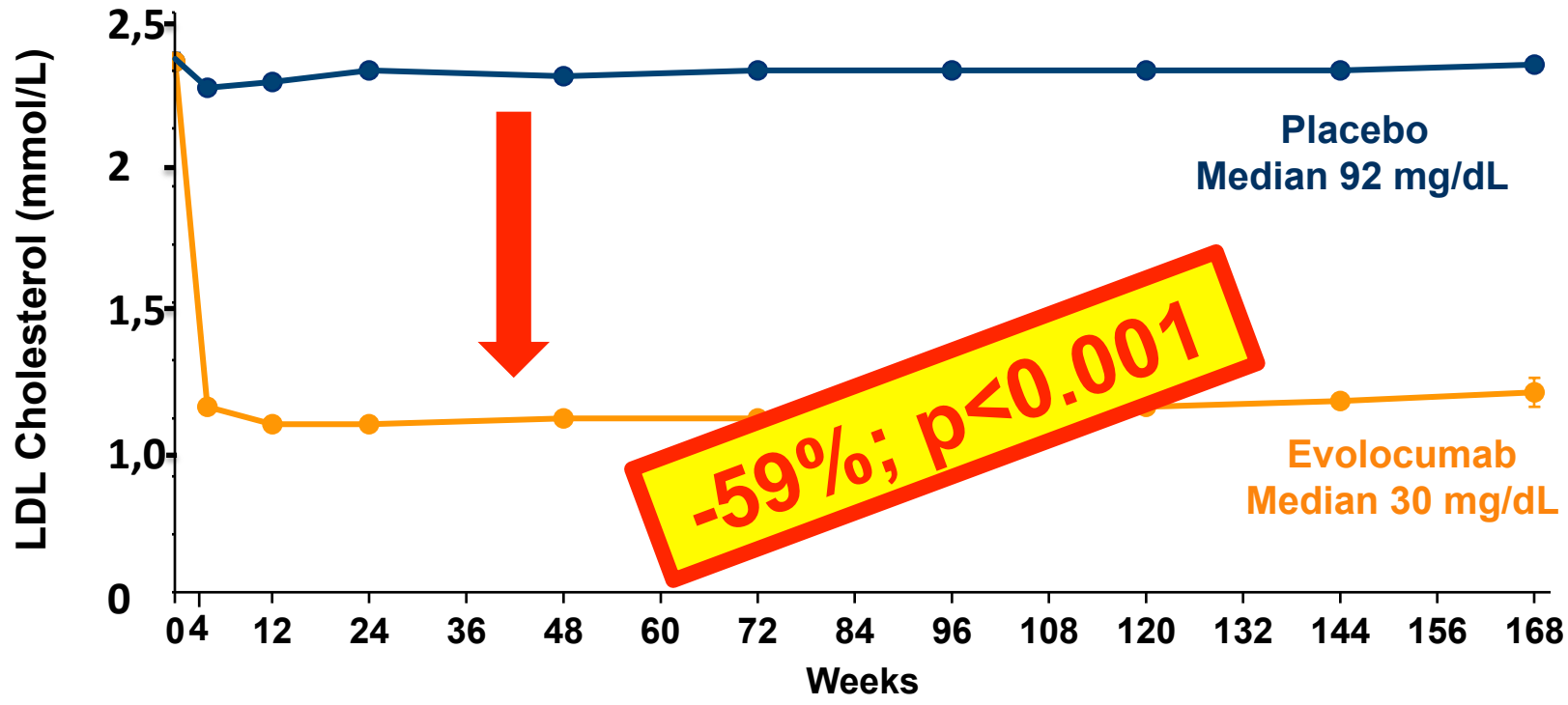
FOURIER: Patients

- N = 27.564; age 40-85 years
- Clinically evident atherosclerotic cardiovascular disease* plus further risk factors
- Statin therapy (atorva 20 mg/d oder more potent)
- LDL-C ≥1.8 mmol/L

* History of MI, non-haemorrhagic stroke, symptomatic PAD

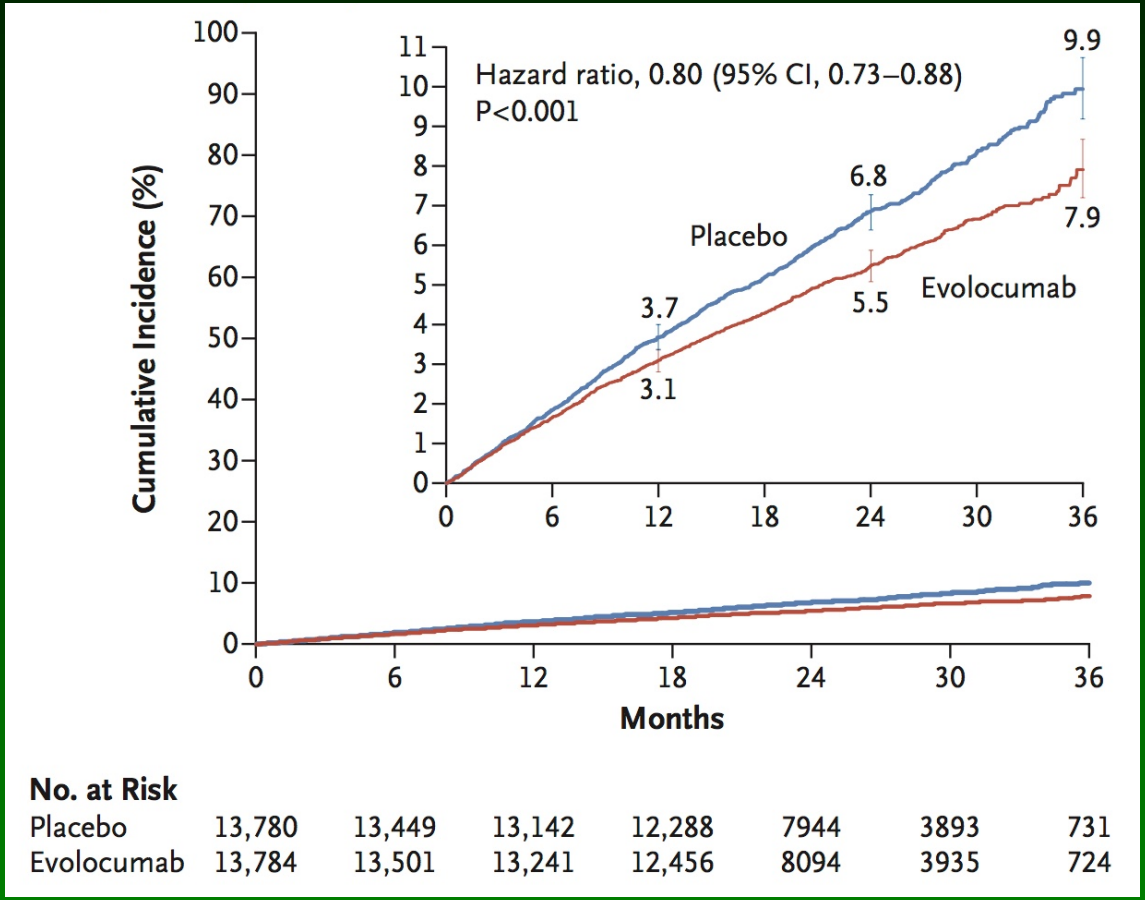
Sabatine MS et al. N Engl J Med 2017; 376: 1713-1722.

LDL-C Reduction



Sabatine MS et al. N Engl J Med 2017; 376: 1713-1722.

Key Secondary Endpoint: CV Death, MI, Stroke



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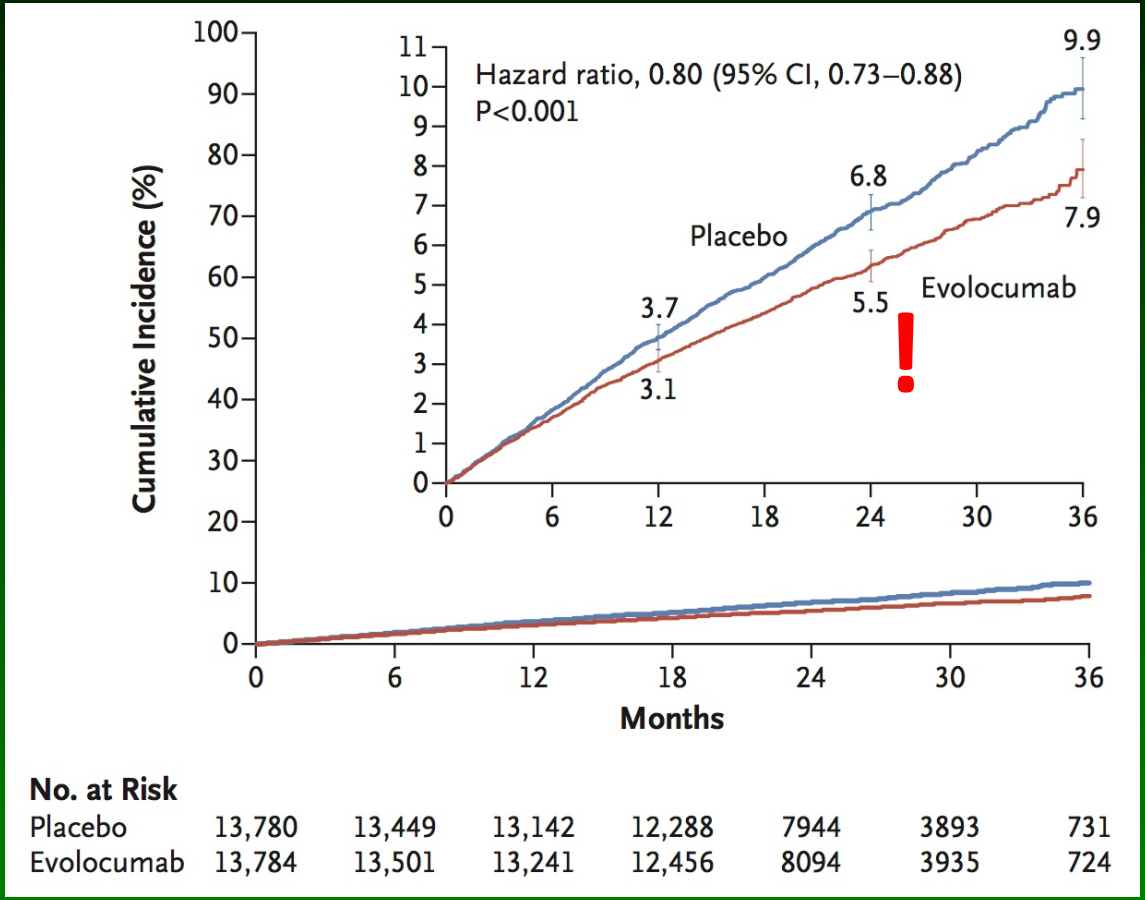


Sabatine MS et al. N Engl J Med 2017; 376: 1713-1722.

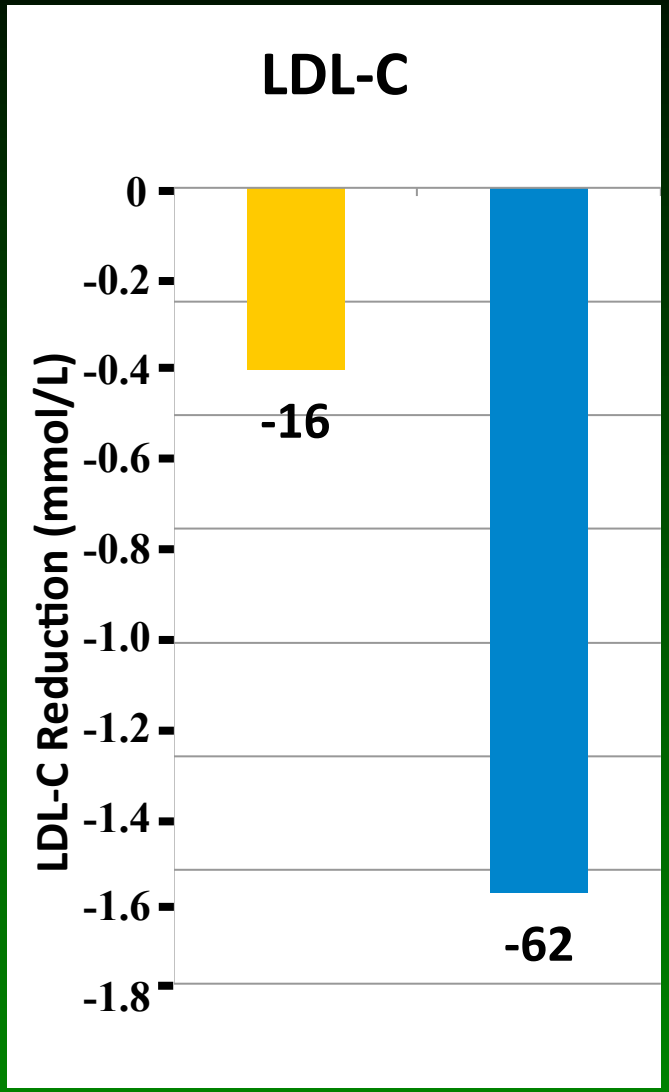
FOURIER: Positive Results

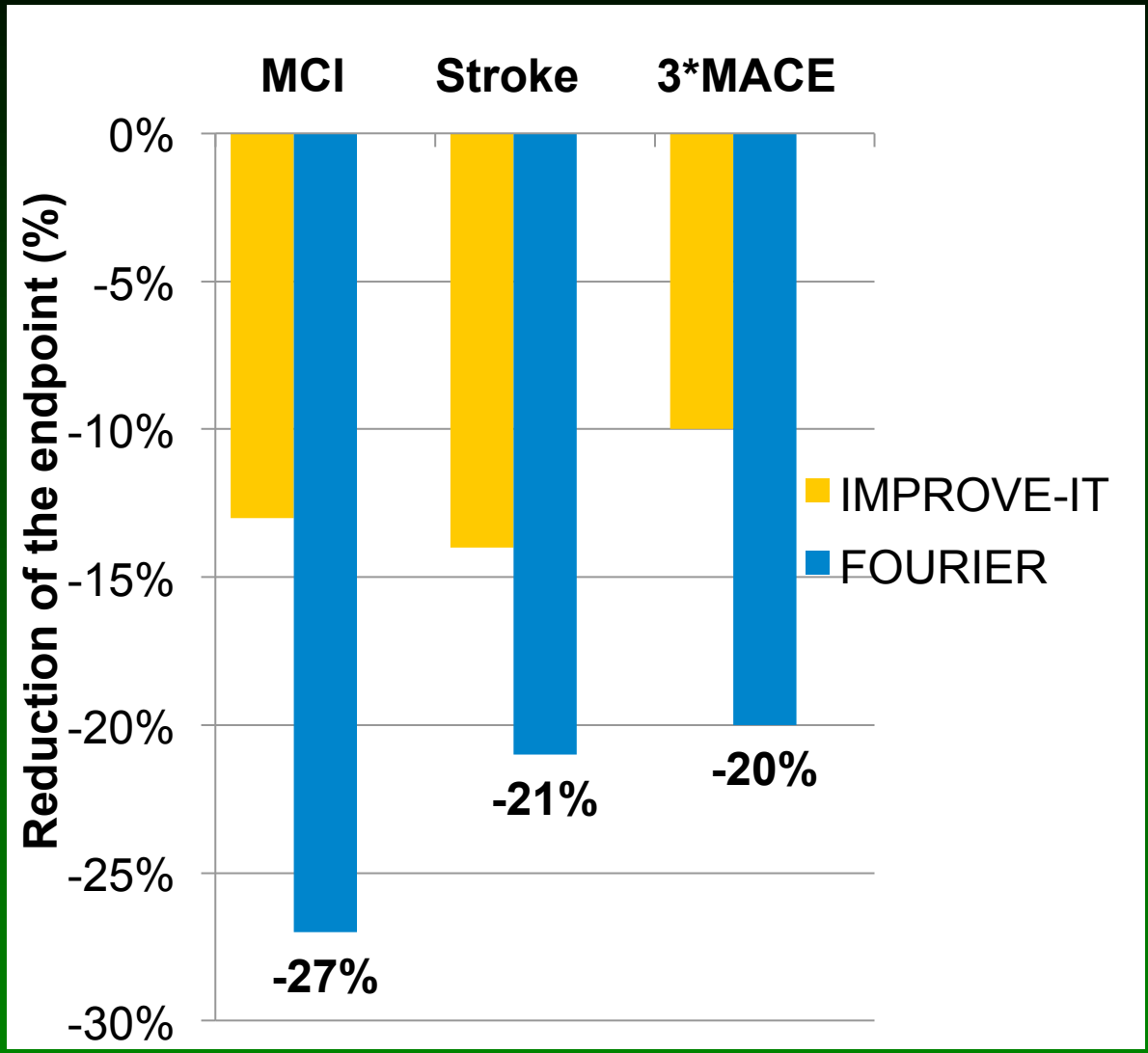
- **Significant reduction of the primary endpoint: cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina or coronary revascularisation.**
- **Significant reduction of myocardial infarction.**

FOURIER: Negative Results

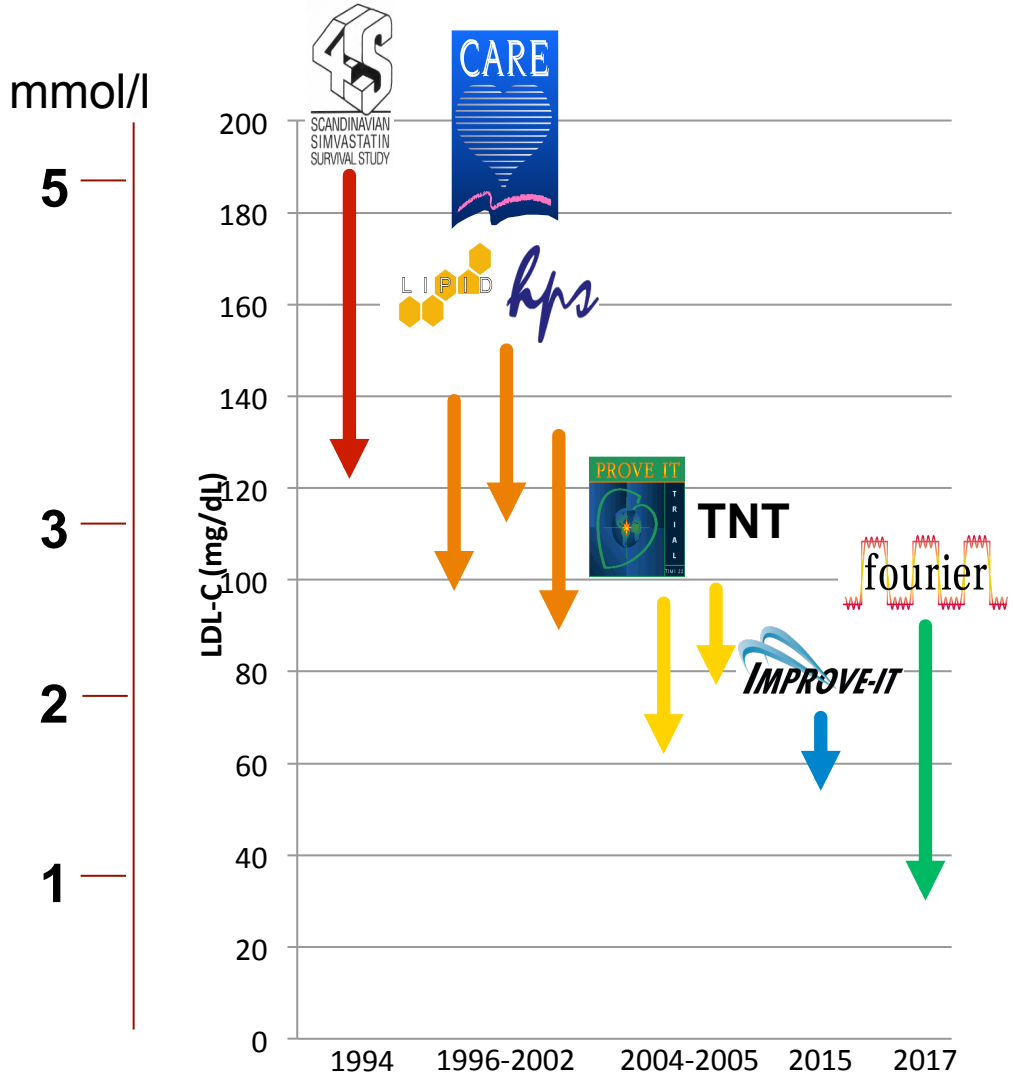
- No effect on cardiovascular mortality.
- No decrease in total mortality.
- No effect on heart failure hospitalisation.

IMPROVE-IT vs. FOURIER





A Quarter of a Century of Treating LDL-C



High is bad

Average is not good

Lower is better

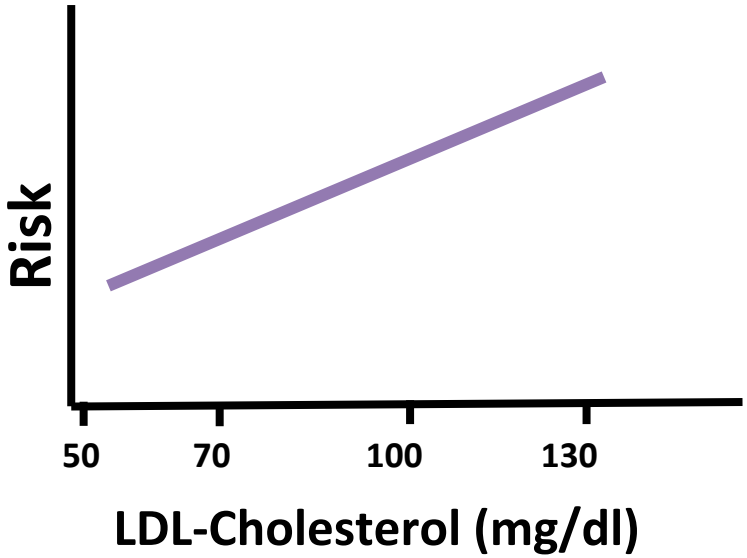
Even lower is even better

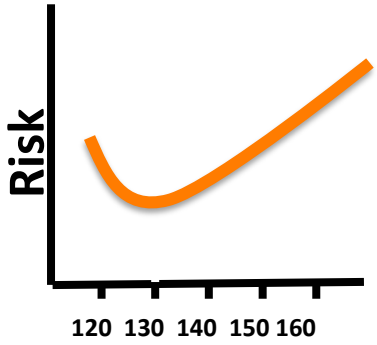
Lowest is best

It‘s LDL-C - What Else?

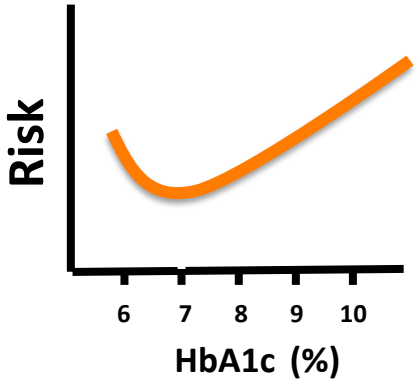
Infraphysiological Target Values

No CAVEAT:
→ no infraphysiological target values





CAVEAT:
Hypotension
→ infraphysiological target values



CAVEAT:
Hypoglycemia
→ infraphysiological target values

Effects of Atorvastatin 40mg/d for 5 Years*: Simpler Mathematics: per Million Patients and Year

Event	Number	Comments
Major CV event with preexisting occlusive vascular disease	-20.000	Irreversible; not identified
Myopathy	+100	Reversible; readily attributed to statin

* Costs per month: <2£

Collins R, Reith C, Emberson J, Armitage J .. et al., Lancet 2016; 388: 2532-2561.

European Heart Journal (2017) **00**, 1–7
doi:10.1093/eurheartj/ehw628

CURRENT OPINION

Comprehensive efforts to increase adherence to statin therapy

Alexander Vonbank[1,2], Stefan Agewall[3], Keld Per Kjeldsen[4,5], Basil S. Lewis[6], Christian Torp-Pedersen[7], Claudio Ceconi[8], Christian Funck-Brentano[9], Juan Carlos Kaski[10], Alexander Niessner[11], Juan Tamargo[12], Thomas Walther[13,14], Sven Wassmann[15], Giuseppe Rosano[16], Harald Schmidt[17], Christoph H. Saely[1,2], and Heinz Drexel[1,2,18]*

A Comprehensive Approach to Statin Adherence

Problem	Response
Unwillingness to start therapy	Counsel about MI and stroke
Early discontinuation	Recounsel
Muscle pain	Specify, check causality
Rechallenge	New problem
Other dosage or combination with ezetimibe	If not successful and high risk
Try PCSK9 inhibition	

Vonbank A, Agewall S, Kjeldsen KP, Lewis BS, Torp-Pedersen C, Ceconi C, Funck-Brentano C, Kaski JC, Niessner A, Tamargo J, Walther T, Wassmann S, Rosano G, Schmidt H, Saely CH & Drexel H. Position Paper. Eur Heart J 2017.

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1. Ansätze zur Atheroskleroseprävention
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Zürcher Herzkurs, 29.09.2017

New drugs and interactions

LDL - what else?

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