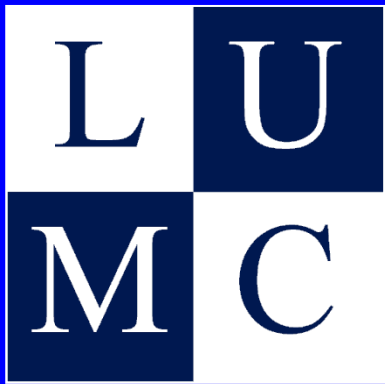


Dyslipidaemia / Diabetes Case in relation to (recent) trial results/guidelines

NVVC congres 5 april 2018



Prof. JW Jukema, MD, PhD
Dept Cardiology, Leiden University Medical Center

Presenter Disclosures

JW Jukema and his department have received research grants from and/or was speaker on, among others, CME accredited meetings sponsored by Amgen, Lilly, Merck-Schering-Plough, Pfizer, Sanofi Aventis, the Netherlands Heart Foundation, the Netherlands Heart Institute and European Union.

Nicolai Anitschkow (1885 – 1964)

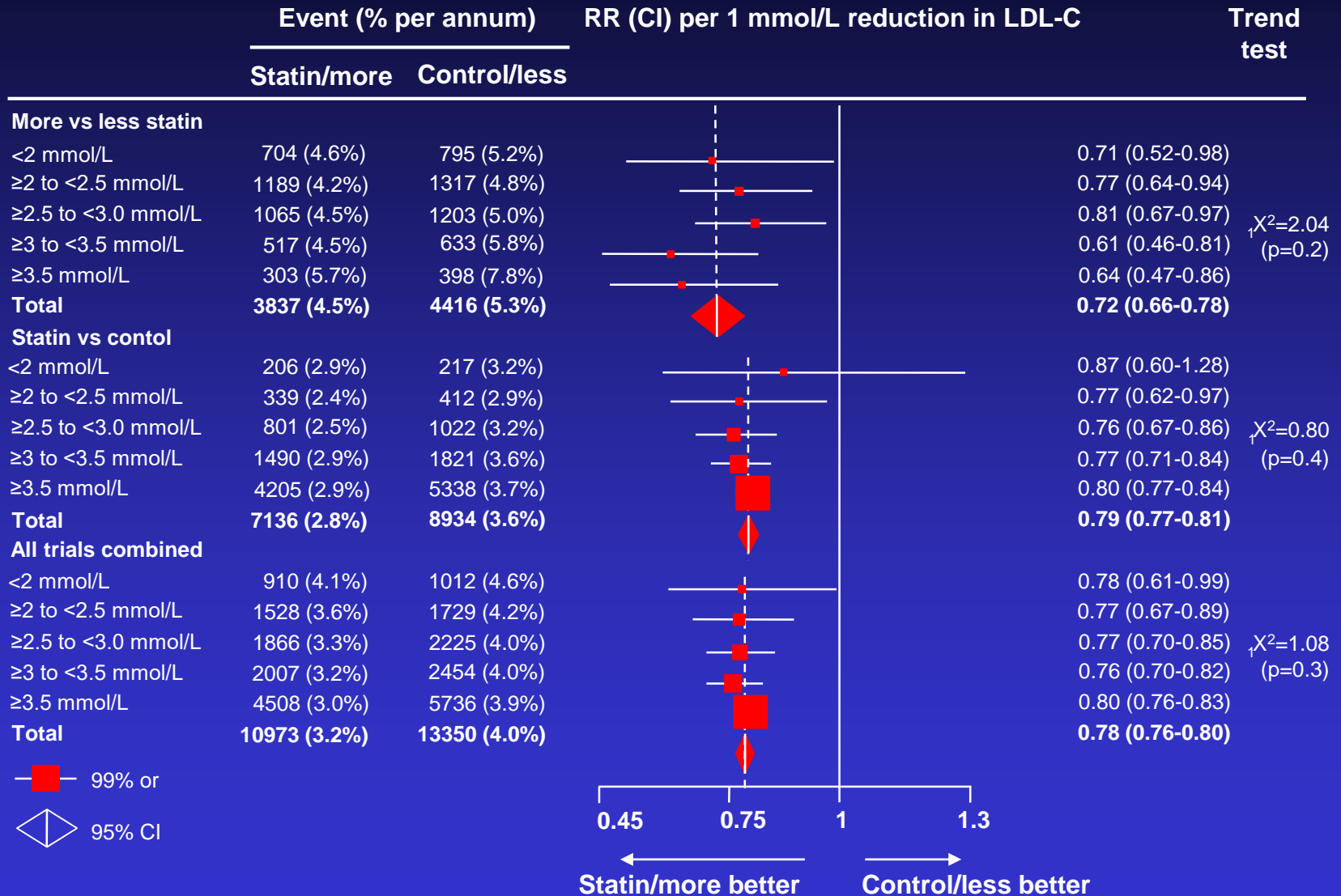
- Identified cell types involved in atherosclerosis
 - Smooth muscle cells
 - Macrophages
 - Lymphocytes
- “There is no atherosclerosis without cholesterol”



Anitschkow NN, Chatalov S (1913). "Über experimentelle Cholesterinsteatose und ihre Bedeutung für die Entstehung einiger pathologischer Prozesse". *Zentralbl Allg Pathol* 24: 1-9.

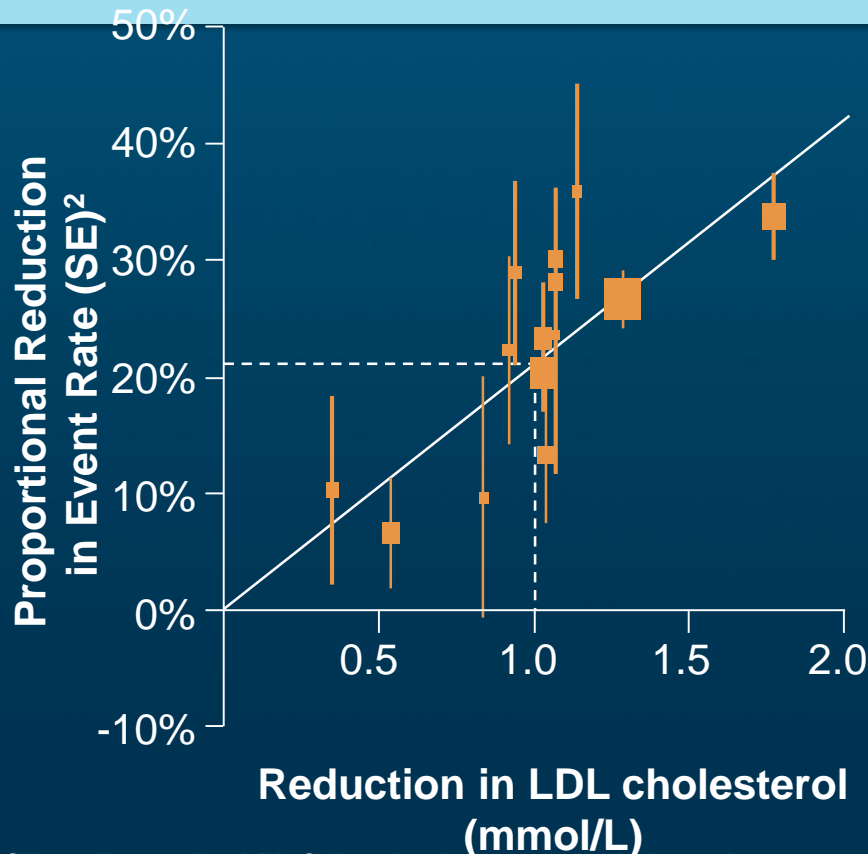
Anitschkow NN (1913). "Über die Veränderungen der Kaninchenaorta bei experimenteller Cholesterinsteatose". *Beitr Pathol Anat* 56: 379-404.

CTT: more intensive LDL lowering can decrease CV events by 40-50%



Statin CV Outcomes Trials Show That The Magnitude of CV Event Reduction is Related to LDL-C Reduction¹

In a meta-analysis of 26 statin trials, reflecting data from 170,000 patients, there was a **22% risk reduction in CV events per 1 mmol/L reduction in LDL-C ($P<0.0001$)¹**



CV event reduction is:

- Independent of baseline LDL-C¹
- Independent of baseline CV risk³

CV=cardiovascular; LDL-C=low-density lipoprotein cholesterol.

1. Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet*. 2010;376:1670-1681. 2. Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet*. 2005;366:1267-1278. 3. Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet*. 2012;380:581-590.

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D.,
Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S.,
Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D.,
Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D.,
Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D.,
KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D.,
Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H.,
Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D.,
for the IMPROVE-IT Investigators*

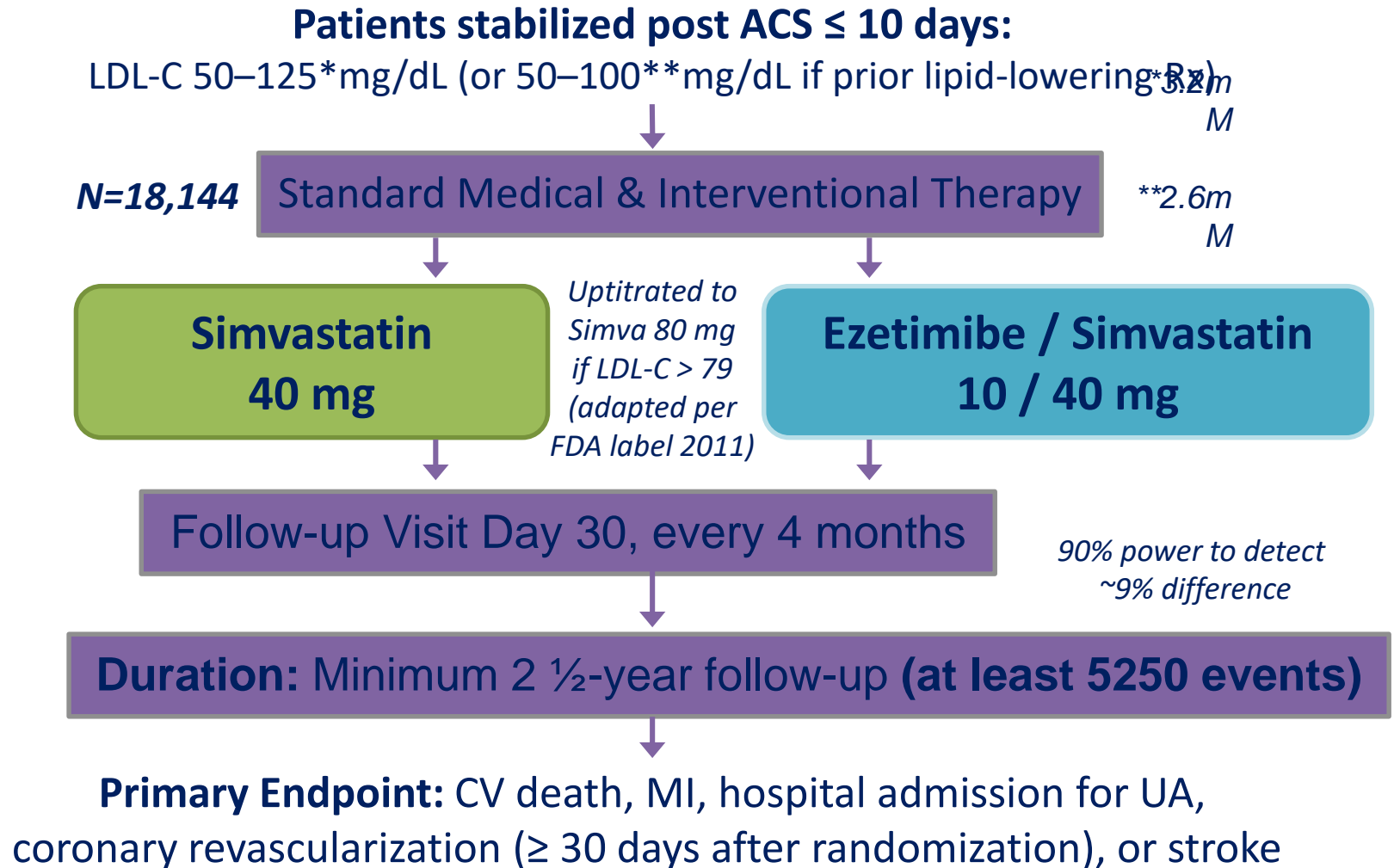
ABSTRACT



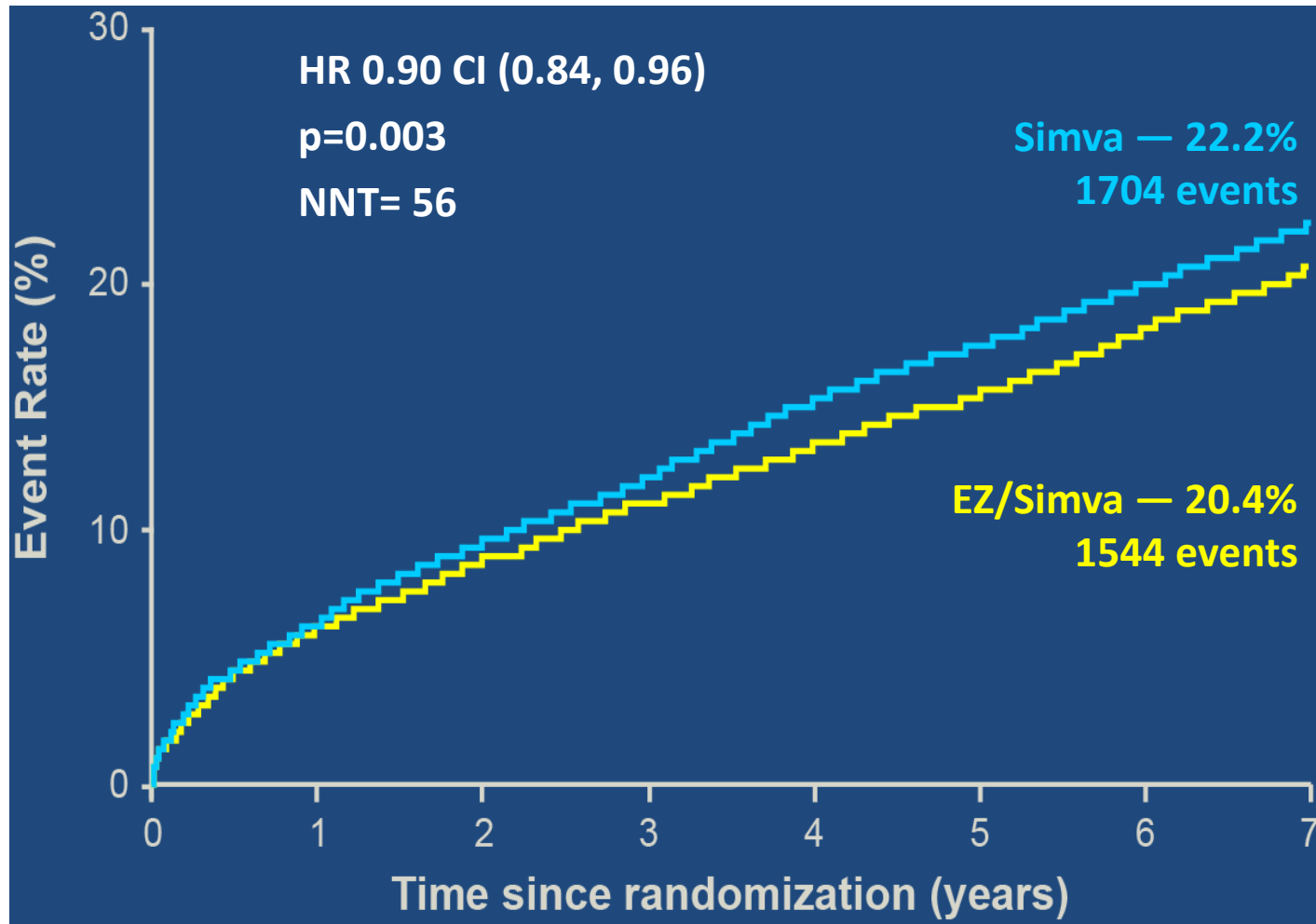
This article was published on June 3, 2015,
at NEJM.org.

N Engl J Med 2015;372:2387-97.
DOI: 10.1056/NEJMoa1410489

Study Design



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

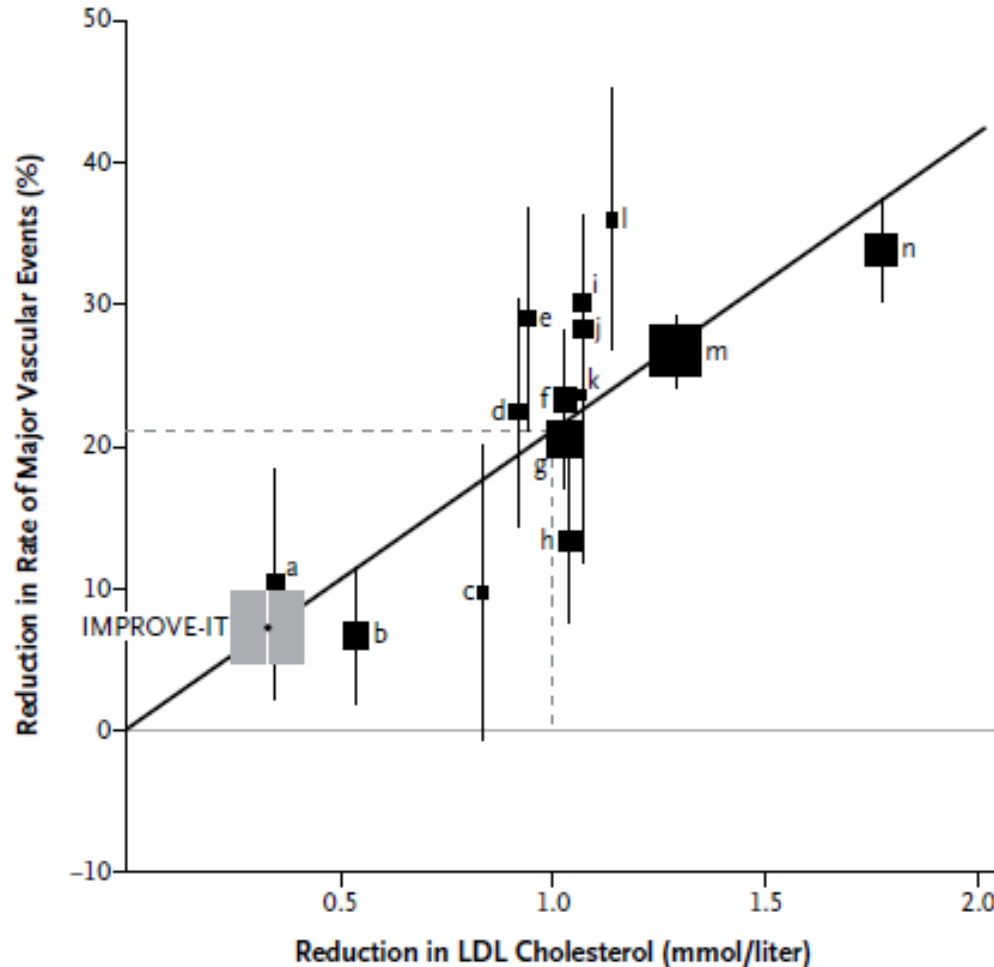


7-year event rates

This article was published on June 3, 2015,
at NEJM.org.

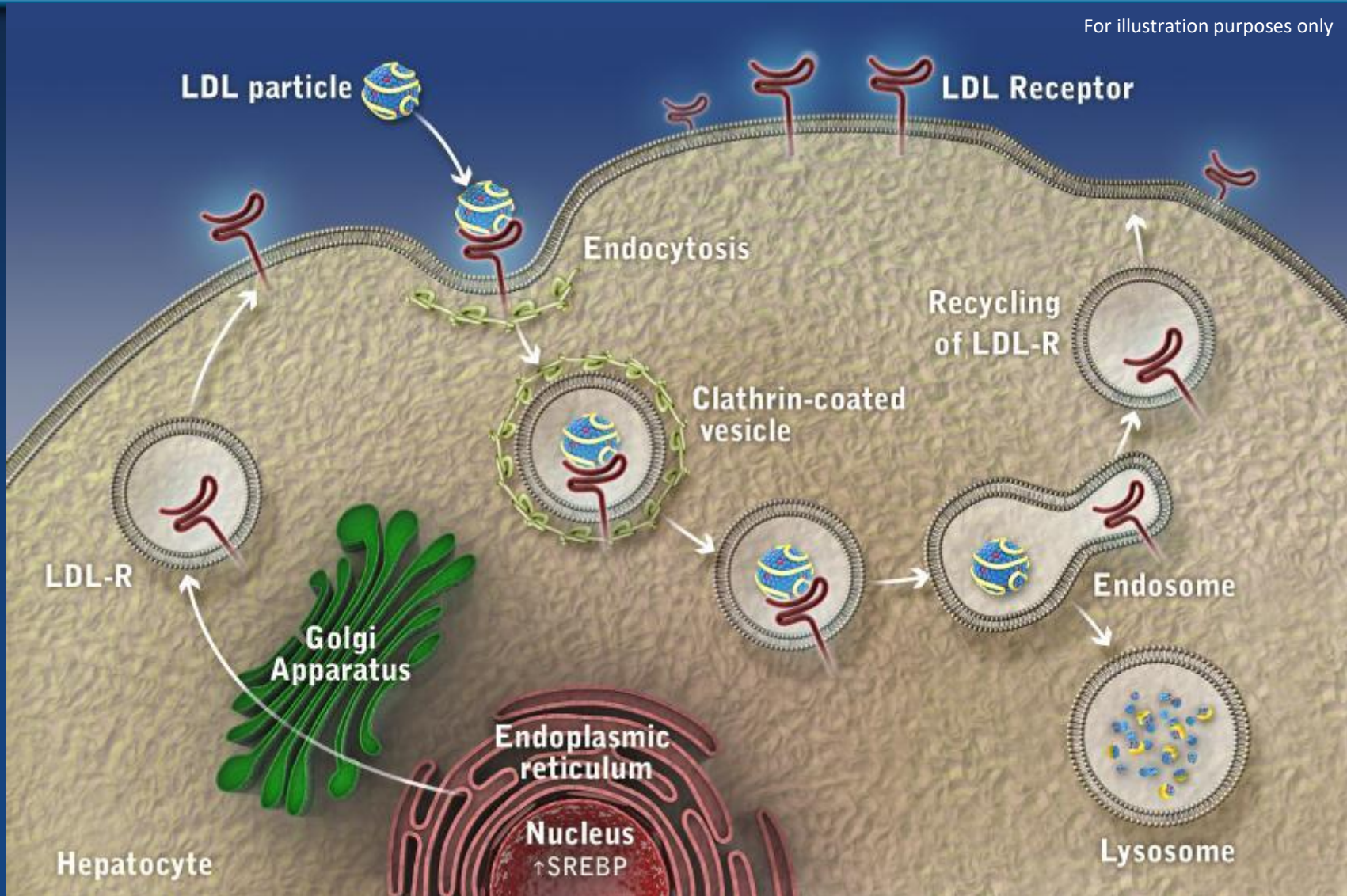
N Engl J Med 2015;372:2387-97.
DOI: 10.1056/NEJMoa1410489

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

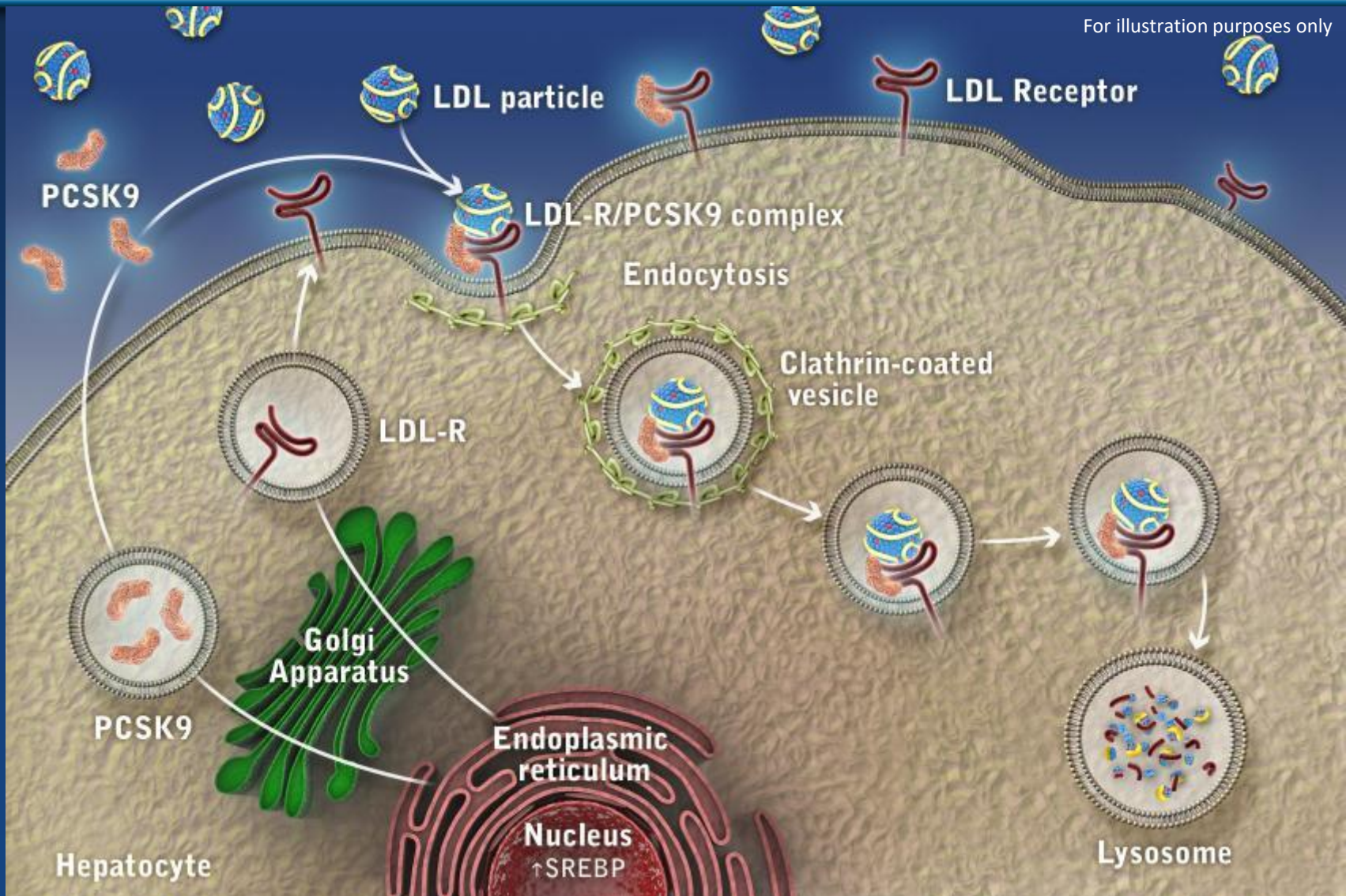


CTT Collaboration.
Lancet 2005; 366:1267-78;
Lancet 2010;376:1670-81
NEJM 2015;372:2387-97.

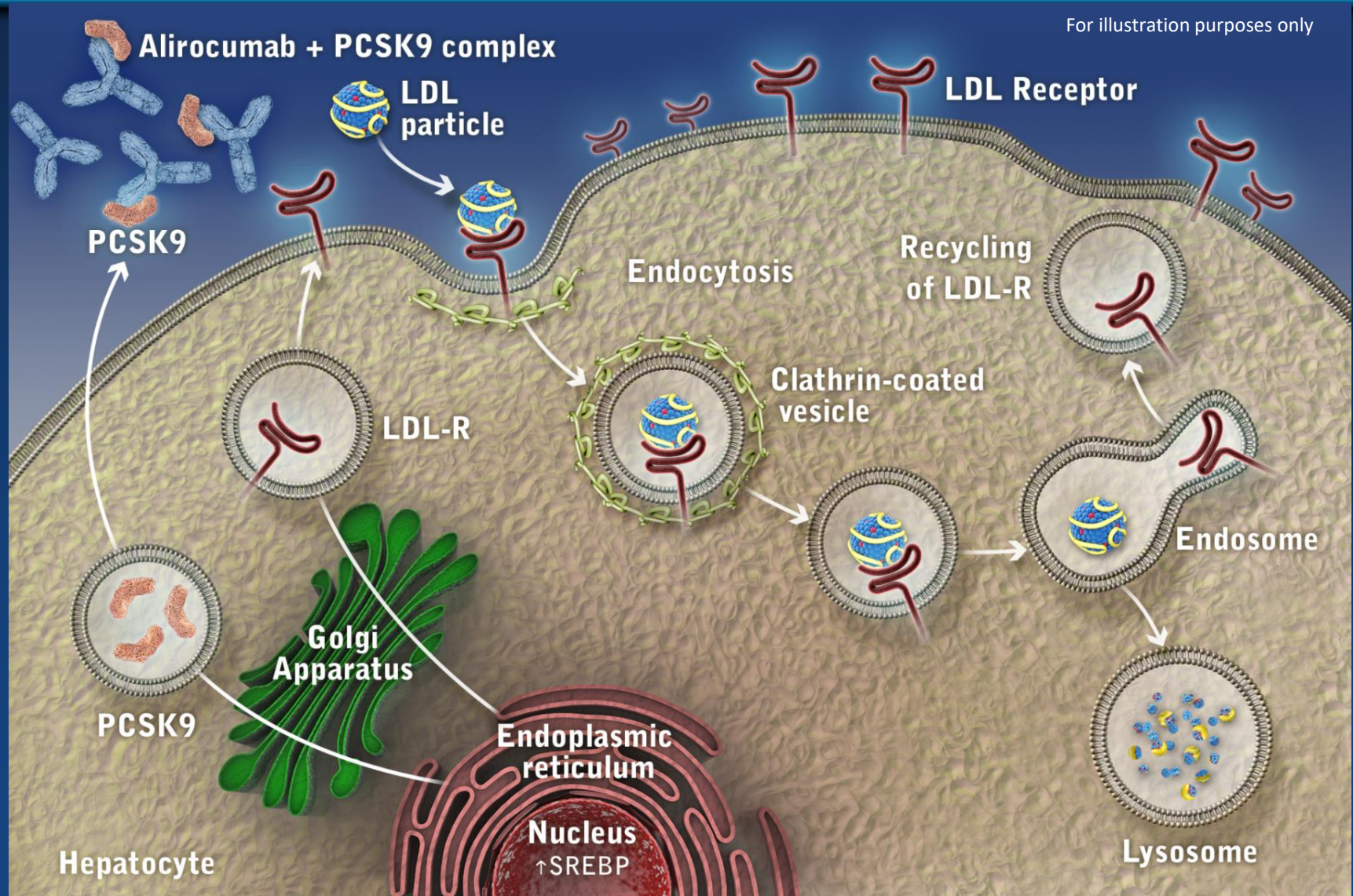
LDL Receptor Function and Life Cycle



The Role of PCSK-9 in the Regulation of LDL Receptor Expression

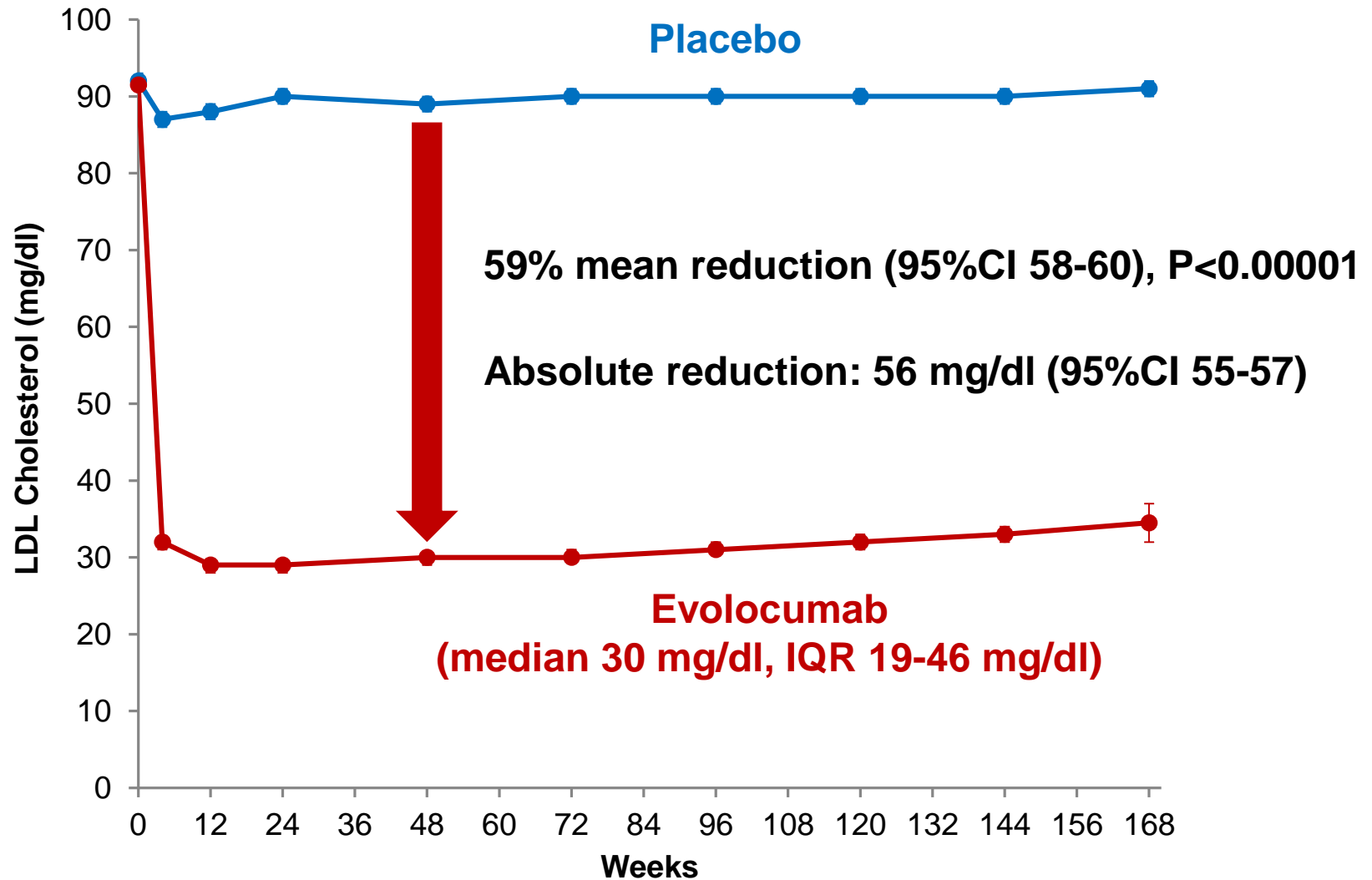
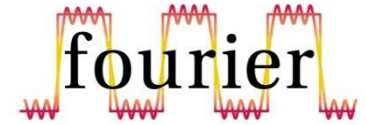


Impact of PCSK-9 inhibitor Alirocumab* on LDL Receptor Expression





LDL Cholesterol





Further Details



The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

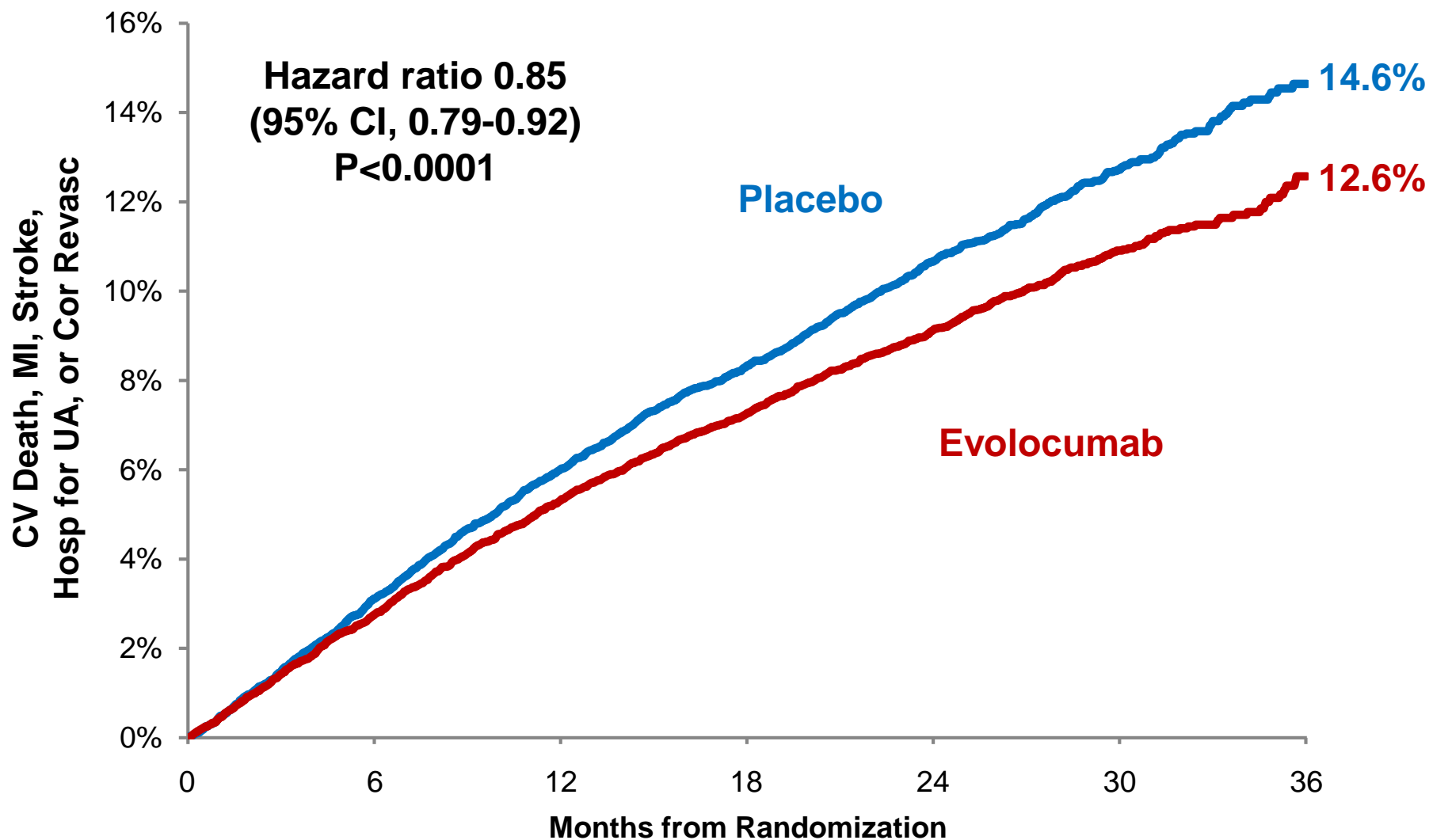
Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

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*





Primary Endpoint



The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg,
Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema,
Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher,

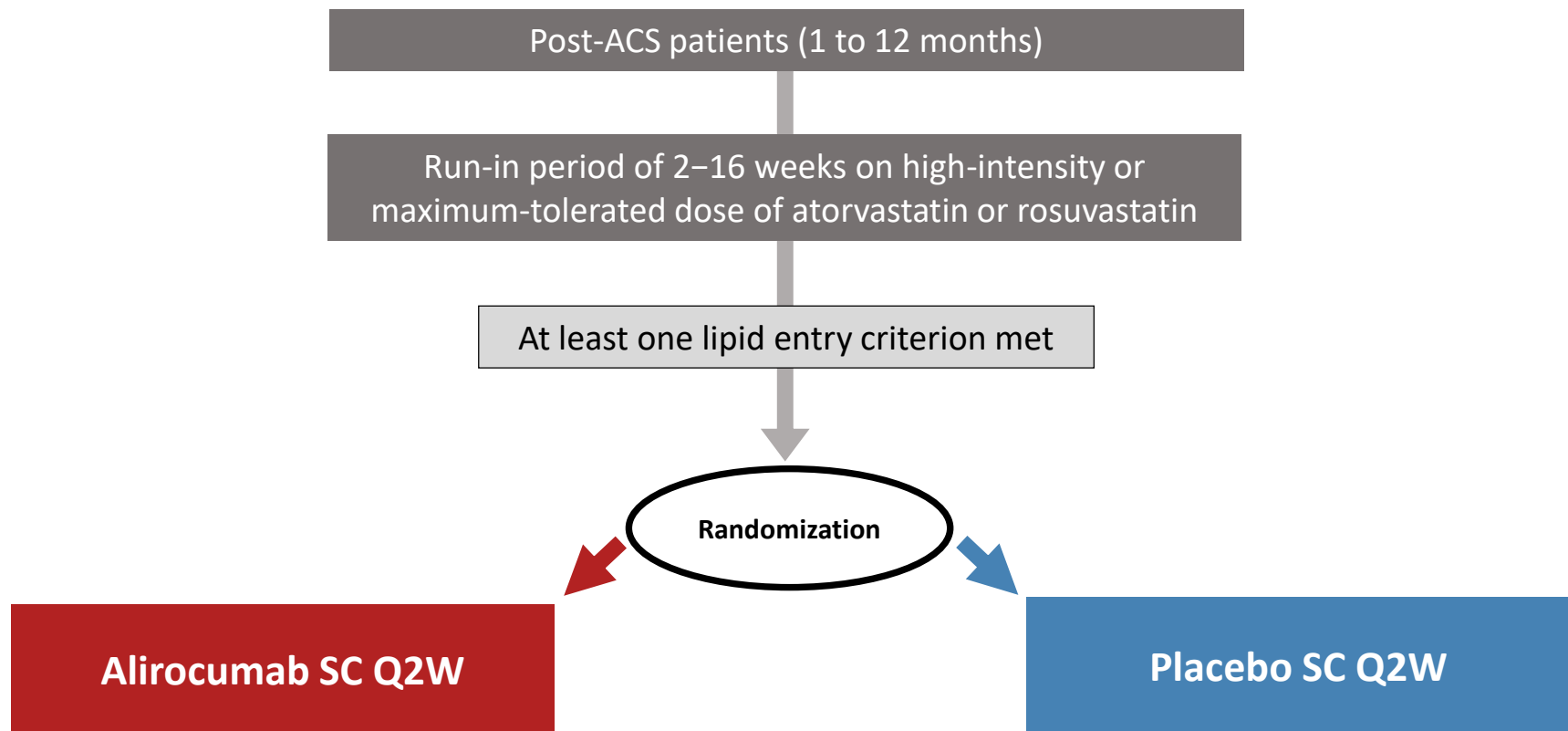
Ph. Gabriel Steg

On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions
March 10, 2018



Treatment Assignment



Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

Odyssey Outcomes: Main Efficacy Endpoints: Hierarchical Testing

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
CHD event	1199 (12.7)	1349 (14.3)	0.88 (0.81, 0.95)	0.001
Major CHD event	793 (8.4)	899 (9.5)	0.88 (0.80, 0.96)	0.006
CV event	1301 (13.7)	1474 (15.6)	0.87 (0.81, 0.94)	0.0003
Death, MI, ischemic stroke	973 (10.3)	1126 (11.9)	0.86 (0.79, 0.93)	0.0003
CHD death	205 (2.2)	222 (2.3)	0.92 (0.76, 1.11)	0.38
CV death	240 (2.5)	271 (2.9)	0.88 (0.74, 1.05)	0.15
All-cause death	334 (3.5)	392 (4.1)	0.85 (0.73, 0.98)	0.026*

*Nominal P-value



PCSK-9 inhibitors Reimbursement Criteria

Patients with hypercholesterolemia **AND** sufficiently high risk (1-5 below), not at LDL-C target* despite:

Maximal tolerated statin **and** ezetimibe

Primary Prevention
(LDL-c > 2,5 mmol/l)

Secondary Prevention
(LDL-c > 1,8 mmol/l)

1. HeFH / HoFH

2. HeFH / HoFH
&
CVE

3. Statin
Intolerance**
&
CVE

4. CVE
&
recurrent event

5. DM type II
&
CVE

* As described in current Guidelines and accepted by relevant professional societies.

**Statin-associated muscle symptoms with at least 3 different statins, determined in line with the therapeutic flow-chart and criteria as described in the EAS/ESC consensus paper (European Heart Journal 2015; 36: 1012-1022).

In patients with homozygous familial hypercholesterolemia the initial recommended dose is 420 mg once monthly. After 12 weeks of treatment, dose frequency can be up-titrated to 420 mg once every 2 weeks if a clinically meaningful response is not achieved.

CardioVascular Events:

- (N)STE-ACS
- PCI
- CABG
- CVA (ischemic) / TIA
- PAD
- Other