LDL HYPOTHESIS IN THE TIME OF PCSK9

LOVE IN THE TIME OF CHOLERA
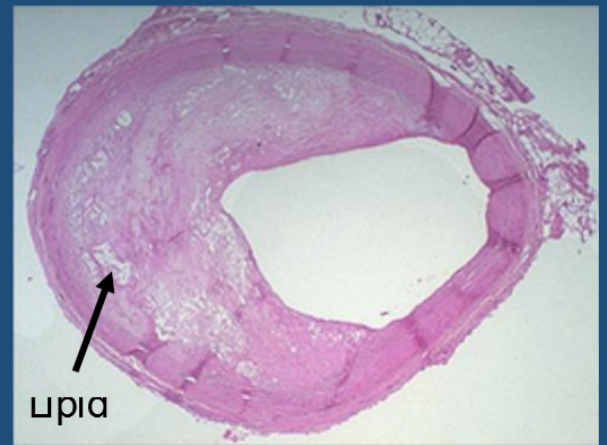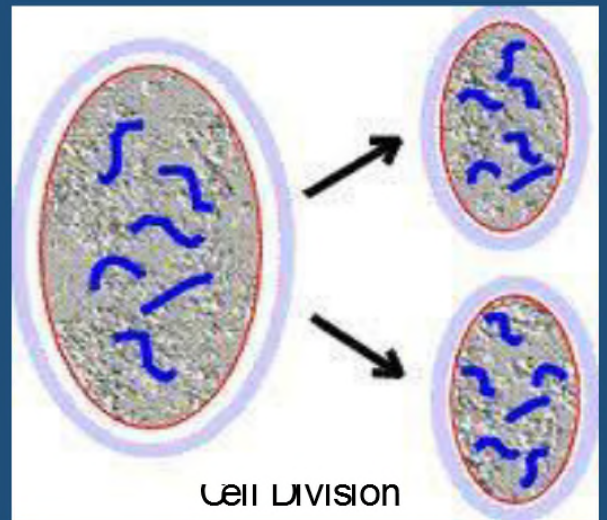
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Disclosure: National Coordinator, ODYSSEY Outcome Trial

The **LDL (lipid) hypothesis** is the concept that excess LDL and other atherogenic lipoproteins are the predominant causal factors in the development of atherosclerotic vascular disease. By extension, this hypothesis also assumes that reducing LDL cholesterol levels, regardless of the means, should produce a corresponding reduction in cardiovascular events.
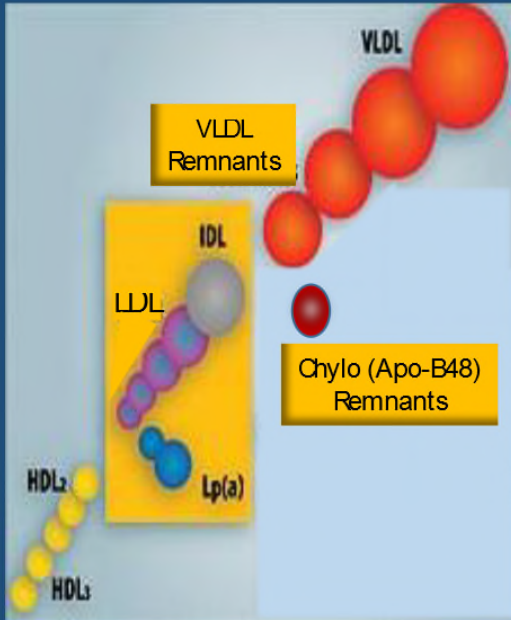
Cell Division

Lipid

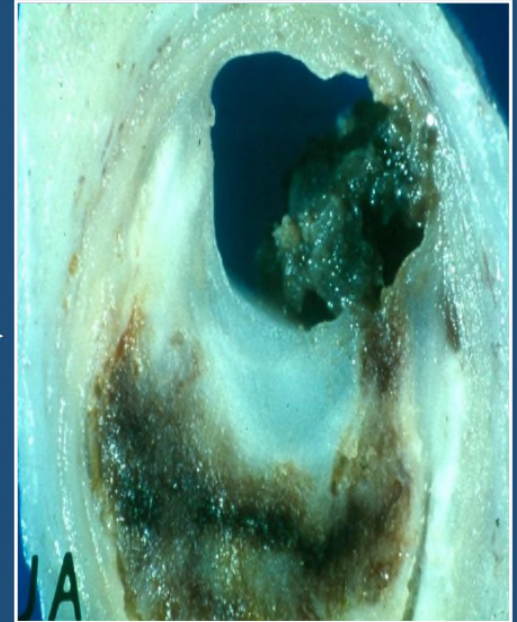Rudolf Virchow   1856

Details of the LDL Hypothesis
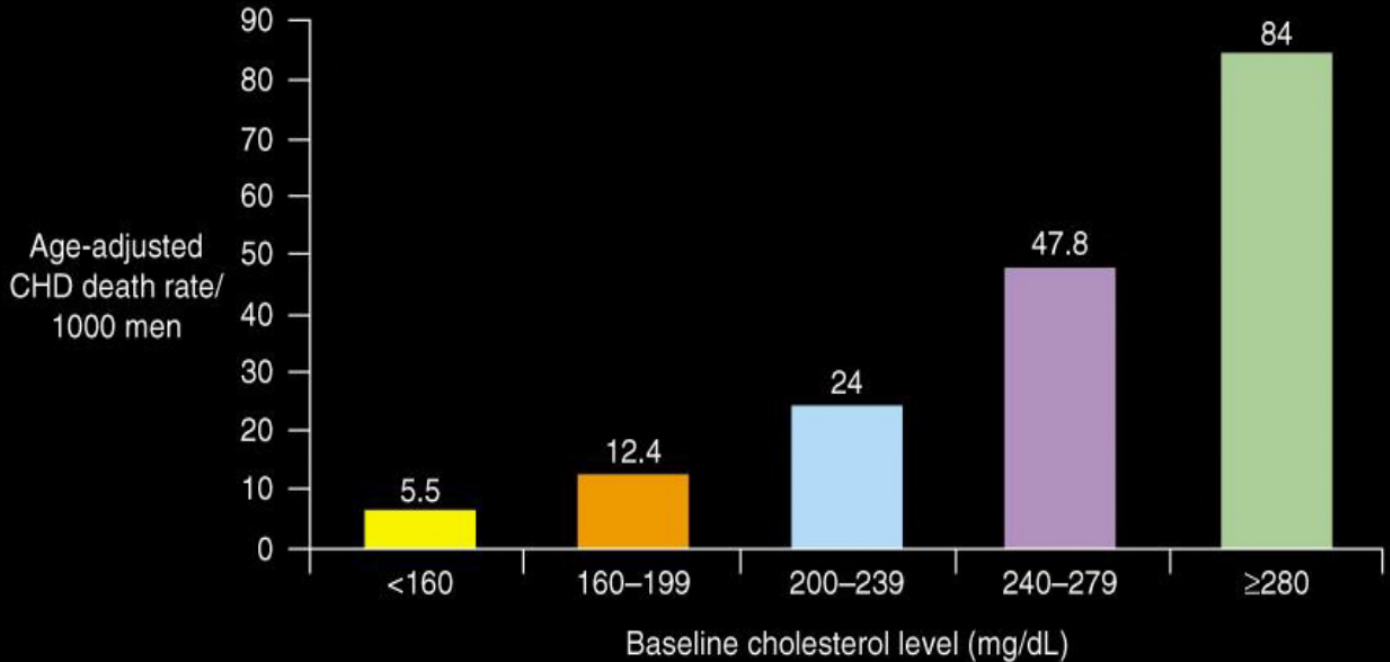

↑ Atherogenic particles

Deposition

Oxidation

Mφ uptake → foam cells

Cellular proliferation

Matrix production

Inflammation

Plaque rupture & erosion

Thrombosis

■ Primary factor

□ Facilitating factors

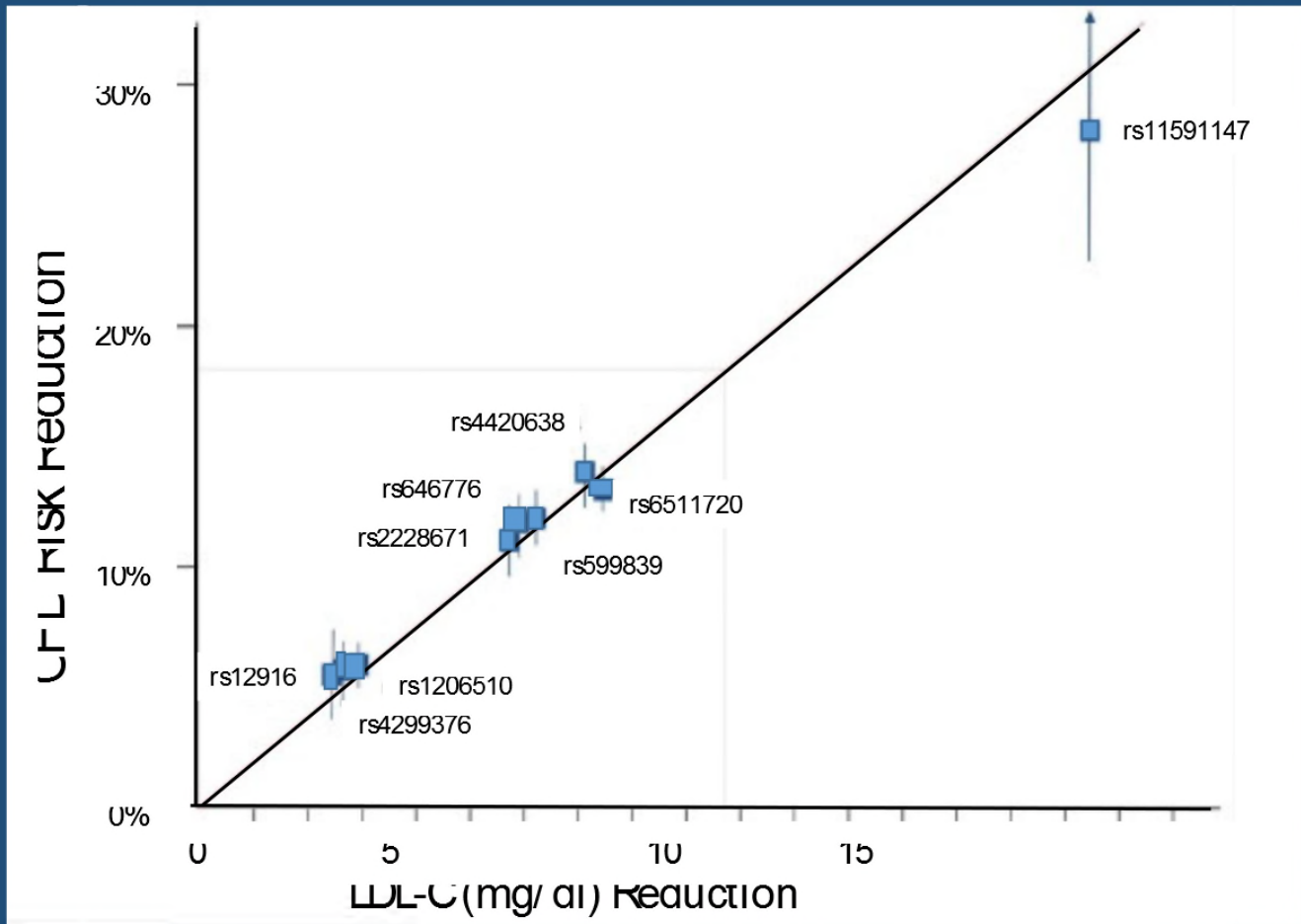# Long-term risk of CHD death in young men according to baseline cholesterol level

Chicago Heart Association Detection Project in Industry
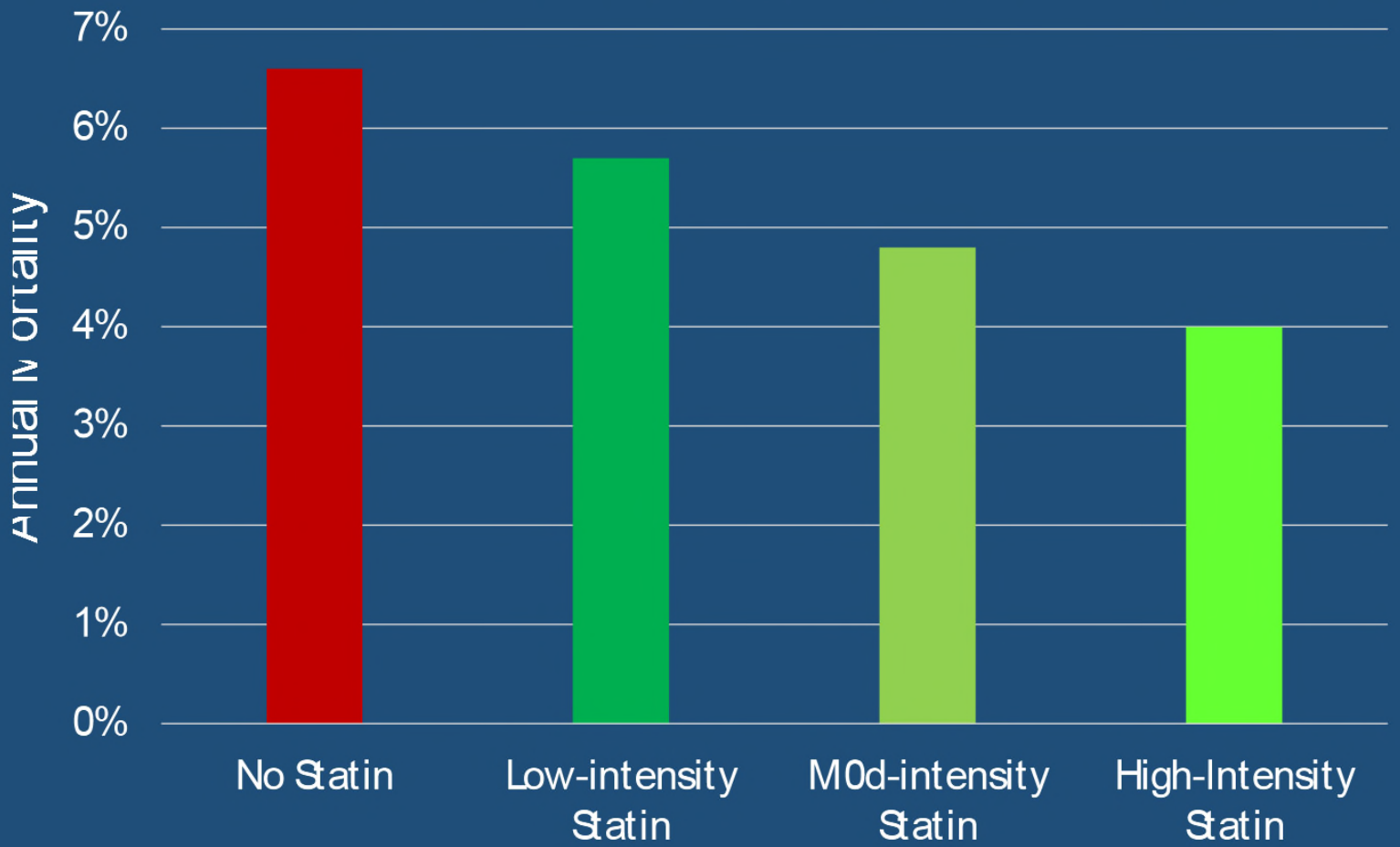25-year follow-up in 11,000 men aged 18 to 39 years

Stamler J, et al. *JAMA*. 2000;284:311-318.
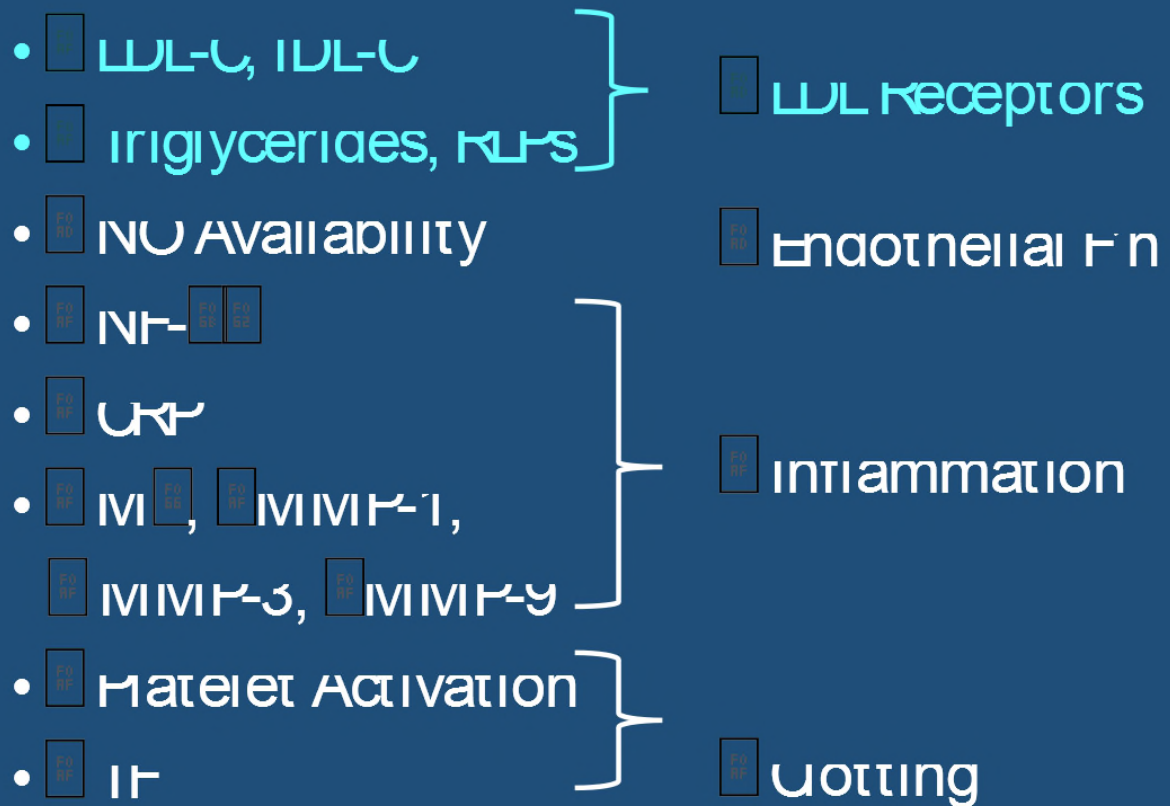
Mendelian Randomization Analysis:
Genetically Lower LDL-C (9 Variants) vs. CHD Risk in 312,321 Subjects

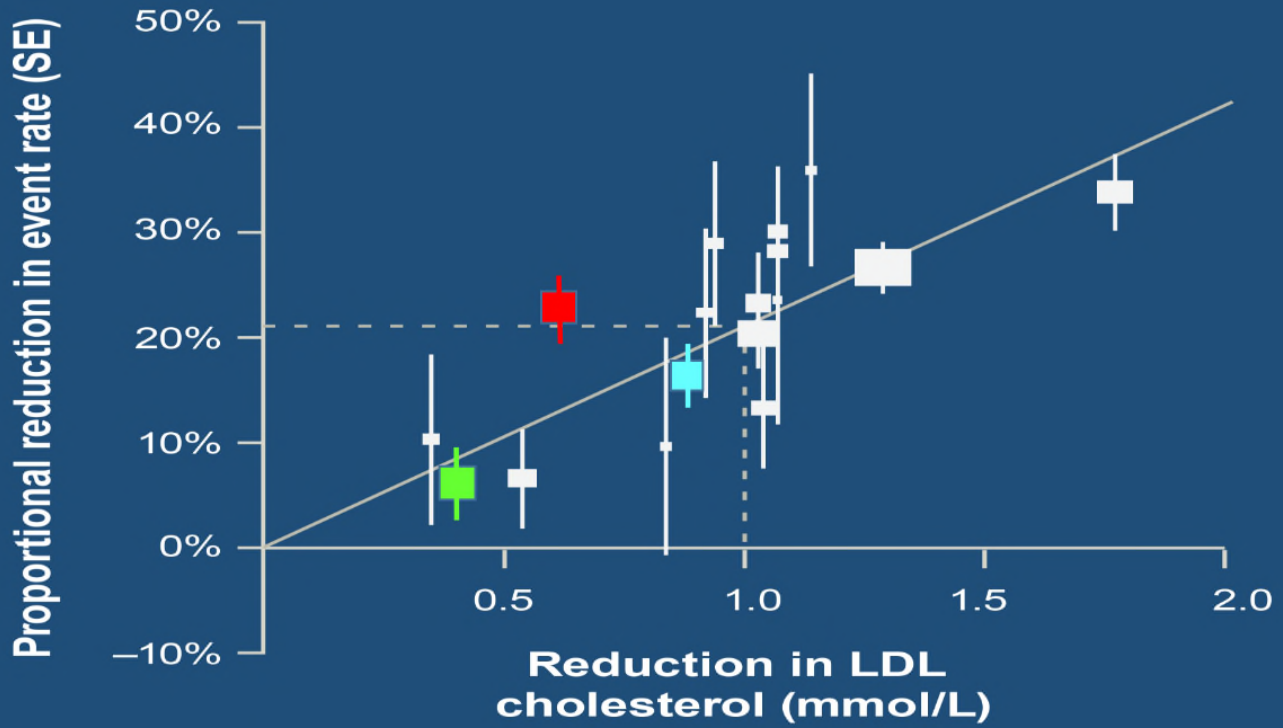# Statin Hypothesis_: Annual Mortality in 509,766 Older VA Patients with ASCVD by Statin Treatment

Annual Mortality by statin treatment group:
- No Statin: ~6.6%
- Low-intensity Statin: ~5.7%
- M0d-intensity Statin: ~4.8%
- High-Intensity Statin: ~4.0%

Effects of Statins on Atherogenic Factors (Lipid + Pleiotropic Effects)

- ↓ LDL-C, IDL-C
- ↓ Triglycerides, RLPs } ↑ LDL Receptors
- ↑ NO Availability   ↑ Endothelial Fn
- ↓ NF-κβ
- ↓ CRP
- ↓ MΦ, ↓ MMP-1,   } ↓ Inflammation
  ↓ MMP-3, ↓ MMP-9
- ↓ Platelet Activation } ↓ Clotting
- ↓ TF

IMPROVE-IT and TNT Added to Statin Trials: Relationship of Absolute LDL-C Lowering to CVE Reduction
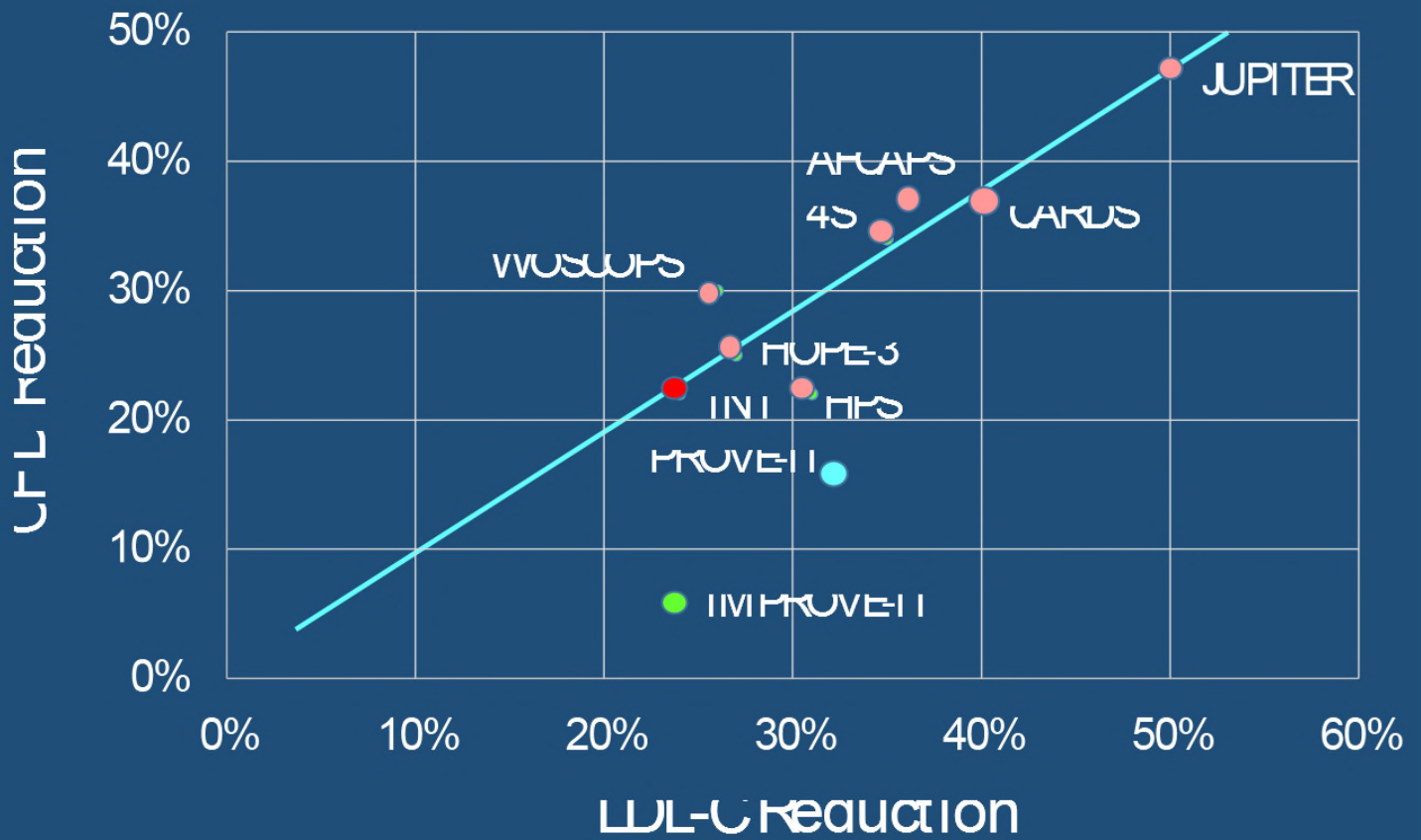

IMPROVE-IT
(simva 40/80 ± eze)

PROVE-IT
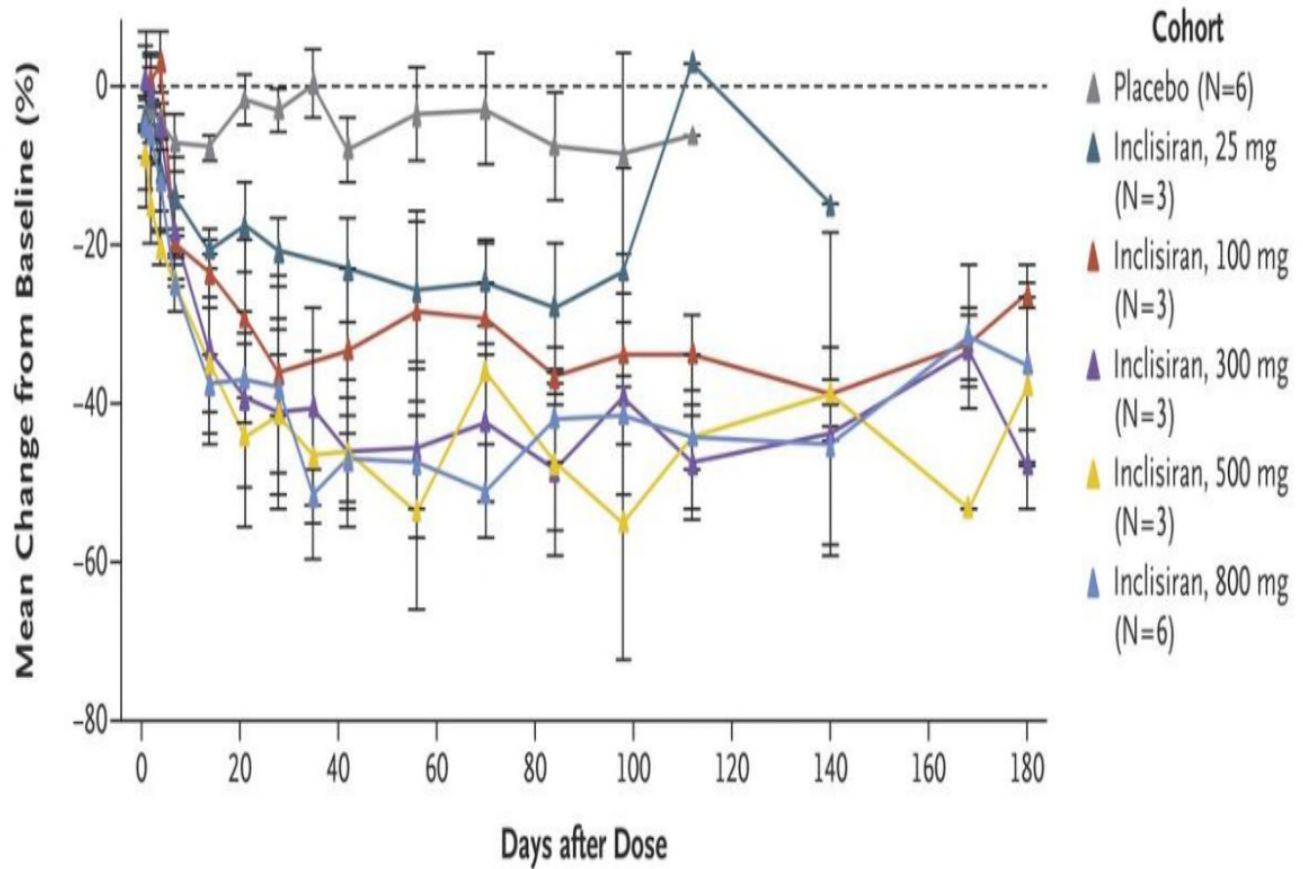(prava 40 vs. atorva 80)

TNT
(atorva 10 vs. 80)

STATIN Trials

IMPROVE-IT and TNT Added to Statin Trials: Relationship of Relative LDL-C Lowering to CVE Reduction

PCSK9 Inhibitor CV Outcome RCTs

	FOURIER	ODYSSEY Outcomes
Inclusion:	ASCVD	Recent ACS
	LDL-C >70	LDL-C >70
# Subjects:	28,000	18,000
Bkgd Statin:	Effective	High-dose Effective
Treatment:	Evolocumab 140/420	Alirocumab 75/150
Baseline LDL-C:	92 mg/dl	87 mg/dl
On-Tx LDL LL:	none	<15
Endpoints:	Death, MI, Stroke	Death, MI, Stroke,
	ACS Hosp, Revasc	ACS Hosp
Event Goal:	1600 (6%)	2000 (11%)
Mean Duration:	2 years	3 years
Estimated End:	ACC 2017	ACC 2018

Effect of Inclisiran (RISC-binding RNAi lipid nanoparticle) on LDL-C after Single S.C. Injections

The LDL Hypothesis in the Time of PCSK9 Inhibitor Outcome Trial Results