BRIGHAM AND WOMEN'S HOSPITAL
| Heart & Vascular Center |

Non-statin therapies to reduce LDL-cholesterol

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January 21, 2023

Case: 61 year old female, prior PCI to RCA

- She reports a long history of hypercholesterolemia
- Family history of CAD: Brother had MI at age 54, Father with fatal MI at age 66
- Current treatment: atorvastatin 80mg, amlodipine 5mg, aspirin 81mg
- Labs: LDL 114 mg/dL, Triglycerides 140 mg/dL, Lp(a) 110 nmol/L

What would you do next?

A. Switch to rosuvastatin 40mg daily

B. Add Ezitimibe 10mg daily

C. Start PCSK9 inhibitor

D. Add icosapent ethyl

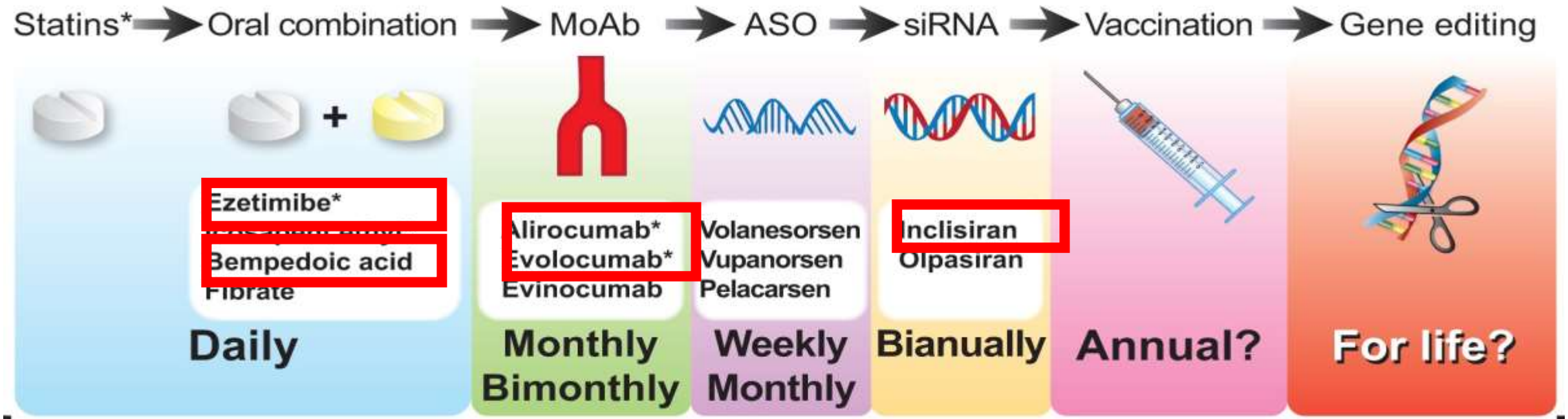
E. Add bempedoic acid

F. Dietary changes

Your answer likely influenced by:

- Cost ($)
- Efficacy (What works best)
- Patient risk profile
- Side effect profile
- Guidelines
- Personal experience

Evolution of Lipid Lowering Therapies:




LDL-C
Main target


Non-HDL (including remnants)
Secondary target


Lp (a)
New target

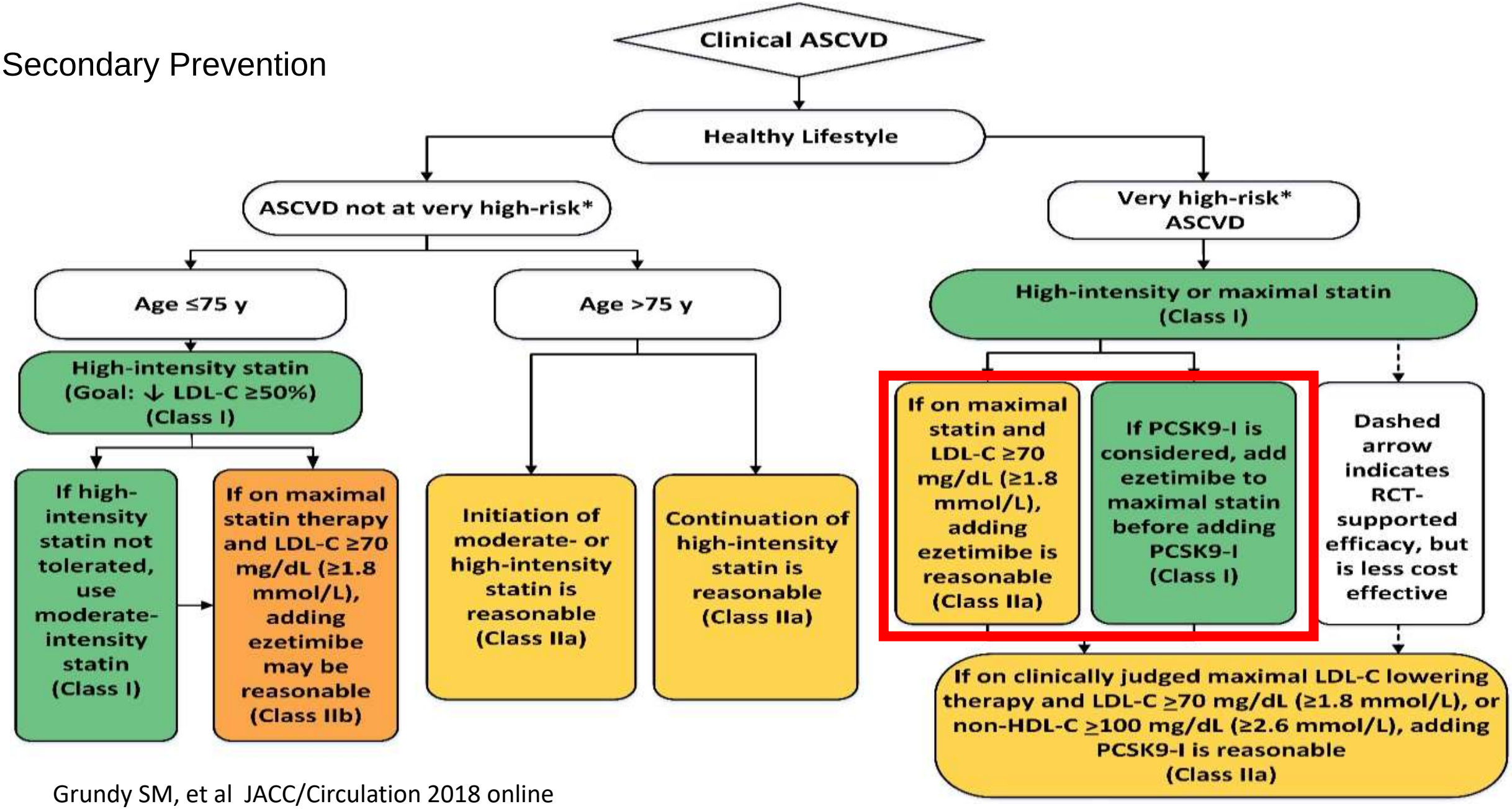
*Therapies shown to decrease CV events

Eur Heart J, 2021. ehab841, https://doi.org/10.1093/eurheartj/ehab841

ESC European Society of Cardiology

2018 ACC/AHA Cholesterol Guidelines

Secondary Prevention

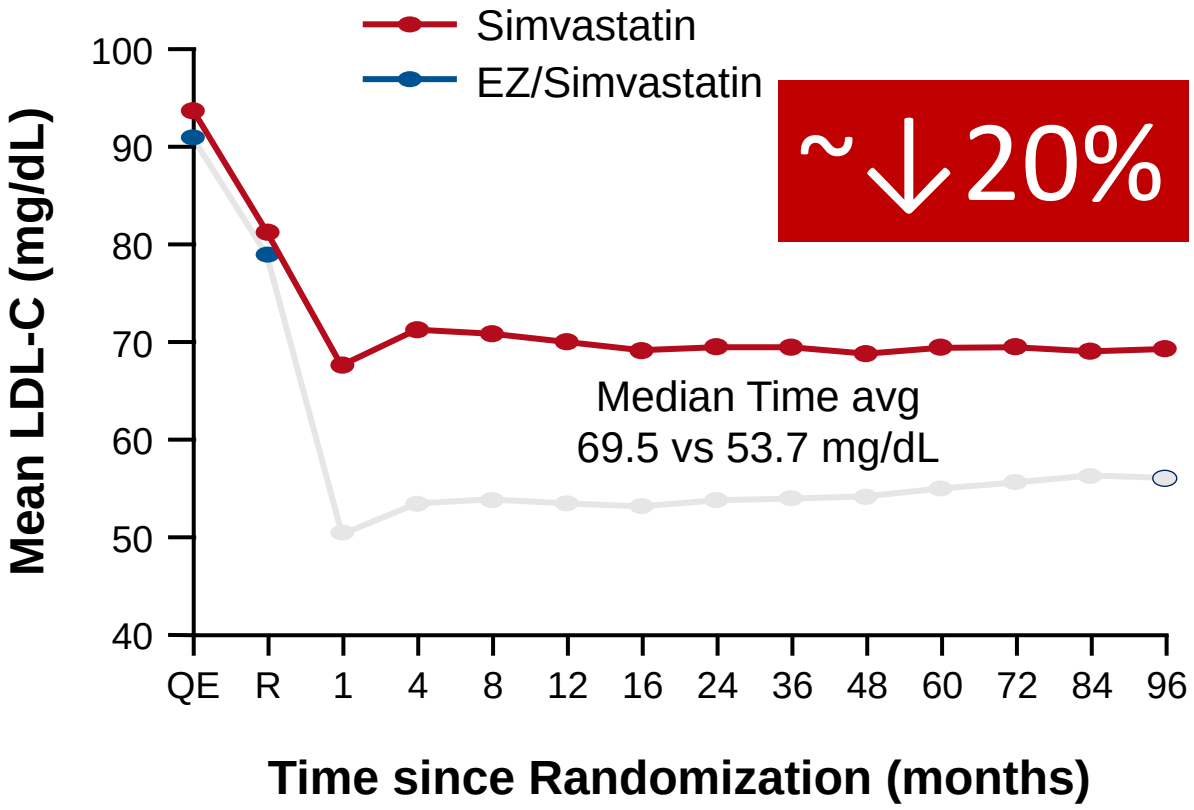


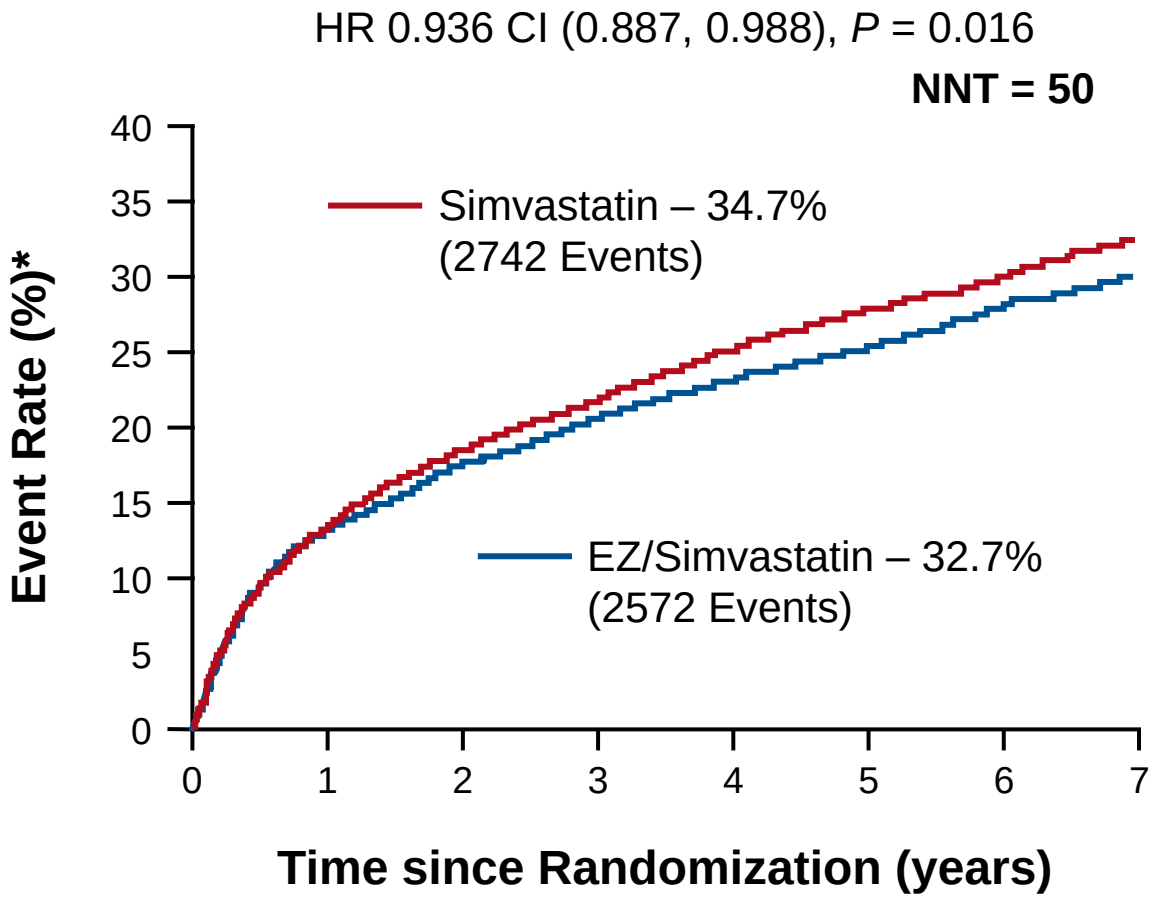
Grundy SM, et al JACC/Circulation 2018 online

IMPROVE-IT: Primary Results

18,144 ACS patients randomized to simvastatin alone or ezetimibe (EZ)/simvastatin, median follow-up 6 years

~↓6.5% (relative risk)



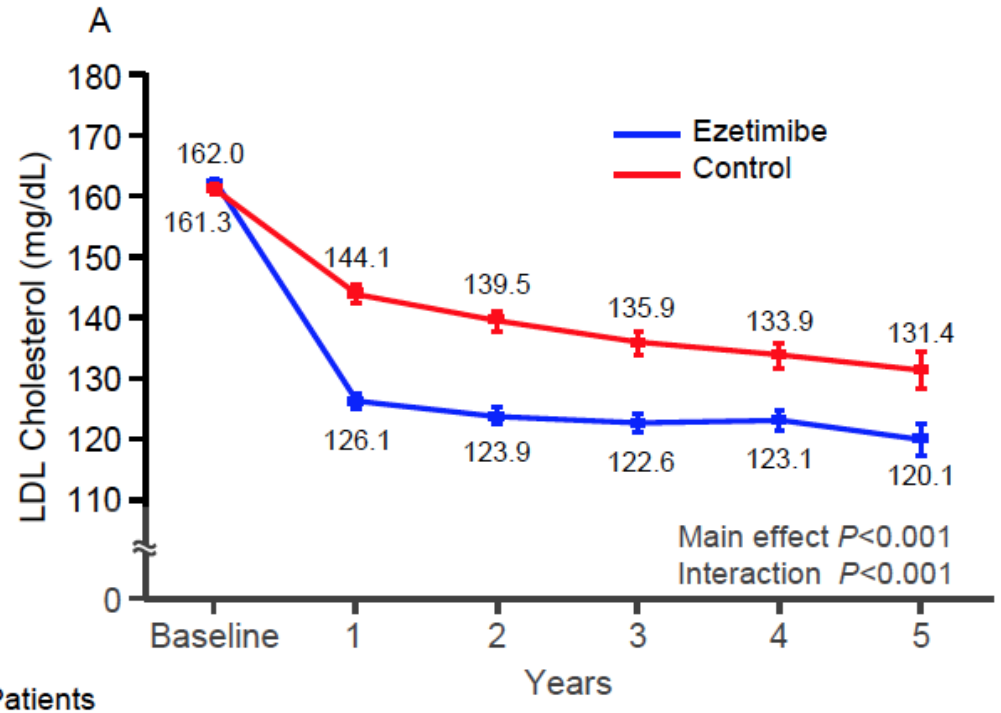


***Primary end point (cardiovascular death, MI, unstable angina, coronary revascularization, or stroke).**

Cannon CP, et al. *N Engl J Med.* 2015;372(25):2387-97.

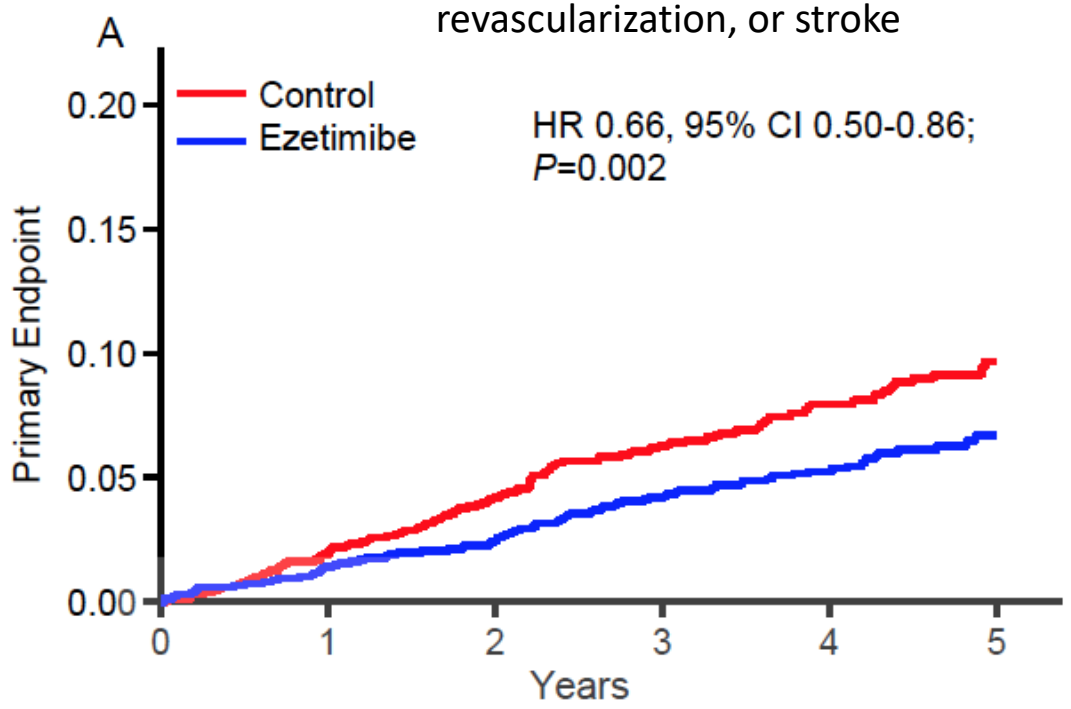
EWTOPIA 75: Ezetimibe vs. Placebo in Primary Prevention in Pts > 75 years old

LDL



Number of Patients						
Ezetimibe	1700	1489	1245	1009	685	311
Control	1685	1464	1227	1023	706	314

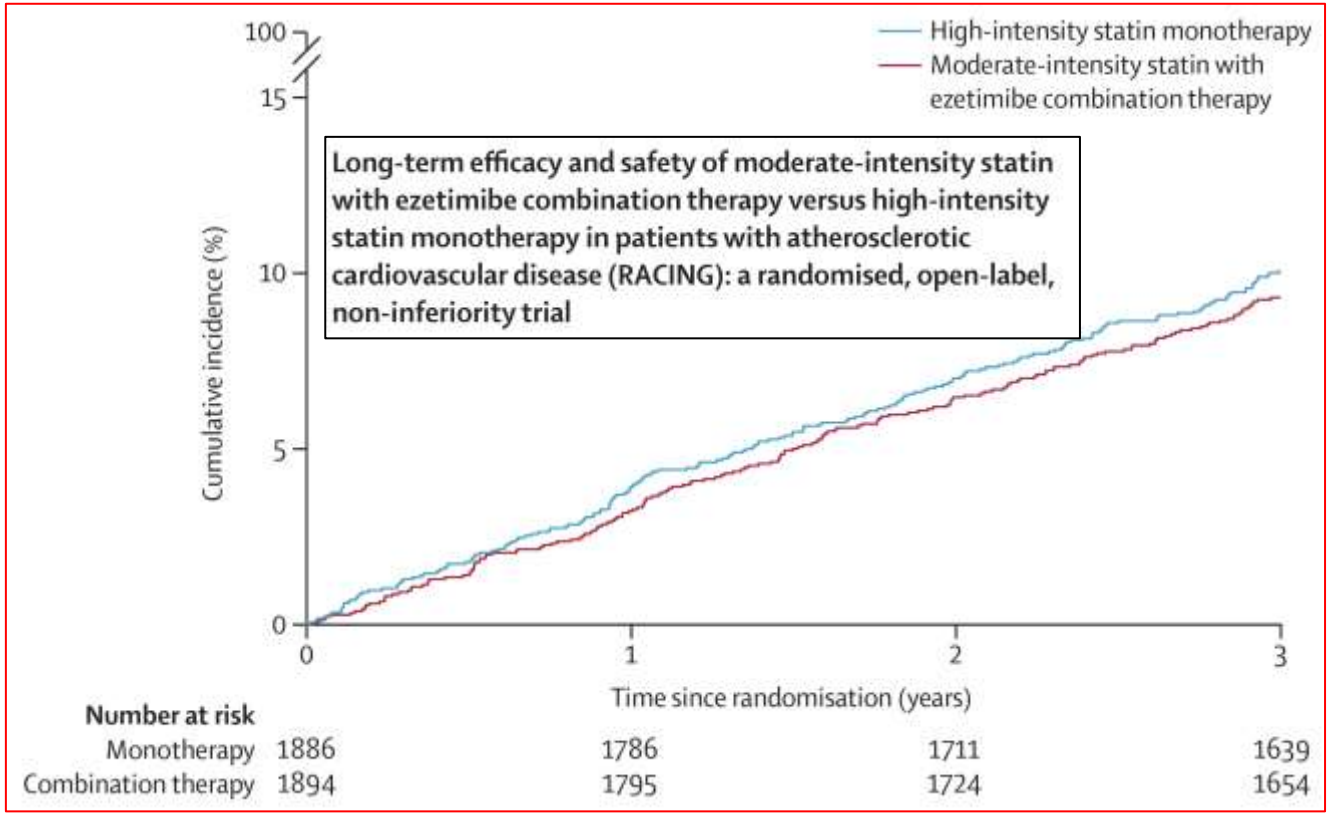
Sudden cardiac death, MI, coronary revascularization, or stroke



No. at Risk						
Control	1695	1582	1418	1217	887	383
Ezetimibe	1716	1617	1445	1219	897	387

Yasuyoshi Ouchi, et al. Circulation 2019

For a patient who is on moderate intensity statin therapy, should I switch to high intensity statin or add ezetimibe?



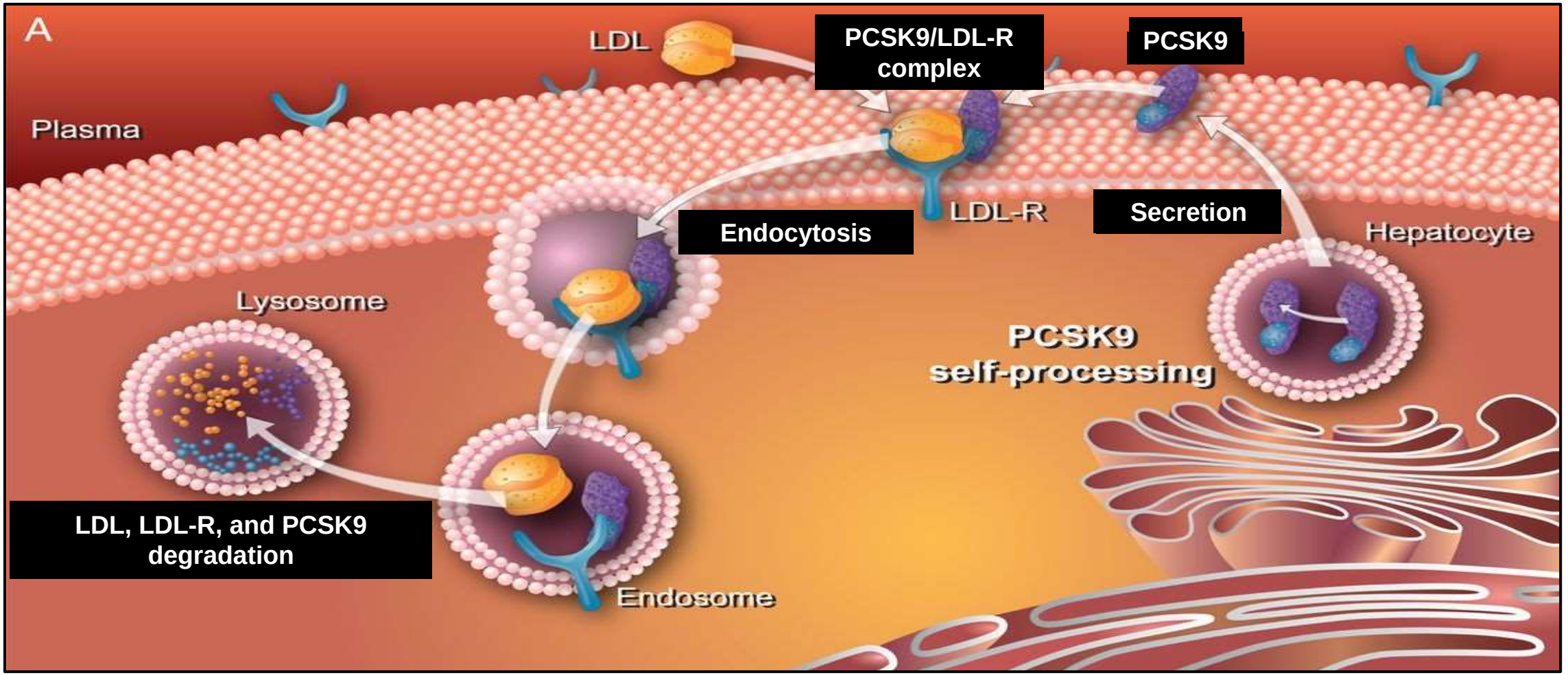
RACING Trial, LANCET 2022

3780 patients w/ ASCVD
26 sites in Korea

Rosuvastatin 20mg vs.
Rosuvastatin 10mg + ezetimibe 10

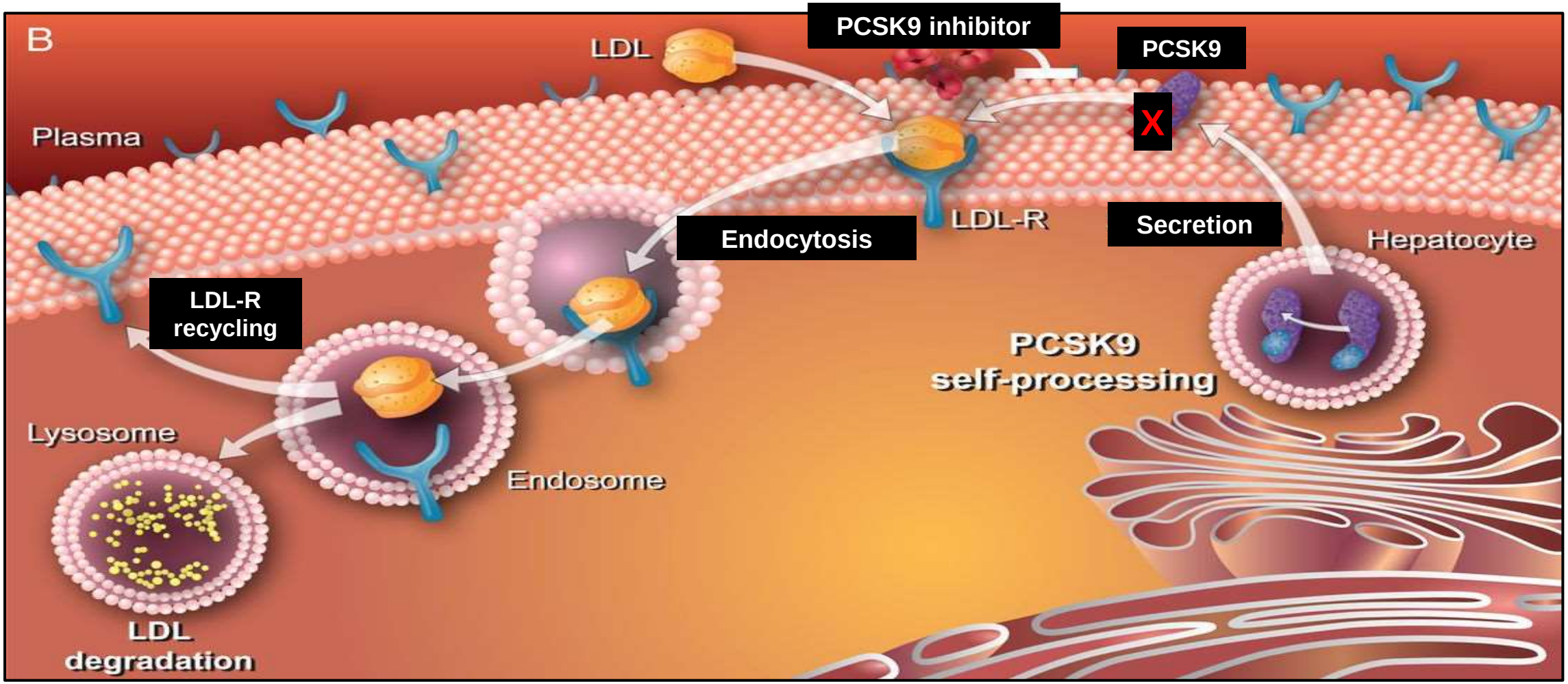
Combination therapy:
- Non-inferior outcomes
- More patients achieving LDL-C<70mg/dL
- Less intolerance

PCSK9 Regulates LDL-R Expression



Shimada YJ, Cannon CP. Eur Heart J. 2015;36:2415–2424.

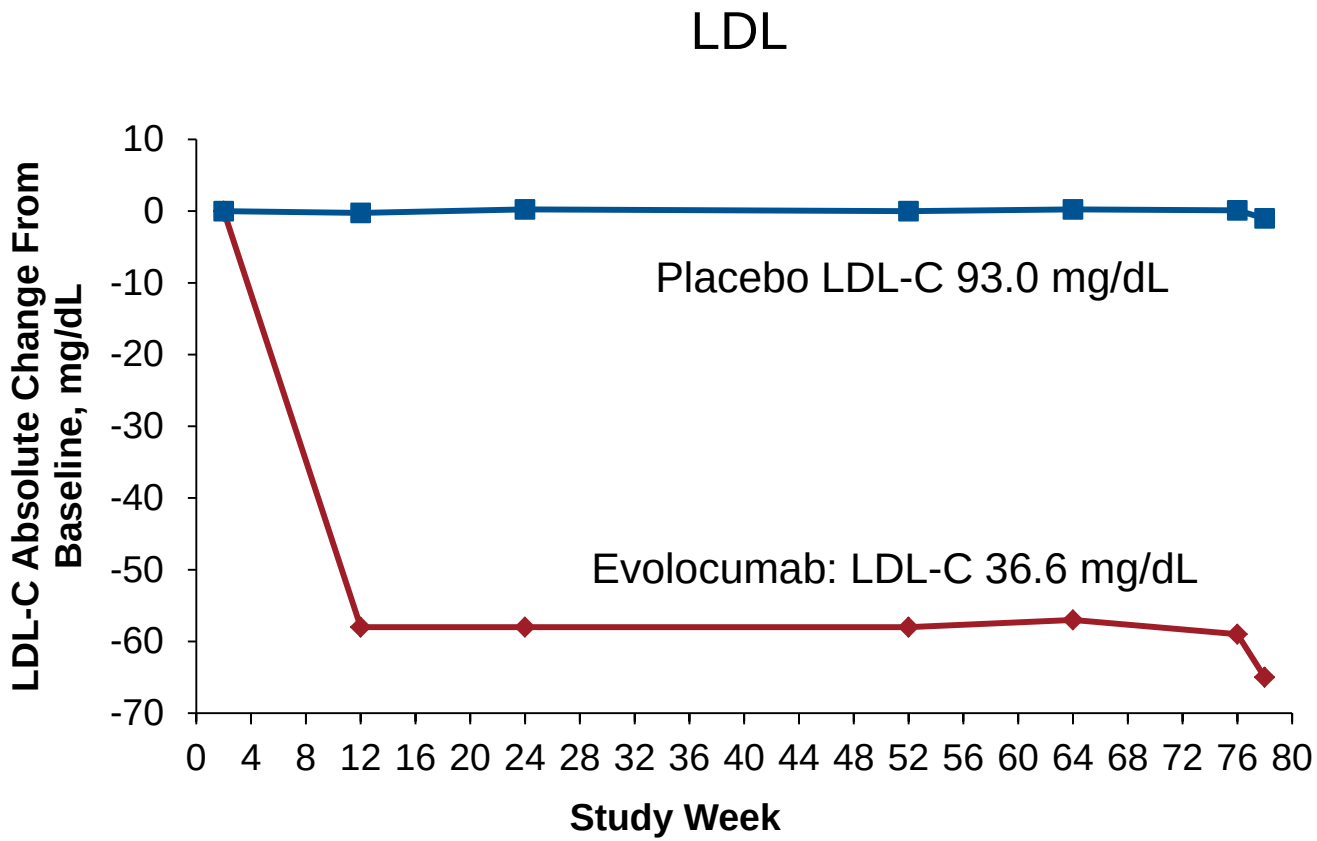
LDL-C Reduction via PCSK9 Inhibition



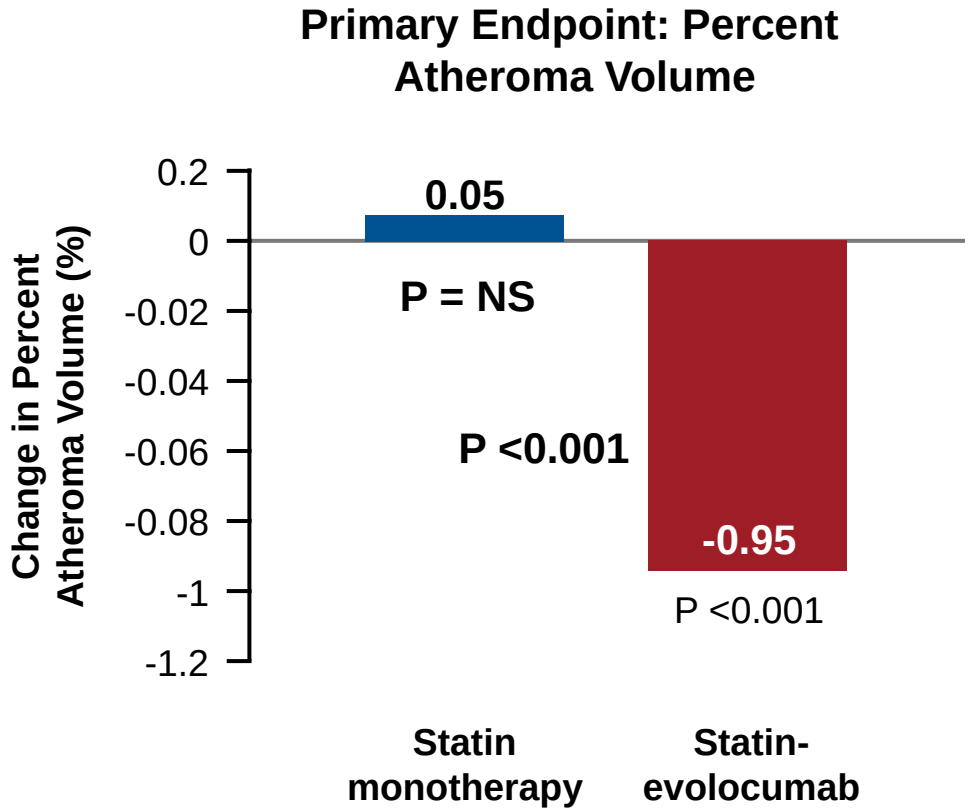
Shimada YJ, Cannon CP. *Eur Heart J.* 2015;36:2415–2424.

"Can PCSK9i regress coronary plaque?"

GLAGOV: IVUS Study of Evolocumab Added to Statins



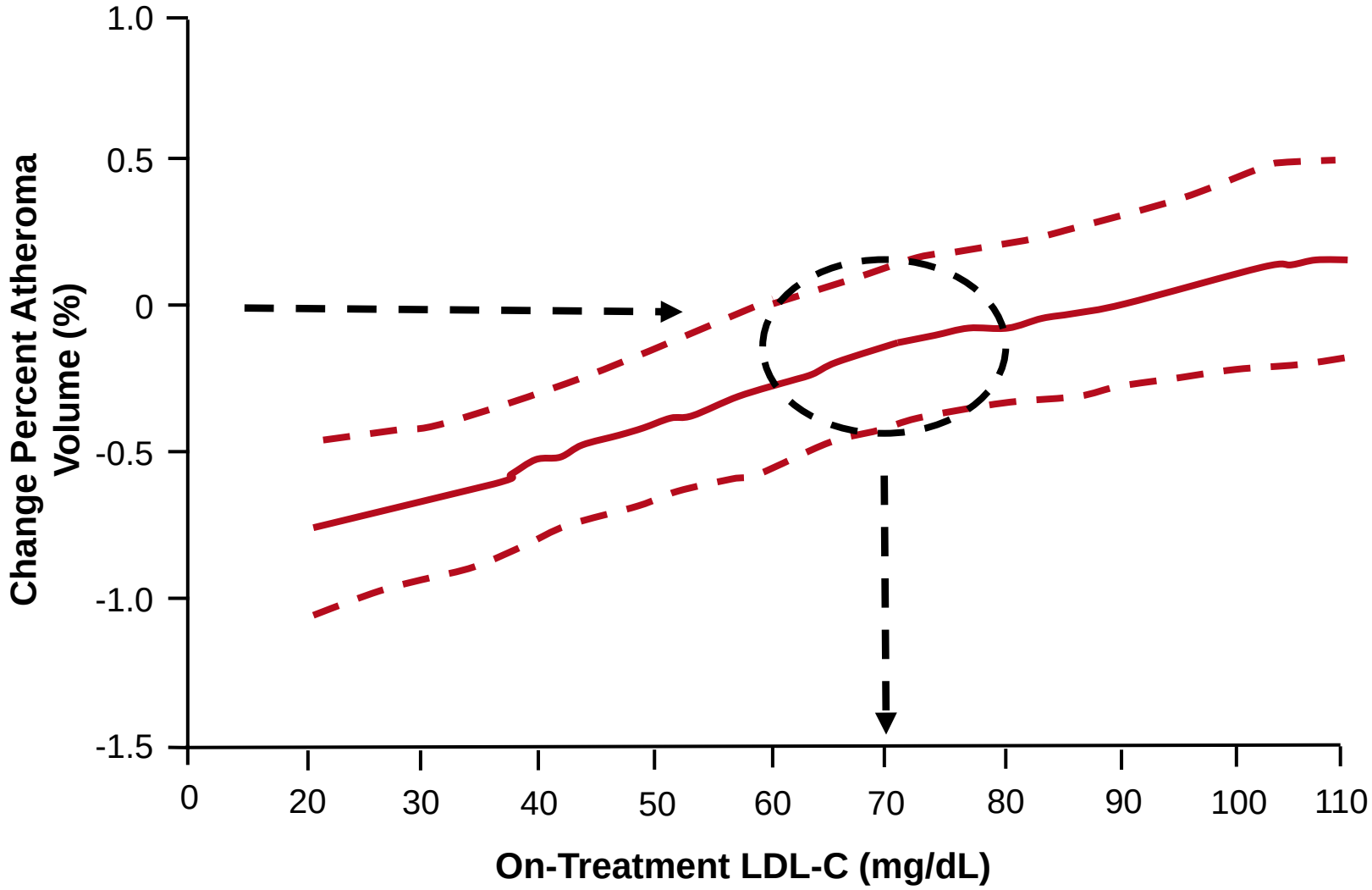
# of Patients								
Placebo	484	446	441		447	441	425	418
Allrocumab	484	456	452		444	449	449	434



Nicholls SJ, et al. *JAMA.* 2016;316(22):2373-2384.

“How low should should we get LDL-C?”

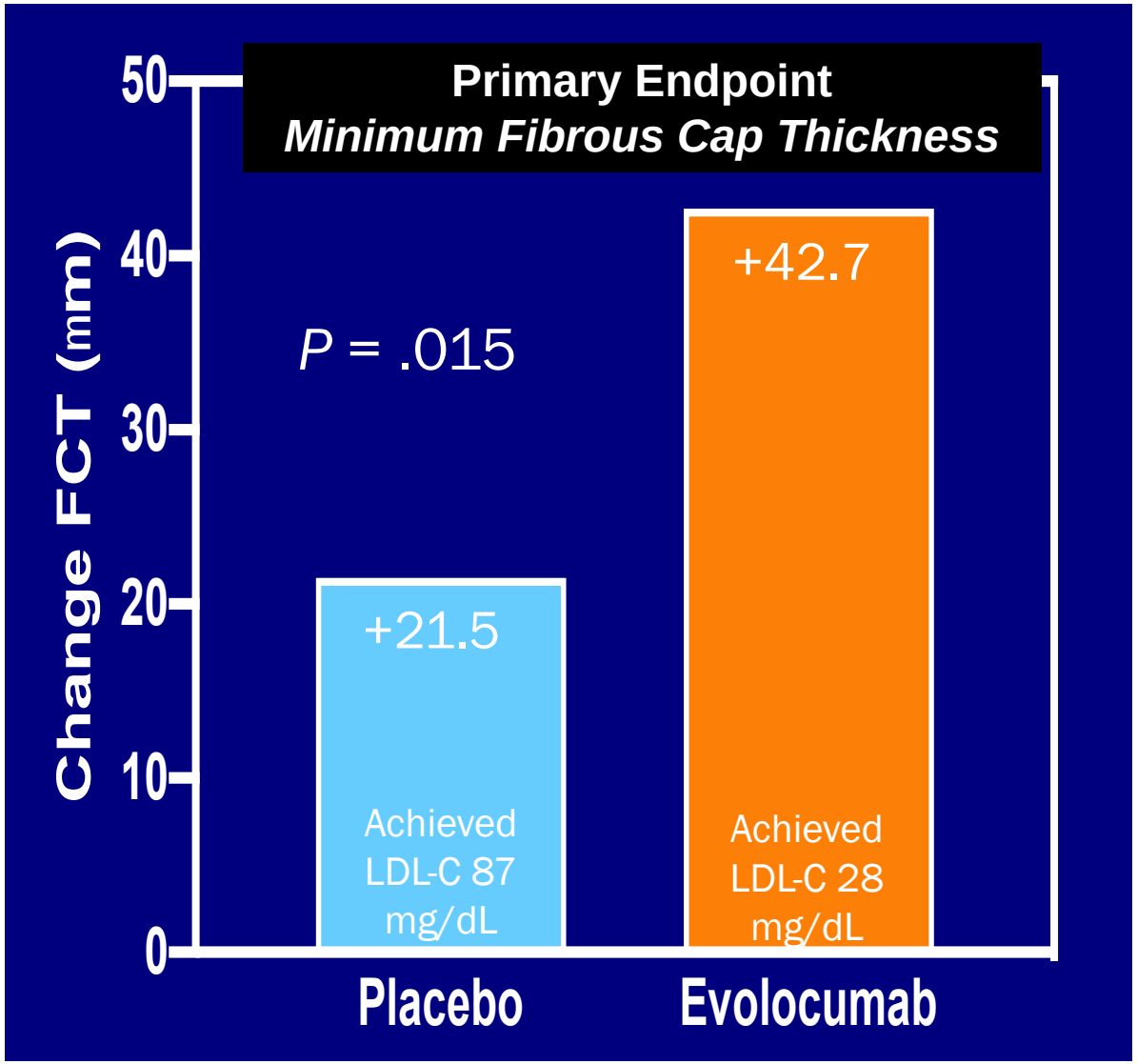
GLAGOV: IVUS Study of Evolocumab Added to Statins

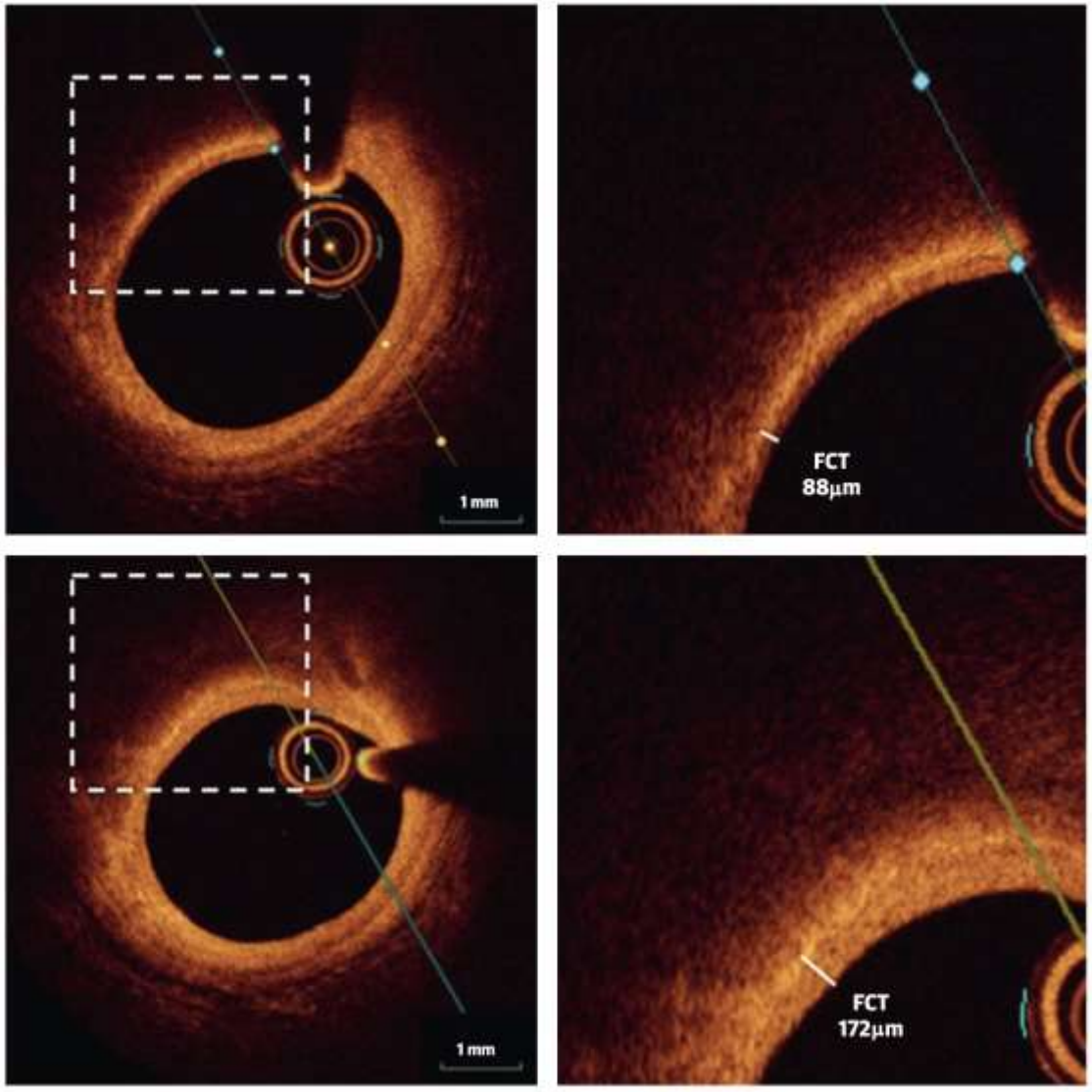


Nicholls SJ, et al. *JAMA.* 2016;316(22):2373-2384.

“Can we get plaques to be more stable?”

HUYGENS OCT Study of Evolocumab Added to Statins

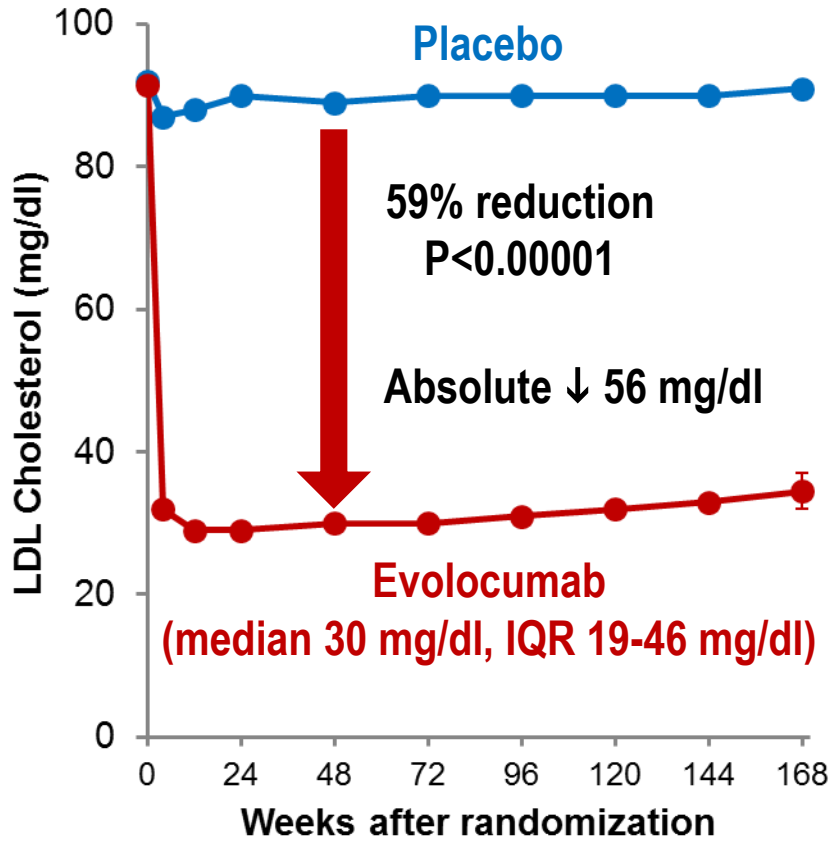


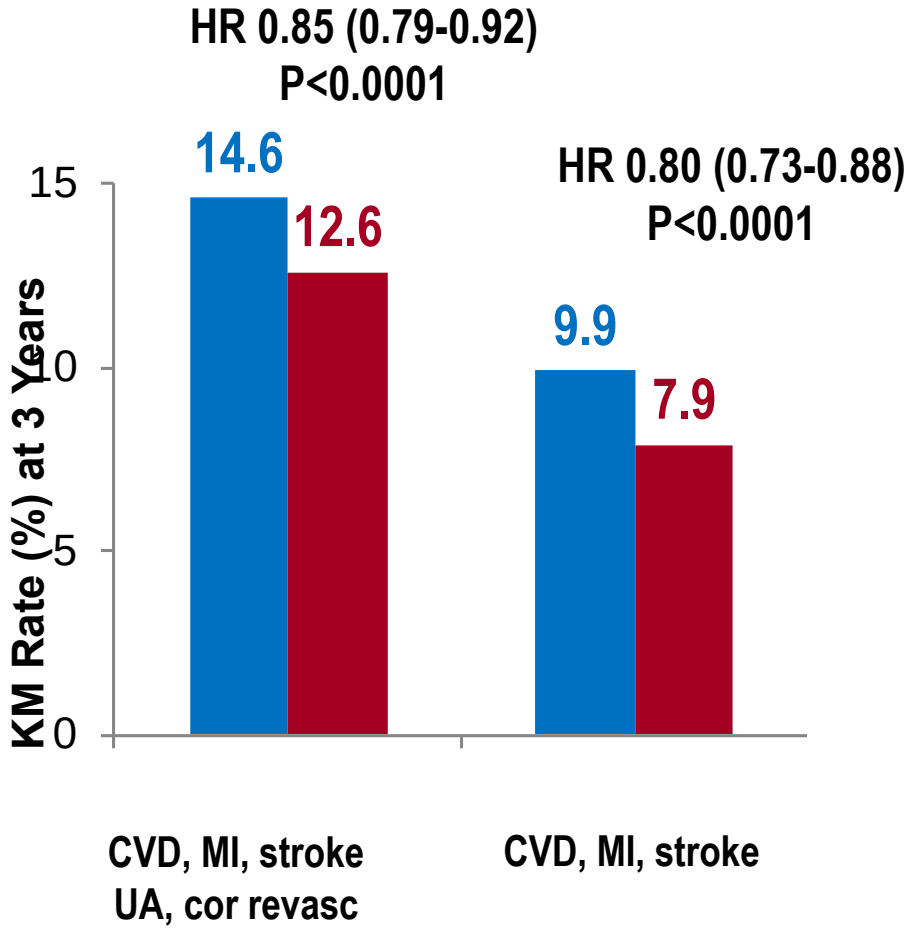


Nicholls, JACCi 2021

FOURIER: Effects of Evolocumab on Outcomes

27,564 high-risk, stable patients with established CV disease
Patients on baseline moderate to high intensity statin

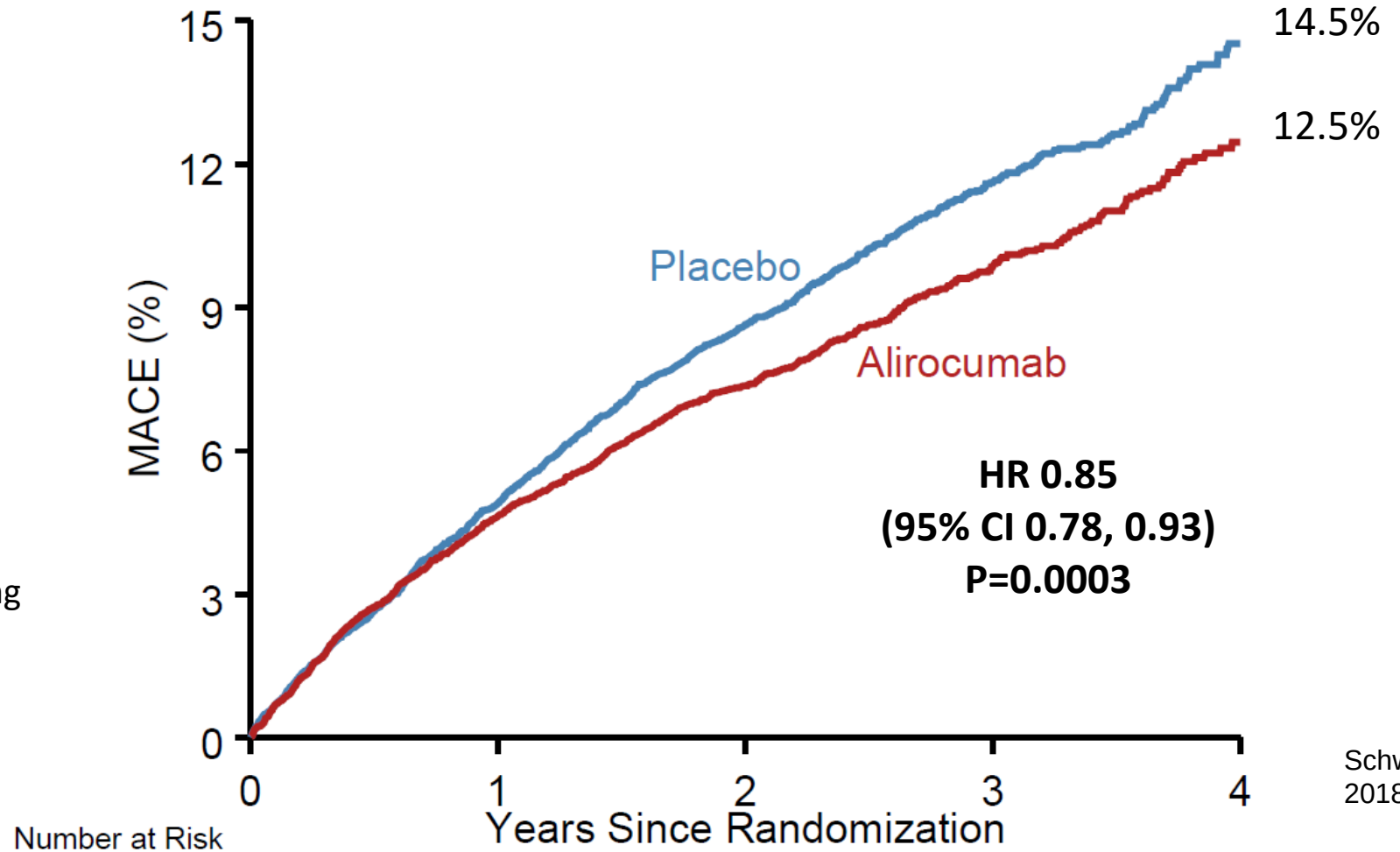




Sabatine MS et al. *NEJM.* 2017; 376: 1713-22.

ODYSSEY OUTCOMES: MACE primary endpoint

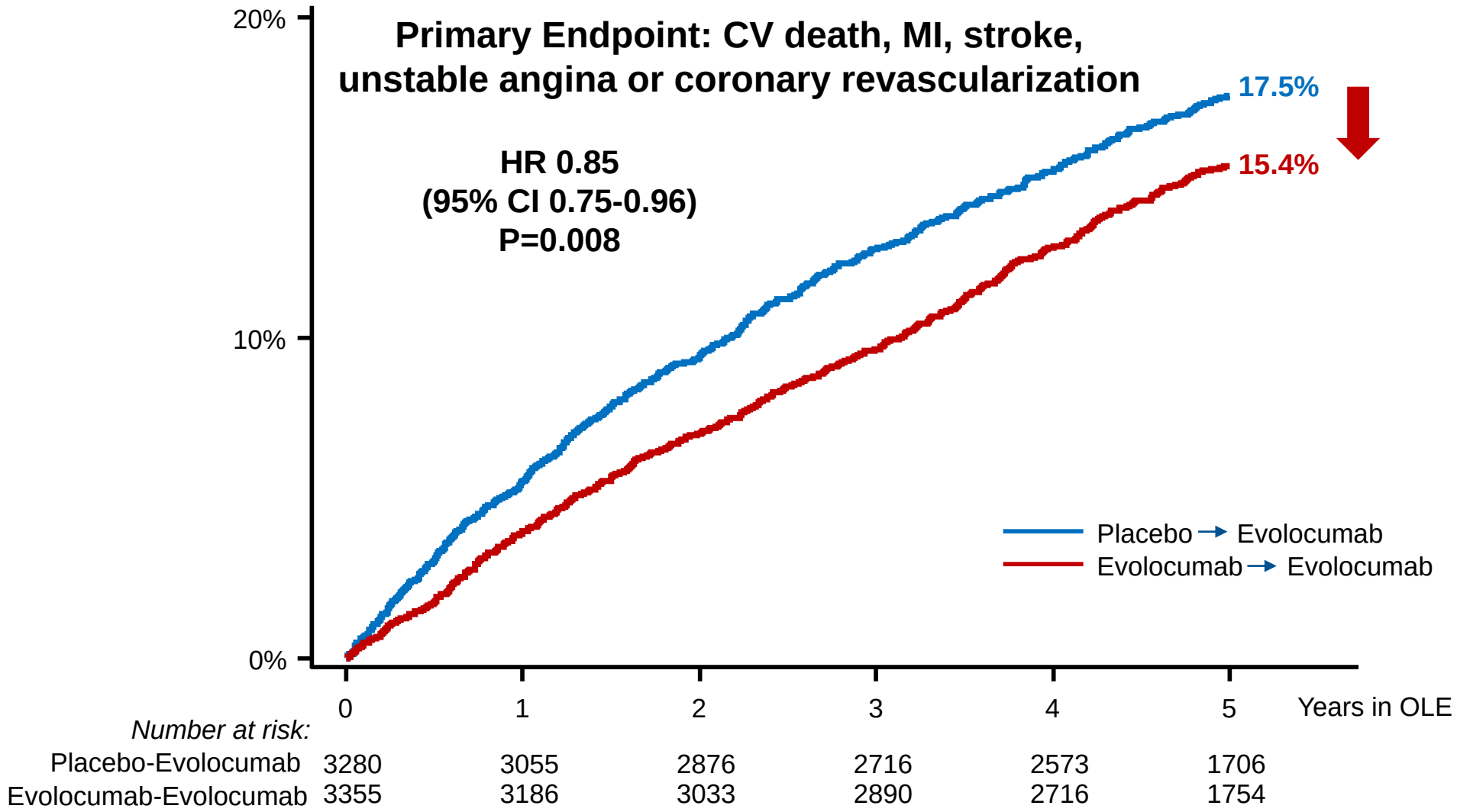
MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization



Schwartz GC et al. N Engl J Med 2018;379:2097-107.

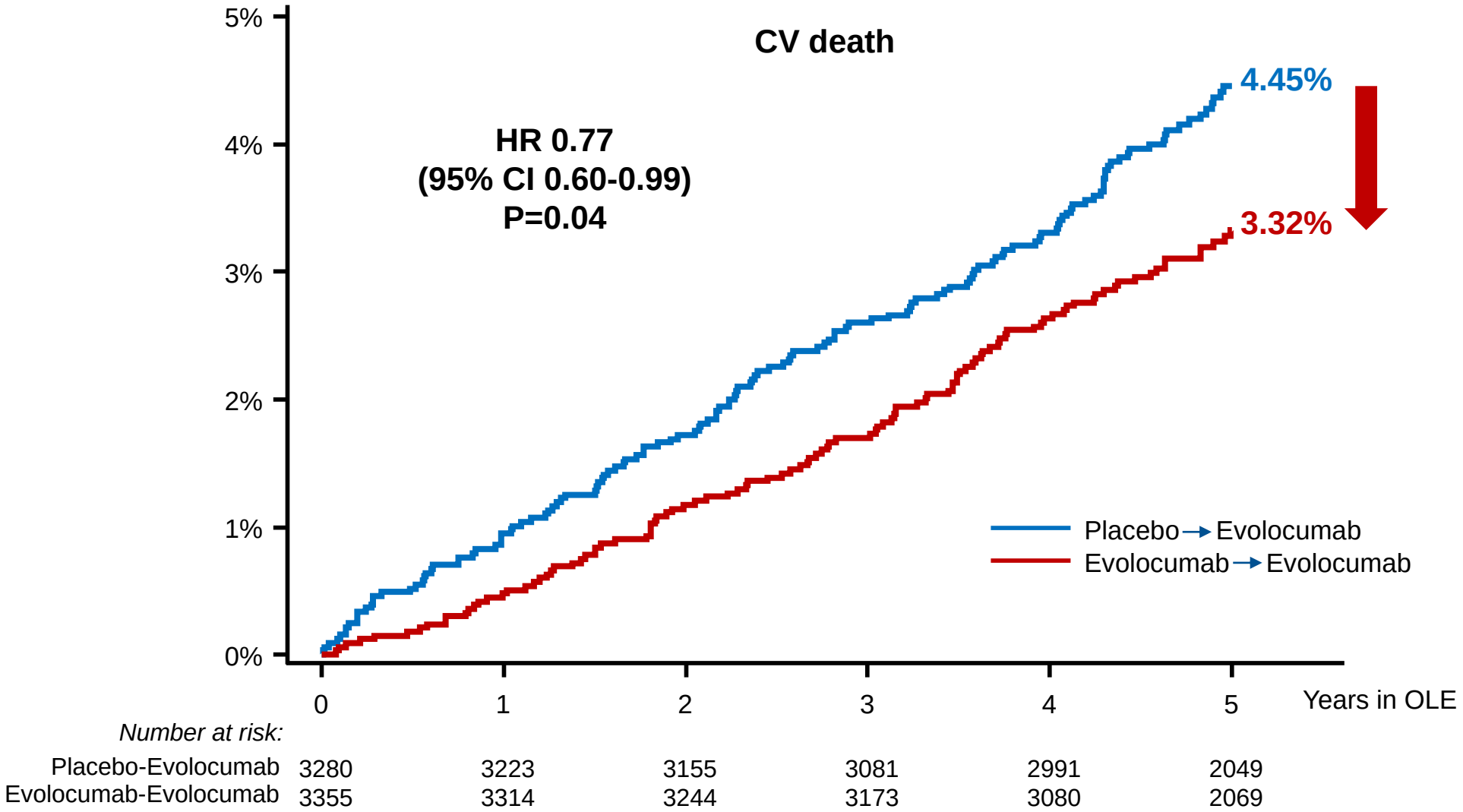
*Based on cumulative incidence

Efficacy during FOURIER-OLE



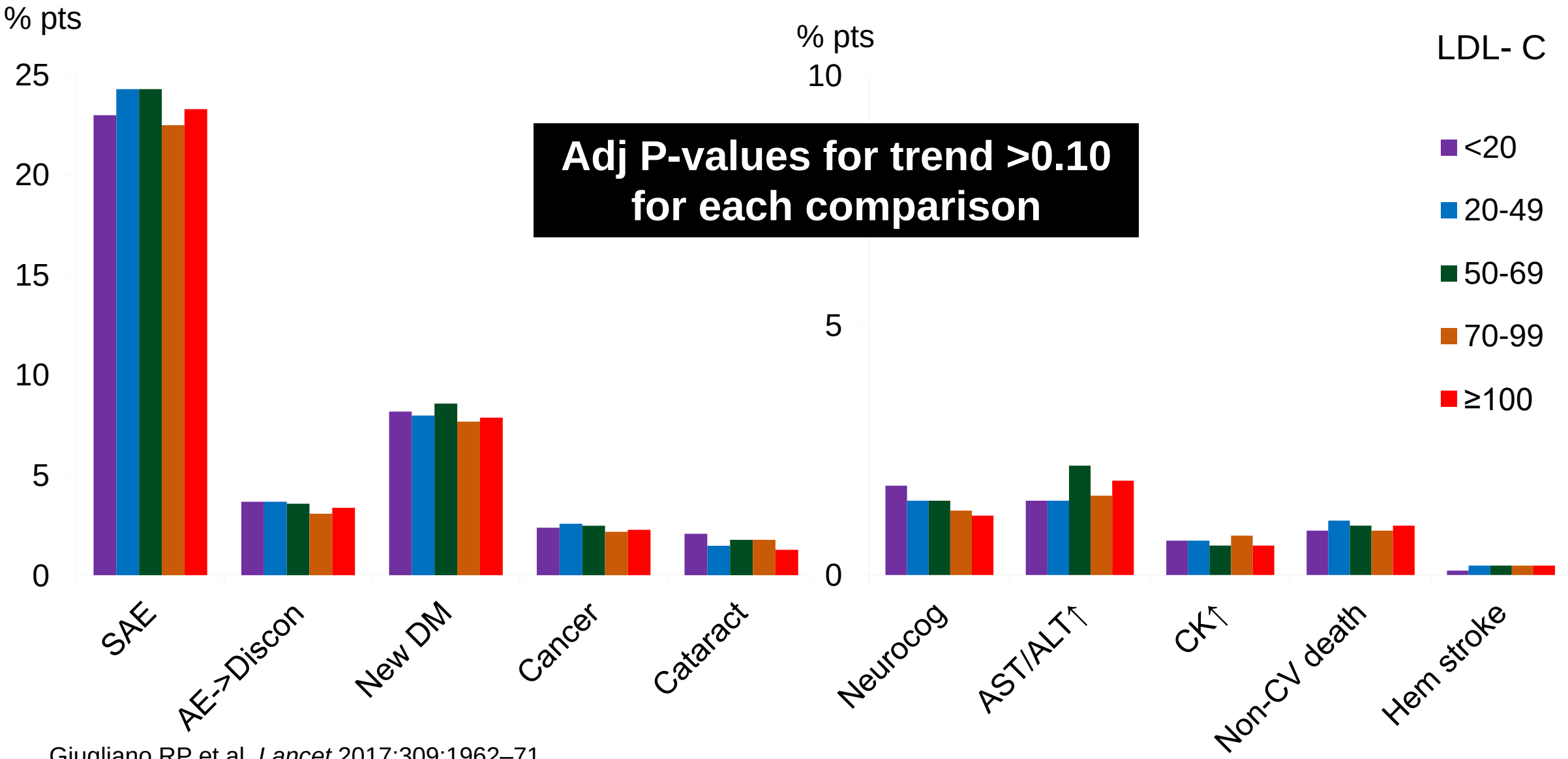
O'Donoghue, Circulation 2022 (ESC 2022)

Efficacy during FOURIER-OLE Time Period



O'Donoghue, Circulation 2022 (ESC 2022)

Safety Events by Achieved LDL-C



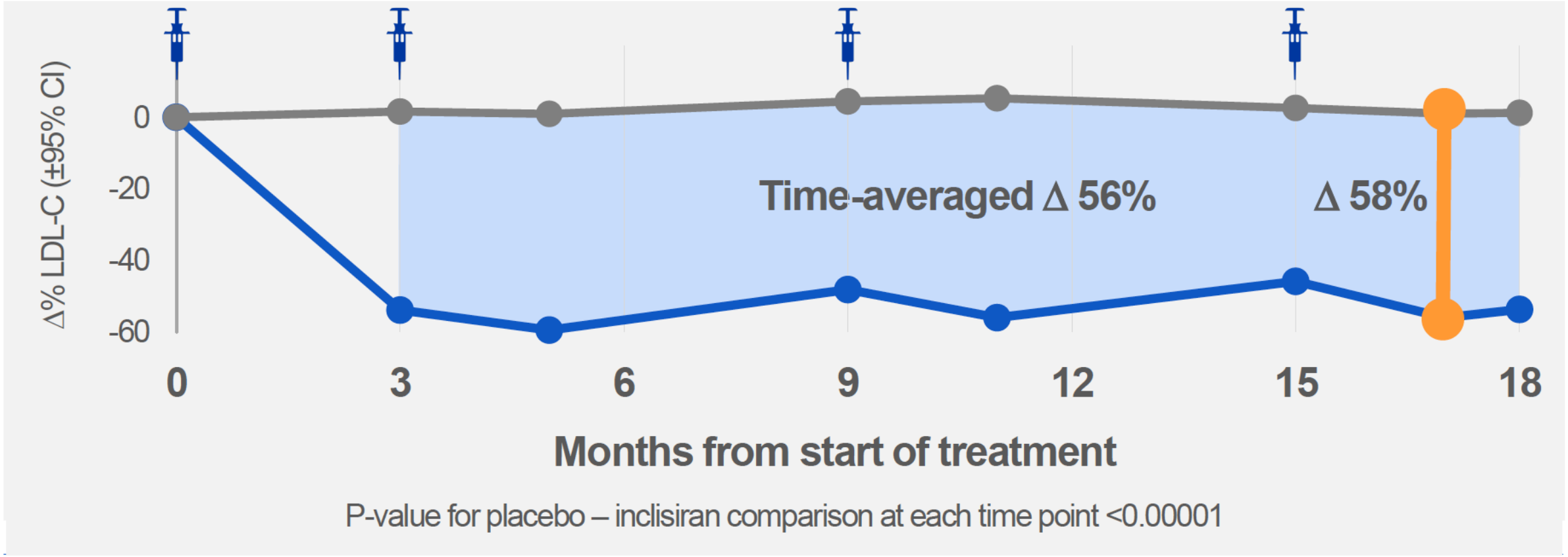
Giugliano RP et al, *Lancet* 2017;309:1962–71

ORION-10: Efficacy

Incliseran vs. placebo

Durable and potent with consistent effect over 18 months

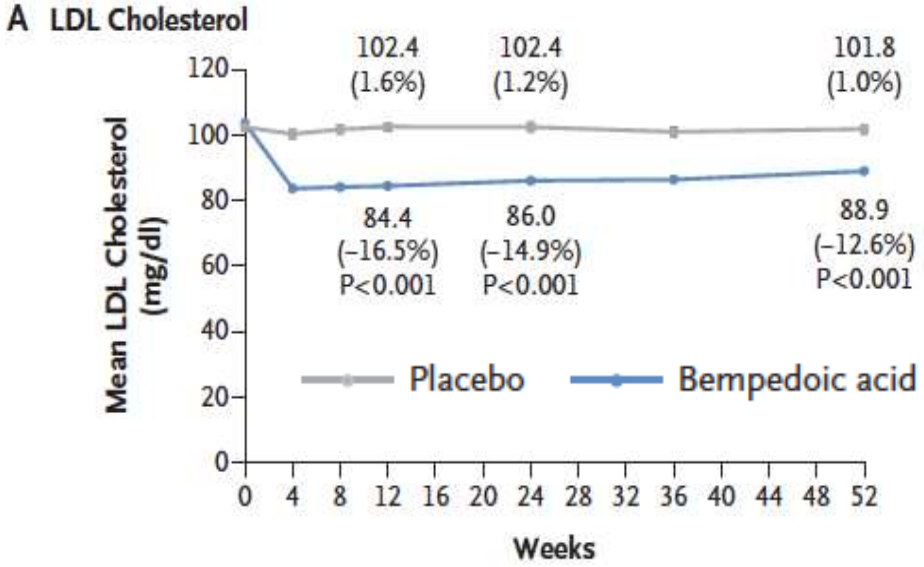
Percent change in LDL-C over time – observed values in ITT patients

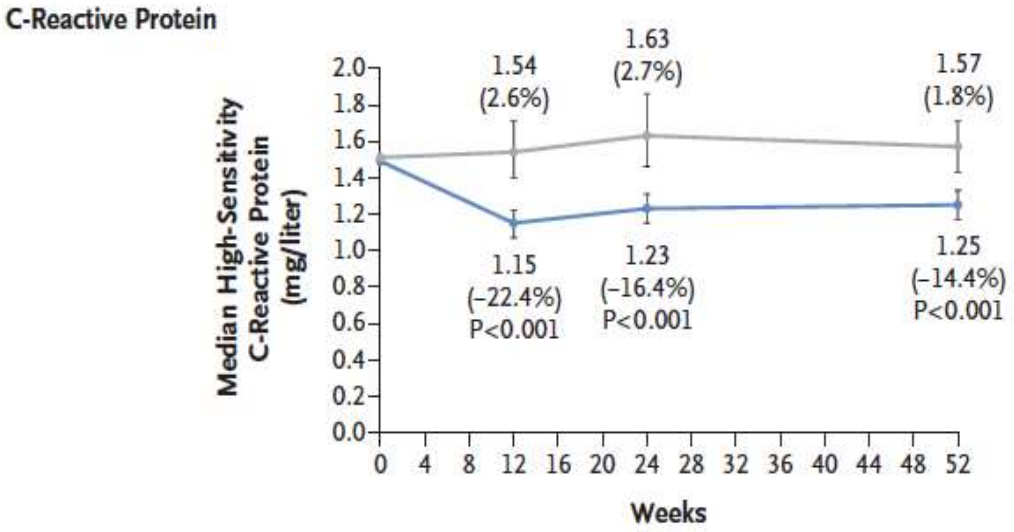


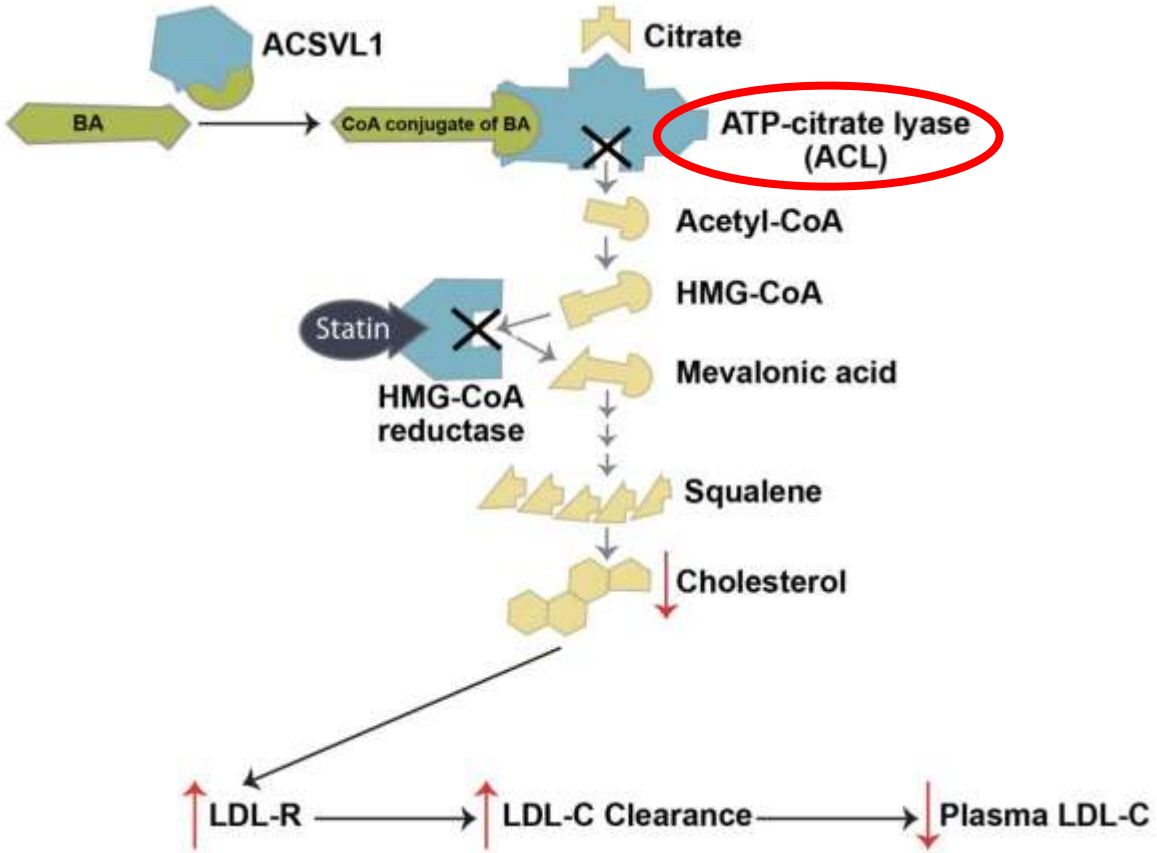
1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

Ray KK et al. N Engl J Med 2020; 382:1507-1519

Use of Bempedoic Acid to Lower LDL-C (Efficacy ~ 16%)







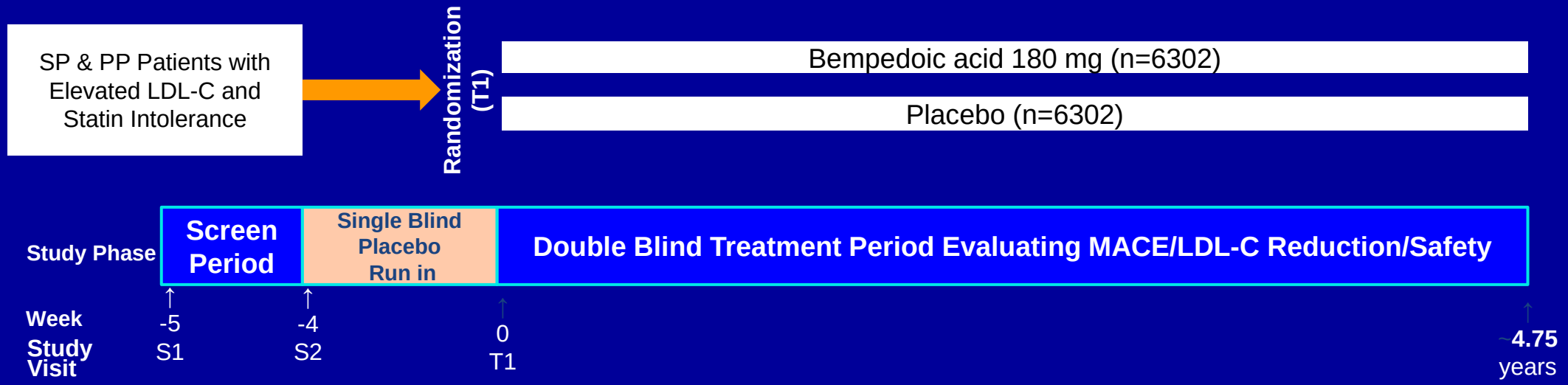
Ray KK, et al. N Engl J Med 2019;380:1022-32.

The NEW ENGLAND JOURNAL of MEDICINE

CLEAR Outcomes: Study Design

LBCT for ACC 2023

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFECTS OF BEMPEDOIC ACID (ETC-1002) ON THE OCCURRENCE OF MAJOR CARDIOVASCULAR EVENTS IN PATIENTS WITH, OR AT HIGH RISK FOR, CARDIOVASCULAR DISEASE WHO ARE STATIN INTOLERANT

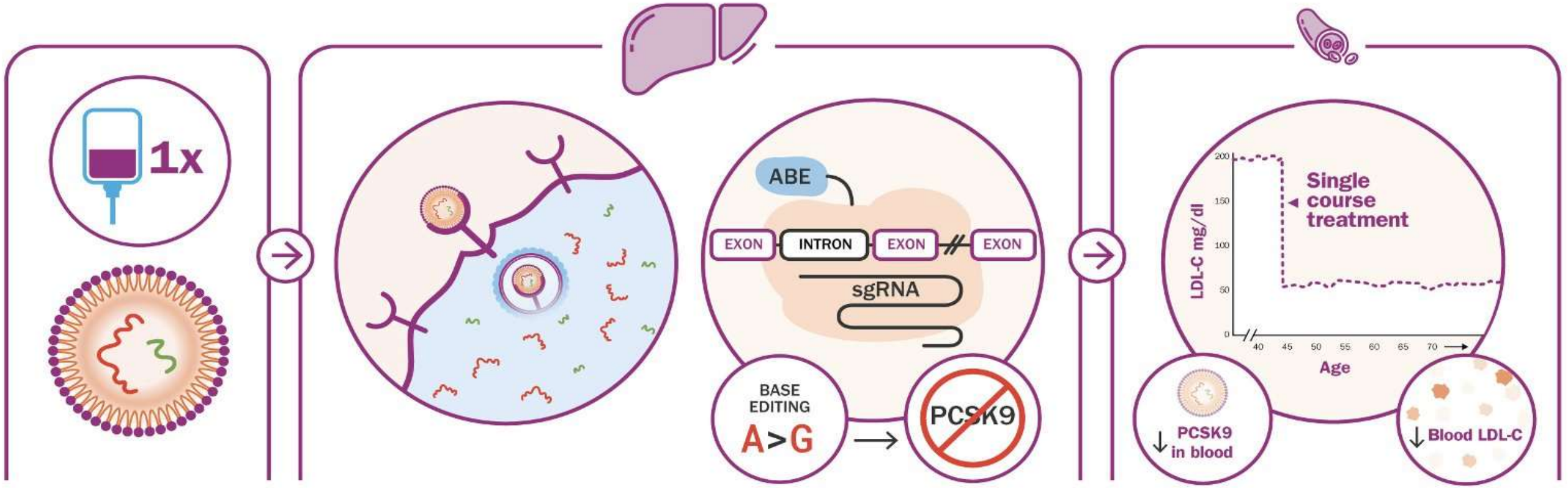


- After T1 Visits at months 1, 3 and 6 alternating phone visits and clinic visits every 3 months thereafter

http://clinicaltrials.gov/ct2/show/NCT02993406

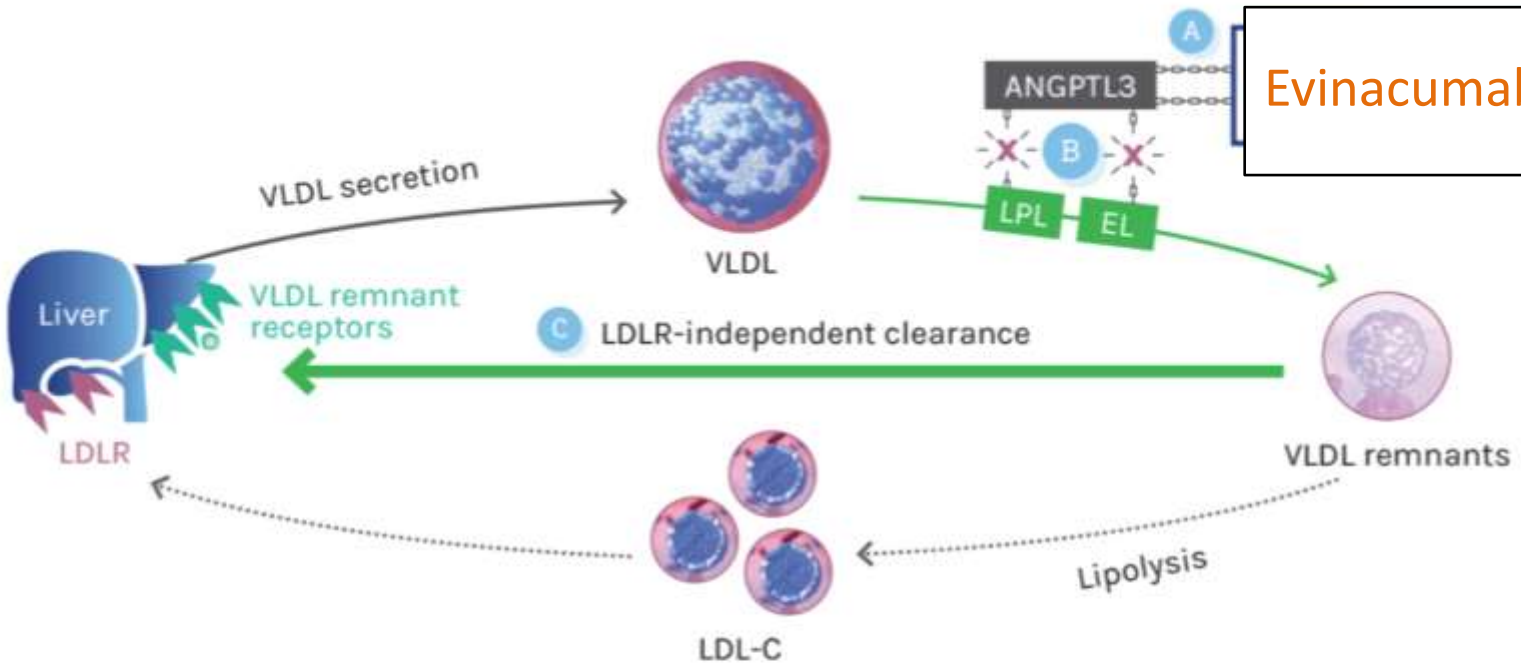
Can a “one and done” injection be the future?

Single course gene editing medicines to treat CVD



mRNA gRNA

Evanicumab: ANGPTL3 inhibitor that lowers LDL-C and other lipoproteins independently of LDLR activity[1,2]



A Evinacumab binds to blocks ANGPTL3.

B By blocking ANGPTL3, EVKEEZA allows LPL and EL to enhance the clearance of VLDL remnants via remnant receptors in the liver.

C By enhancing VLDL remnant clearance, EVKEEZA reduces LDL-C levels in an LDLR-independent manner.

Summary: Beyond statins….several effective options for lowering LDL-C

- Diet: impact can be sizeable (but also highly variable) – to lower LDL-C, decrease saturated fat / cholesterol ; plant based diet
- PCSK9i: ~ 60% LDL reduction, small reduction in plaque size, reduction in CV events
- Ezitimibe: ~20% LDL reduction, good option as add-on to statin when need additional LDL reduction (Tip: drug of choice is sitosterolemia)
- Bempedoic acid: ~16% LDL reduction (outcomes data ACC 2023)
- Good safety profile: PCSK9i → injection related ; rare allergic reactions / Ezitimibe → ? GI / Bempedoic acid → gout / tendon rupture (0.5%)

Thank You