# Δυσλιπιδαιμίες

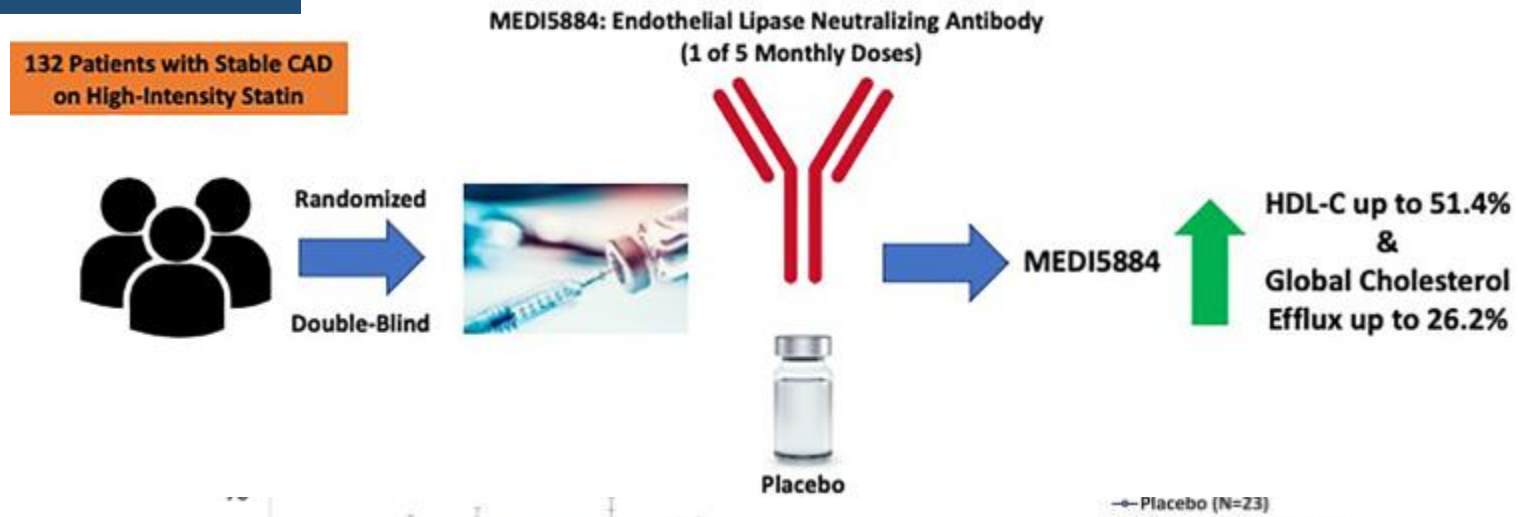
## ΘΕΡΑΠΕΥΤΙΚΕΣ ΕΞΕΛΙΞΕΙΣ 2022

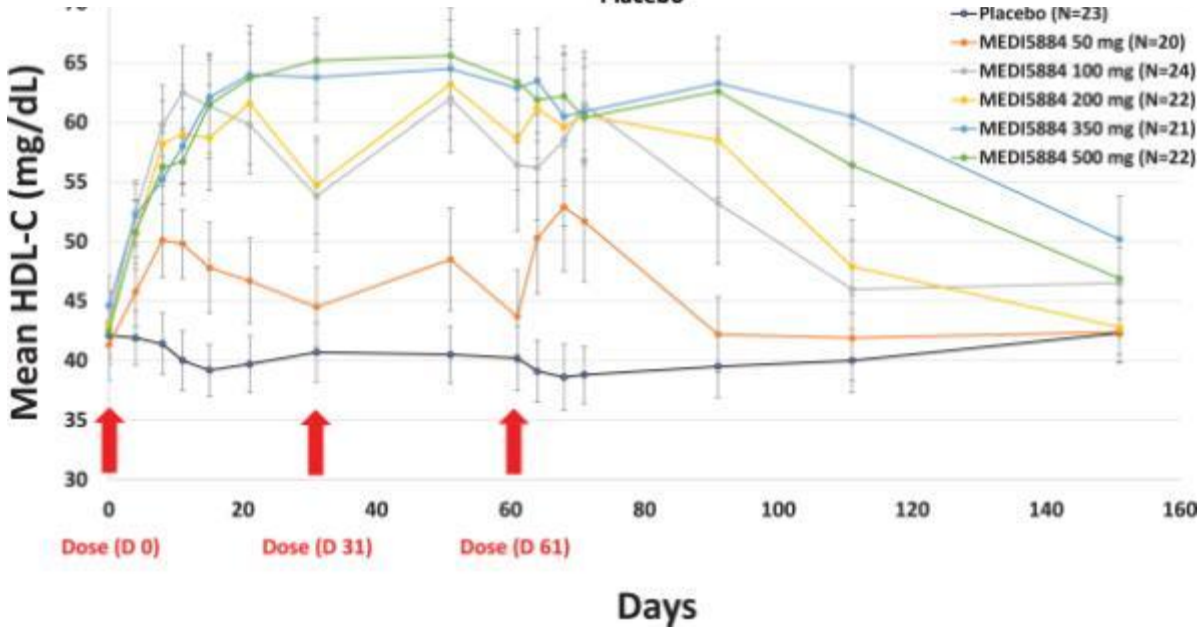
Κίμων Σταματελόπουλος

# Νεότερα δεδομένα στην αντιμετώπιση της υπερχοληστεριναιμίας

# Inhibition of Endothelial Lipase by MEDI5884 increases the quantity and improves quality of functional HDL

Monoclonal antibody
target: endothelial lipase (EL)



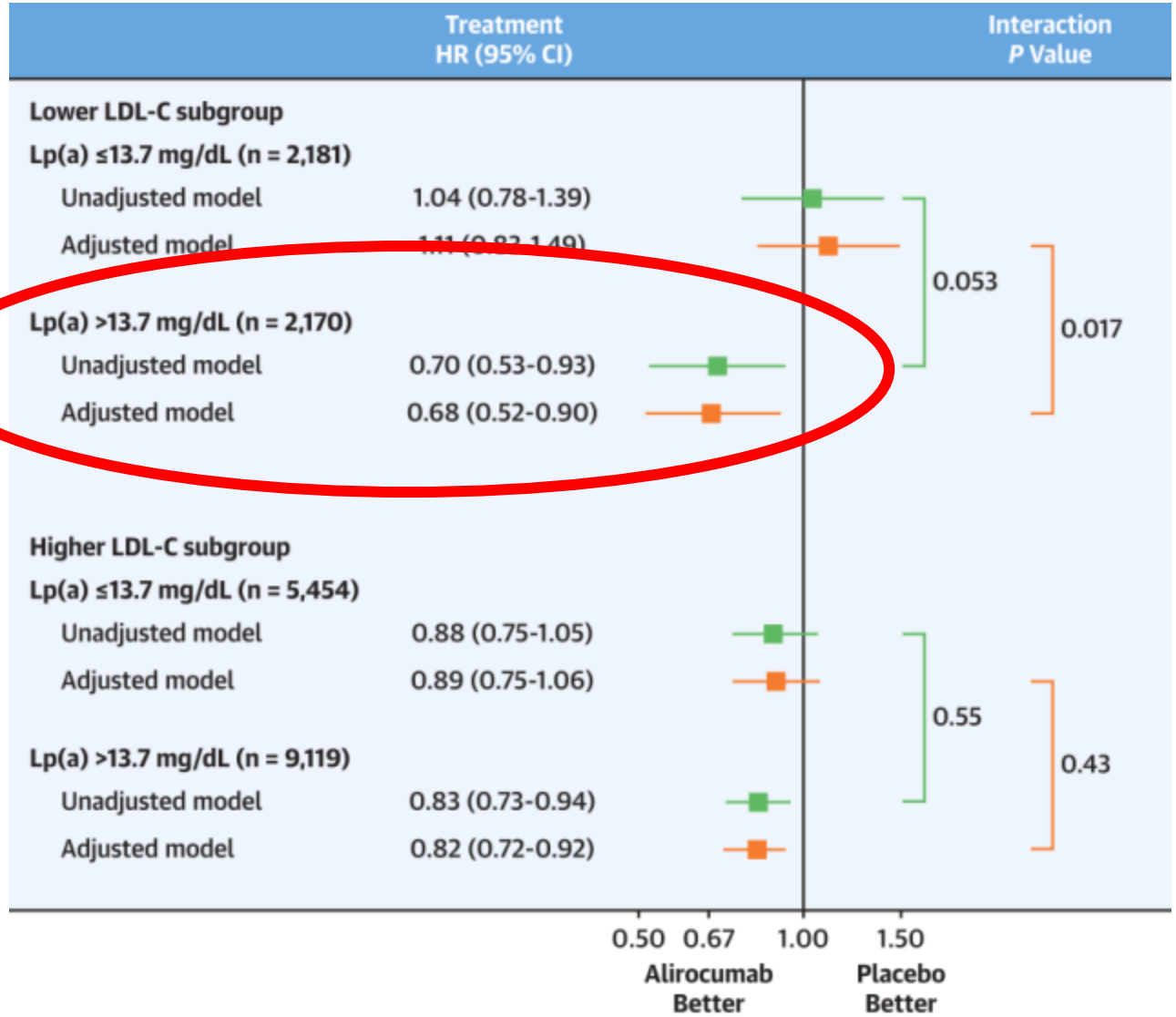




Ruff et al. Arterioscler Thromb Vasc 2021

# At LDL<70 mg/dl, alirocumab reduces MACE on top of statins only in patients with at least mildly elevated Lp(a)

**Monoclonal antibody target: PCSK9**

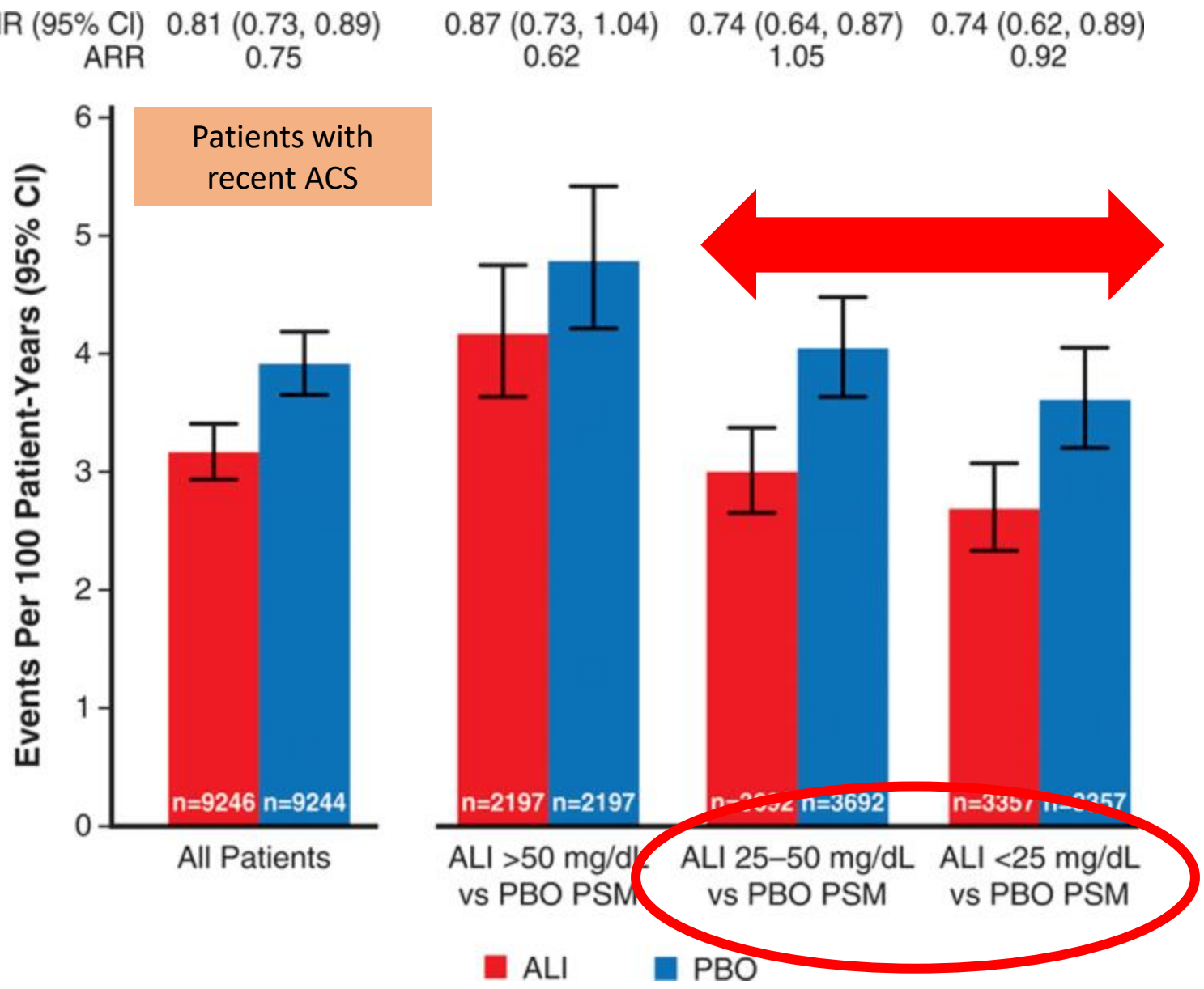
Patients with recent ACS on optimized statin therapy and LDL-C <70 mg/dl




Schwartz et al. J Am Coll Cardiol 2021

# No additional beneficial effect of Alirocumab achieved at **LDL-C <25mg/dl** compared to to LDL-C 25-50 mg/dl

Monoclonal antibody target: PCSK9



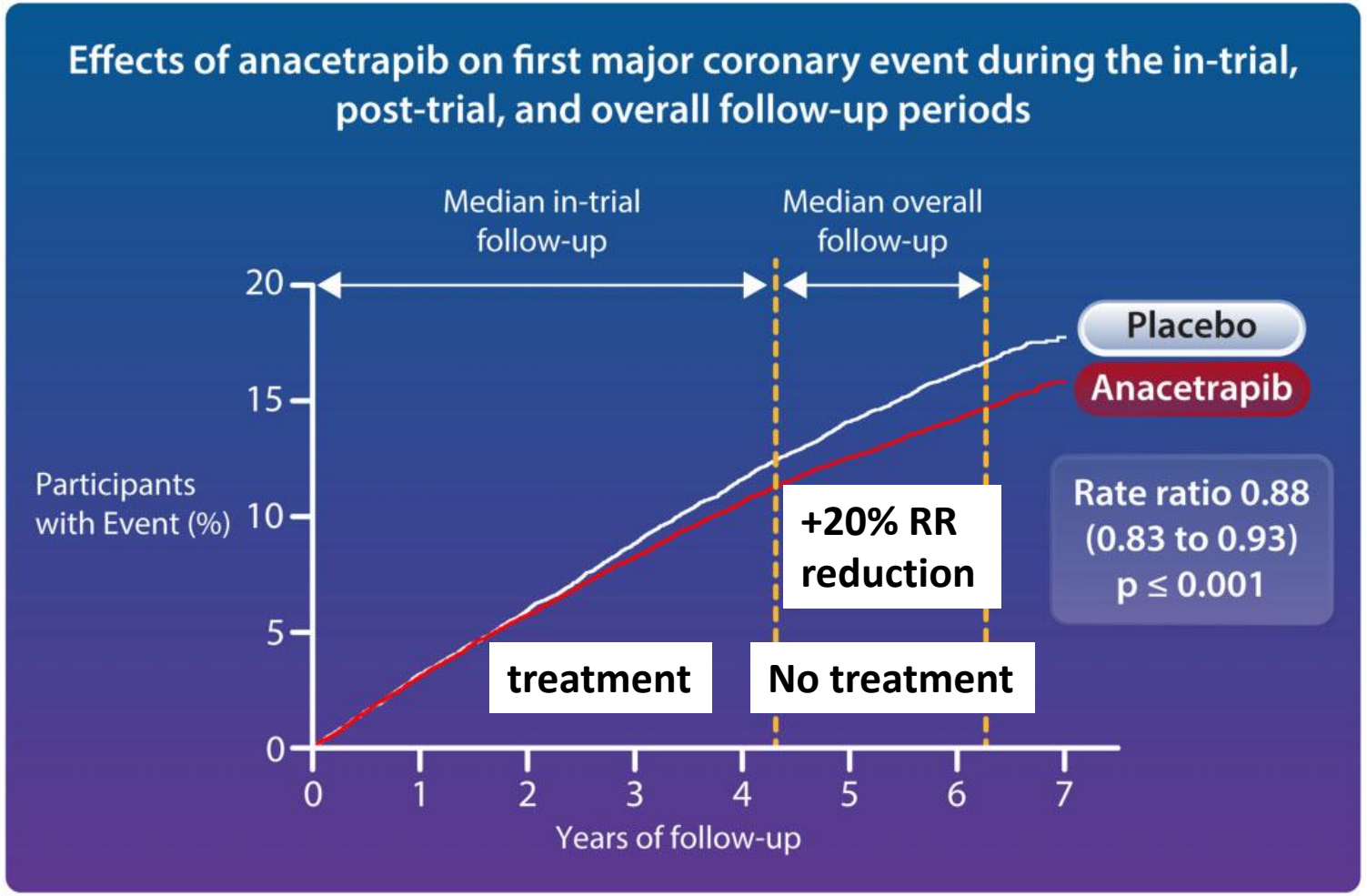

ALI = Alirocumab
PBO = Placebo

Schwartz et al. Circulation 2021

# Anacetrapib confers extended reduction in major coronary events in patients with established ASCVD

Cholesteryl ester transfer protein (CETP) inhibitor

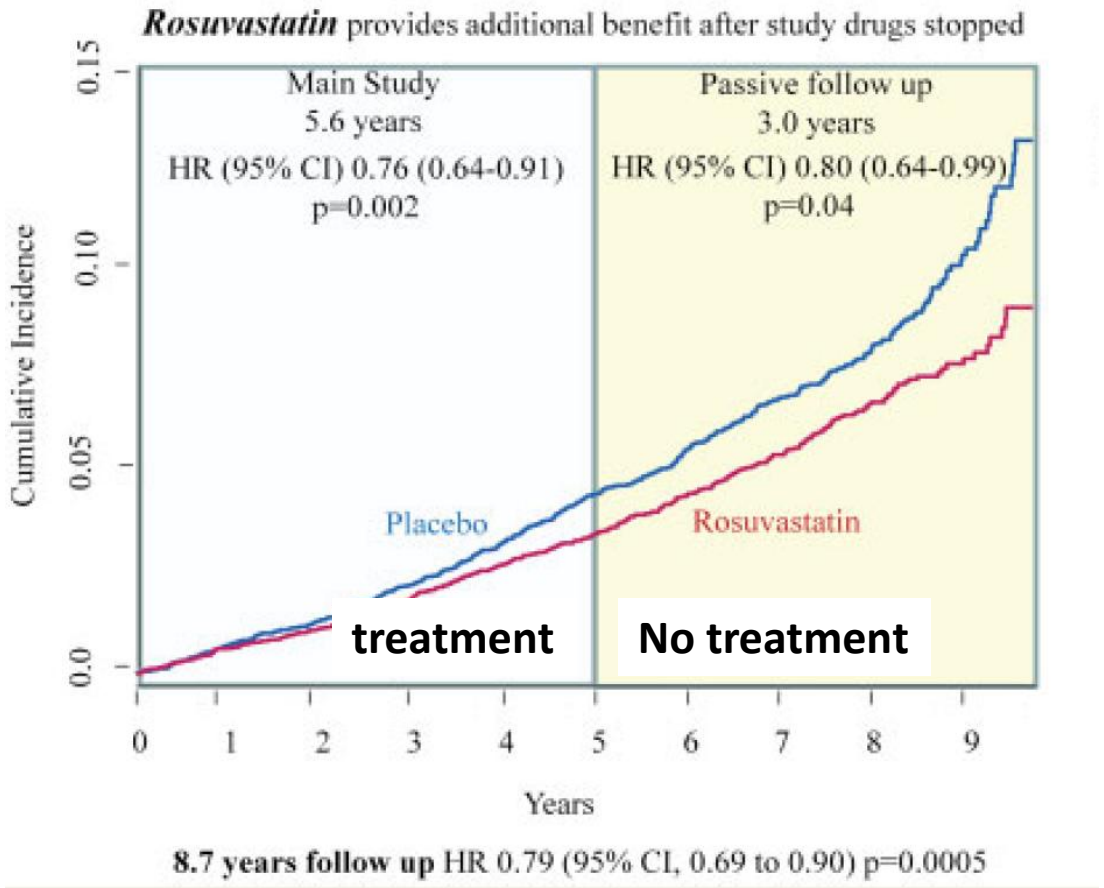
26,129 patients of REVEAL study after cessation of randomly allocated treatment




Sammons et al. Eur Heart J 2021

# Rosuvastatin reduce MACE for at least 3 years after cessation of treatment in patients at moderate CV risk

(HOPE)-3 study: 9,326 patients without established CVD, with at least one CVD factor




**CVD factors for inclusion:** elevated waist-to-hip ratio, current smoking, impaired fasting glucose, impaired glucose tolerance or diabetes requiring only diet control, estimated GFR 45-60 mL/min/1.73 m2 and family history of premature heart disease in first degree relatives.

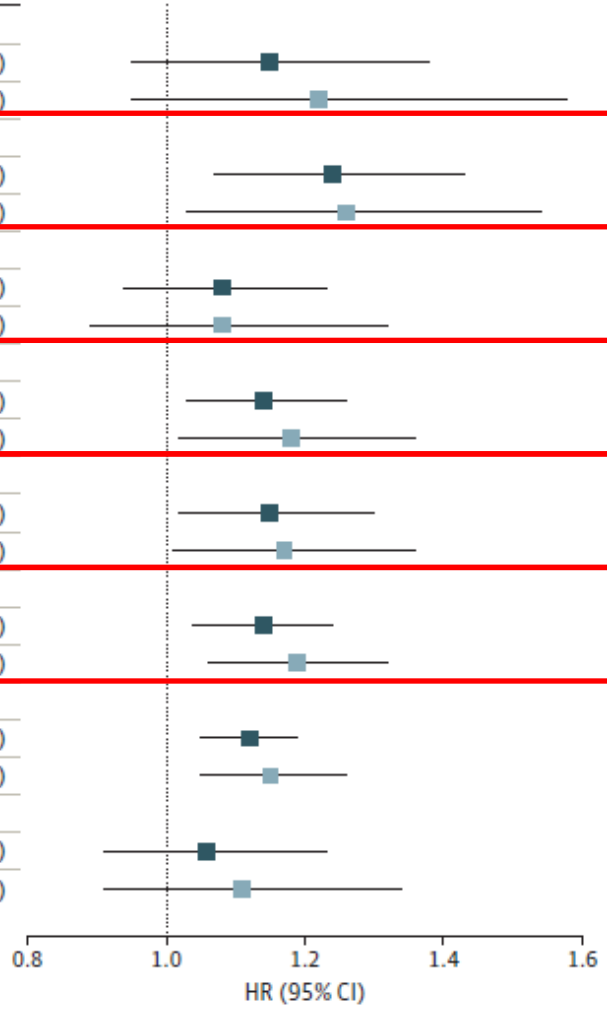
**+17- 20% RR reduction**

Bosch et al. Eur Heart J 2021

# Discontinuation of statins increases CV outcomes in elderly patients with polypharmacy

| Outcome | Events, No. (discontinuing cohort/maintaining cohort) | RR (95% CI) | *P* value |
|---|---|---|---|
| Cerebrovascular disease | 235/208 | | |
| Main analysis | | 1.15 (0.95-1.38) | .15 |
| Time-varying exposure and IPCW approach | | 1.22 (0.95-1.58) | .12 |
| Heart failure | 408/337 | | |
| Main analysis | | 1.24 (1.07-1.43) | .004 |
| Time-varying exposure and IPCW approach | | 1.26 (1.03-1.54) | .03 |
| Ischemic heart disease | 439/413 | | |
| Main analysis | | 1.08 (0.94-1.23) | .28 |
| Time-varying exposure and IPCW approach | | 1.08 (0.89-1.32) | .44 |
| Composite CV outcome | 786/711 | | |
| Main analysis | | 1.14 (1.03-1.26) | .01 |
| Time-varying exposure and IPCW approach | | 1.18 (1.02-1.36) | .03 |
| Death for any cause | 528/463 | | |
| Main analysis | | 1.15 (1.02-1.30) | .02 |
| Time-varying exposure and IPCW approach | | 1.17 (1.01-1.36) | .04 |
| Composite CV outcome and deaths | 1076/974 | | |
| Main analysis | | 1.14 (1.04-1.24) | .005 |
| Time-varying exposure and IPCW approach | | 1.19 (1.06-1.32) | .003 |
| ED, any cause | 2209/2055 | | |
| Main analysis | | 1.12 (1.05-1.19) | .001 |
| Time-varying exposure and IPCW approach | | 1.15 (1.05-1.26) | .003 |
| ED, neurologic disorders | 346/330 | | |
| Main analysis | | 1.06 (0.91-1.23) | .45 |
| Time-varying exposure and IPCW approach | | 1.11 (0.91-1.34) | .30 |

ED: emergency department




5 years follow-up

29,047 patients >65 years who were receiving uninterrupted treatment with statins, blood pressure–lowering, antidiabetic, and antiplatelet agents

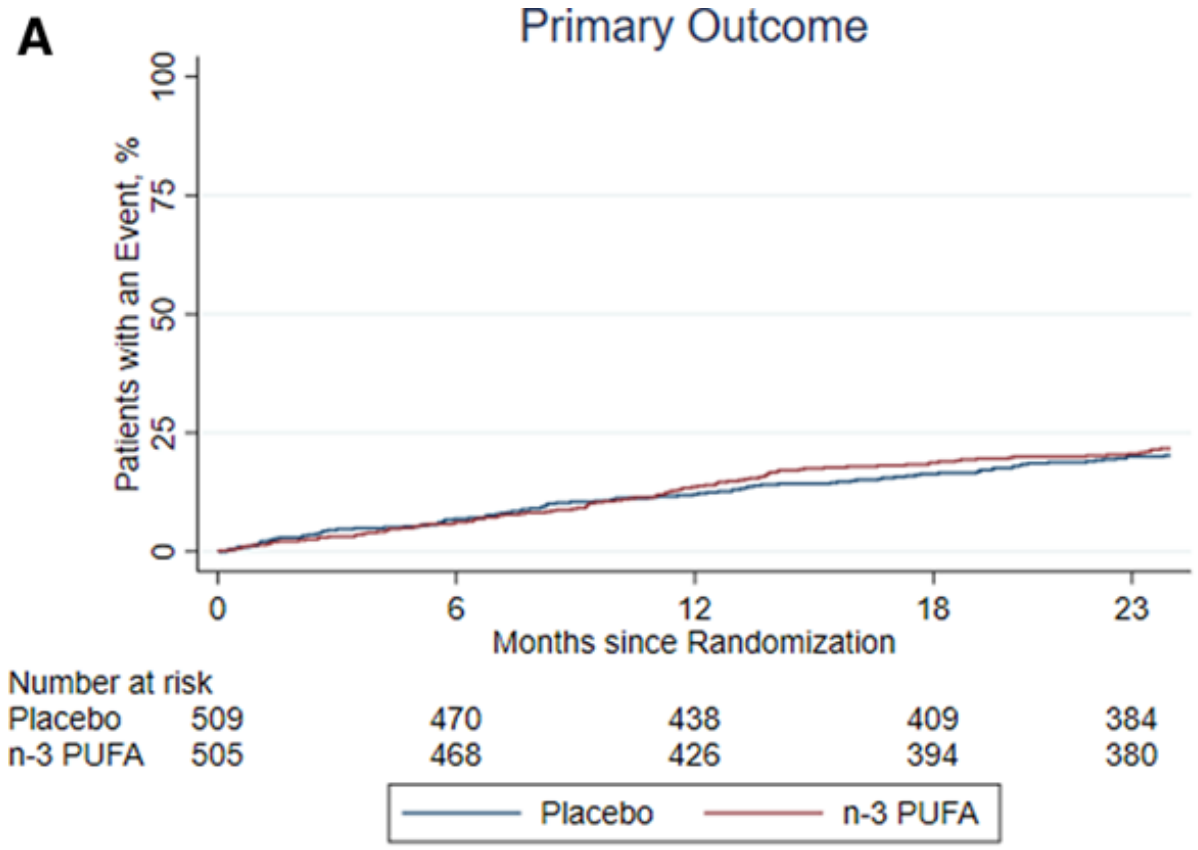
**Composite CV outcome:** hospital admission for CV causes (cerebrovascular disease, heart failure, or ischemic heart disease)

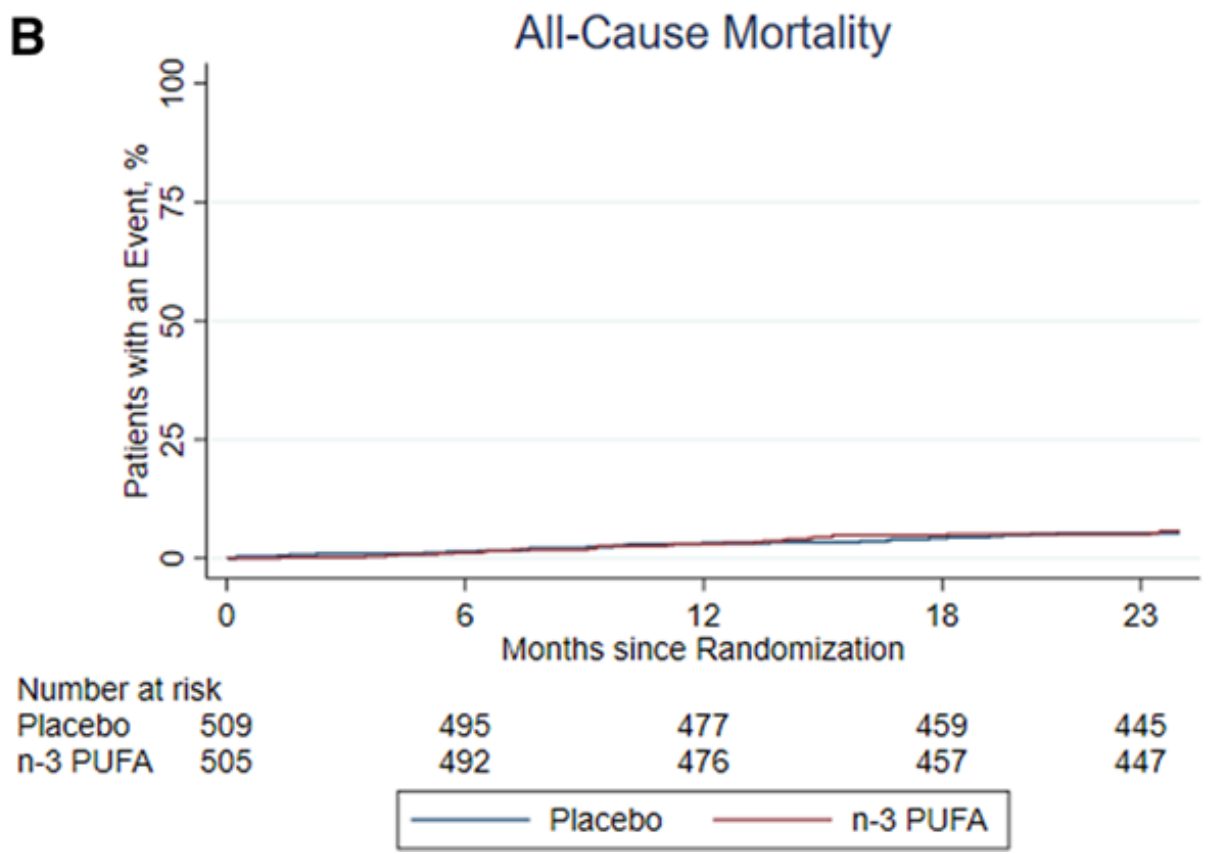
Rea et al. JAMA Network Open 2021

# Νεότερα δεδομένα στην αντιμετώπιση της υπερτριγλυκεριδαιμίας

# N-3 PUFAs (EPA&DHA) do not reduce adverse events in elderly patients with recent AMI

age range 70 to 82 years




1.8 g n-3 PUFA (930 mg eicosapentaenoic acid and 660 mg docosohexaenoic acid) daily

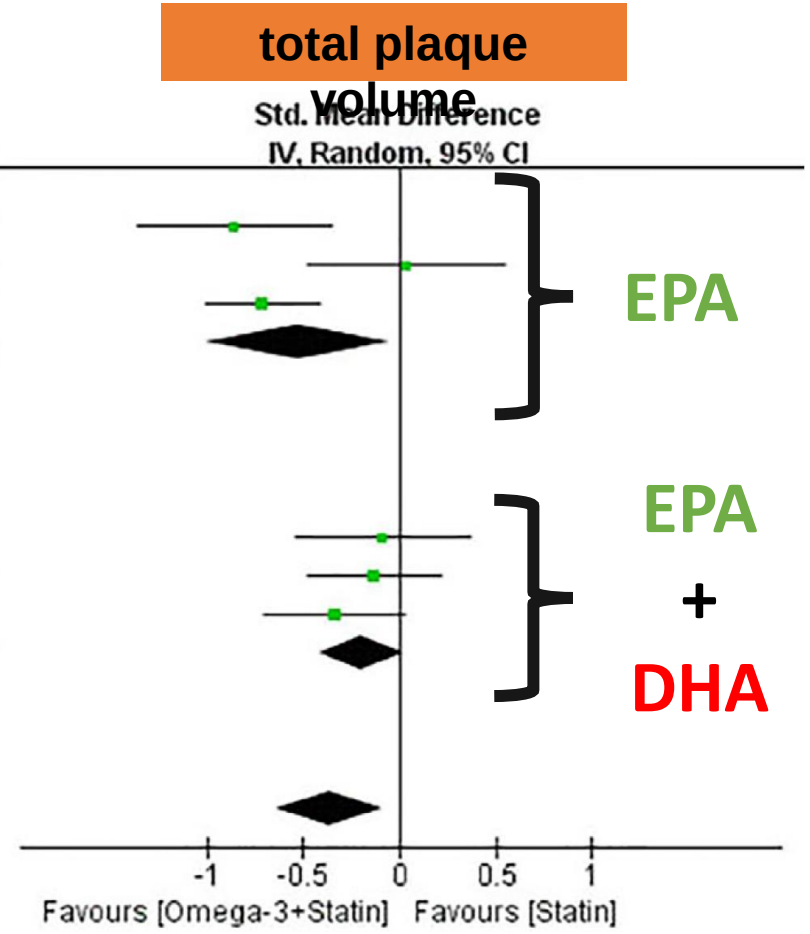
Primary outcome: a composite of nonfatal AMI, unscheduled revascularization, stroke, all-cause death, heart failure hospitalization after 2 years

Kalstad et al. Circulation 2021

# EPA but not EPA & DHA stabilize coronary plaque characteristics

**total plaque volume**

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.9.1 EPA** | | | | | | | | |
| Budoff 2020 | -0.5 | 0.8 | 31 | 0.4 | 1.2 | 37 | 14.2% | -0.86 [-1.36, -0.36] |
| Niki 2015 | -0.5 | 3.7 | 29 | -0.6 | 2.8 | 30 | 13.9% | 0.03 [-0.48, 0.54] |
| Watanable 2017 | -8.76 | 10.61 | 97 | -1.62 | 9.32 | 96 | 20.3% | -0.71 [-1.00, -0.42] |
| **Subtotal (95% CI)** | | | **157** | | | **163** | **48.3%** | **-0.53 [-1.01, -0.06]** |
| Heterogeneity: Tau² = 0.13; Chi² = 7.44, df = 2 (P = 0.02); I² = 73% | | | | | | | | |
| Test for overall effect: Z = 2.19 (P = 0.03) | | | | | | | | |
| **1.9.2 EPA+DHA** | | | | | | | | |
| Ahn 2015 | -12.65 | 30.19 | 36 | -8.51 | 55.5 | 38 | 15.3% | -0.09 [-0.55, 0.37] |
| Alfaddagh (high-intensity statin) 2017 | 9.11 | 20.15 | 65 | 12.04 | 23.11 | 61 | 18.5% | -0.13 [-0.48, 0.22] |
| Alfaddagh (low-intensity statin) 2017 | 3.33 | 20.83 | 61 | 10.45 | 20.75 | 53 | 17.8% | -0.34 [-0.71, 0.03] |
| **Subtotal (95% CI)** | | | **162** | | | **152** | **51.7%** | **-0.20 [-0.42, 0.02]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 2 (P = 0.64); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 1.75 (P = 0.08) | | | | | | | | |
| **Total (95% CI)** | | | **319** | | | **315** | **100.0%** | **-0.36 [-0.64, -0.08]** |
| Heterogeneity: Tau² = 0.08; Chi² = 14.43, df = 5 (P = 0.01); I² = 65% | | | | | | | | |
| Test for overall effect: Z = 2.55 (P = 0.01) | | | | | | | | |
| Test for subgroup differences: Chi² = 1.55, df = 1 (P = 0.21), I² = 35.6% | | | | | | | | |

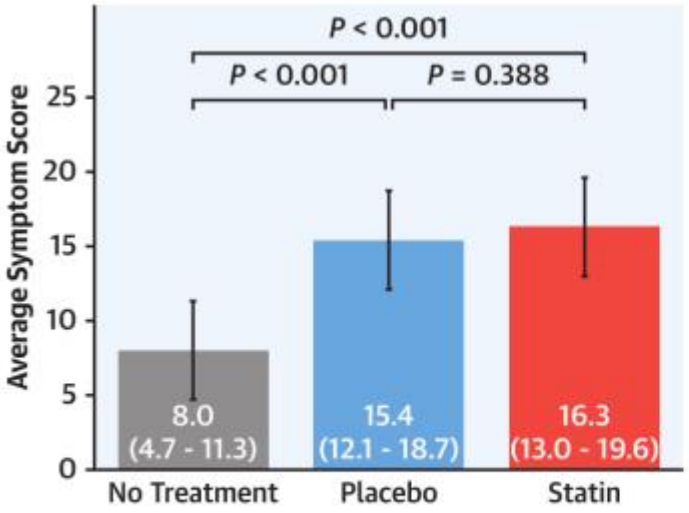


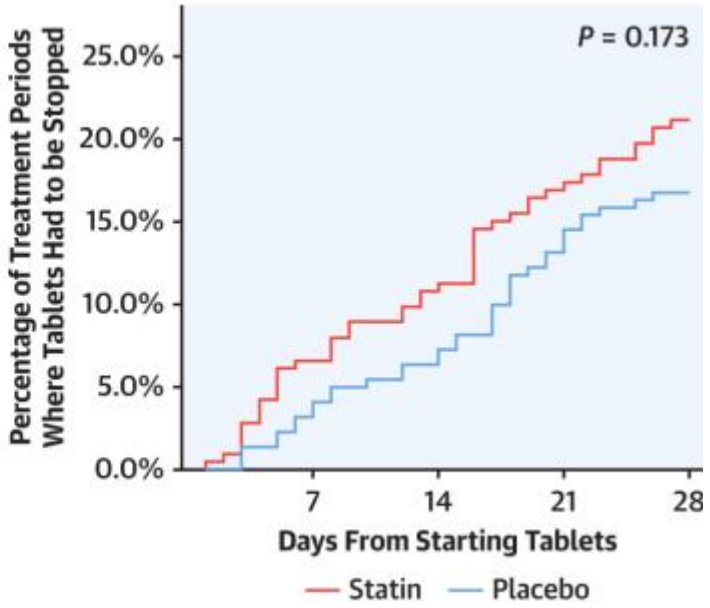

*Fan et al. Am J Cardiol 2021*

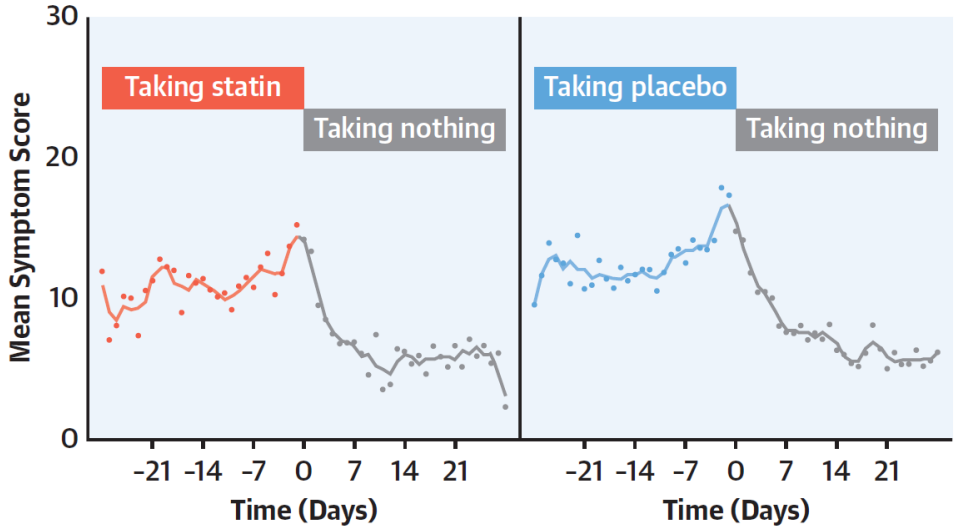
# Παρενέργειες στατινών

# The majority of symptoms caused by statin tablets are nocebo

## Identical adverse event pattern with placebo and statin
**(muscle ache, fatigue or tiredness and cramps)**




Howard et al. J Am Coll Cardiol 2021

# High-intensity atorvastatin increases insulin resistance and insulin secretion

open-label clinical trial
75 individuals enrolled
10 weeks follow-up

**Statins are associated with increased insulin resistance and secretion**

Individuals without diabetes and ASCVD

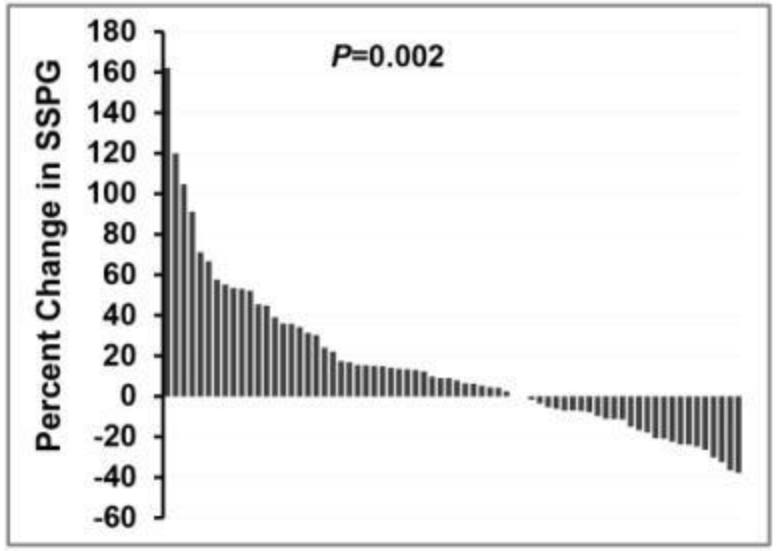
Baseline

**Insulin Resistance**
Insulin Suppression Test
Higher SSPG → greater insulin resistance

**Insulin Secretion**
Graded Glucose Infusion Test
Higher ISR → greater insulin secretion

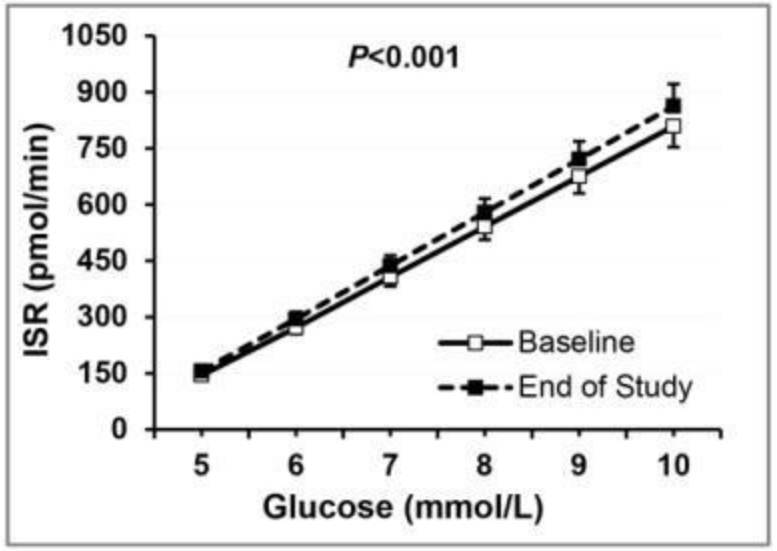
**Atorvastatin 40 mg daily**

**Insulin Resistance**




**Insulin resistance increased by 8%**

**Insulin Secretion**




**Insulin secretion increased by 9%**

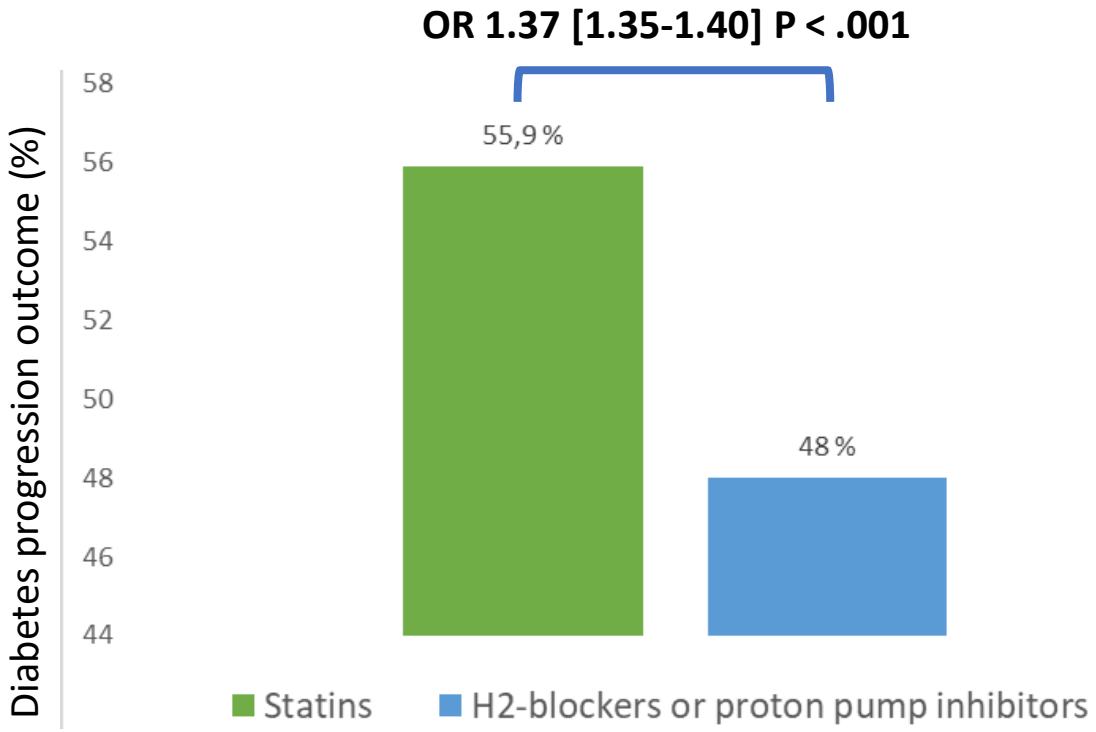
ISR = insulin secretion rate
SSPG = steady-state plasma glucose

Insulin resistance and insulin secretion increase by high-intensity atorvastatin treatment

Abbasi et al. Arterioscler Thromb Vasc 2021

# Statin use is associated with diabetes progression

**Retrospective propensity-score matched cohort study**
**83 022 pairs from 705 774 patients with diabetes**




## Dose-dependent increase in risk for diabetes progression

| Cholesterol-lowering intensity in overall cohort | | | HR | |
|---|---|---|---|---|
| High intensity | | | | |
| No. | 38 823 | 110 195 | NA | NA |
| Diabetes progression | 26 547 (68.4) | 49 328 (44.8) | 1.83 (1.78-1.88) | <.001 |
| Moderate intensity | | | | |
| No. | 180 884 | 110 195 | NA | NA |
| Diabetes progression | 120 246 (66.5) | 49 328 (44.8) | 1.55 (1.53-1.58) | <.001 |
| Low intensity | | | | |
| No. | 375 872 | 110 195 | NA | NA |
| Diabetes progression | 244 760 (65.1) | 49 328 (44.8) | 1.45 (1.42-1.47) | <.001 |

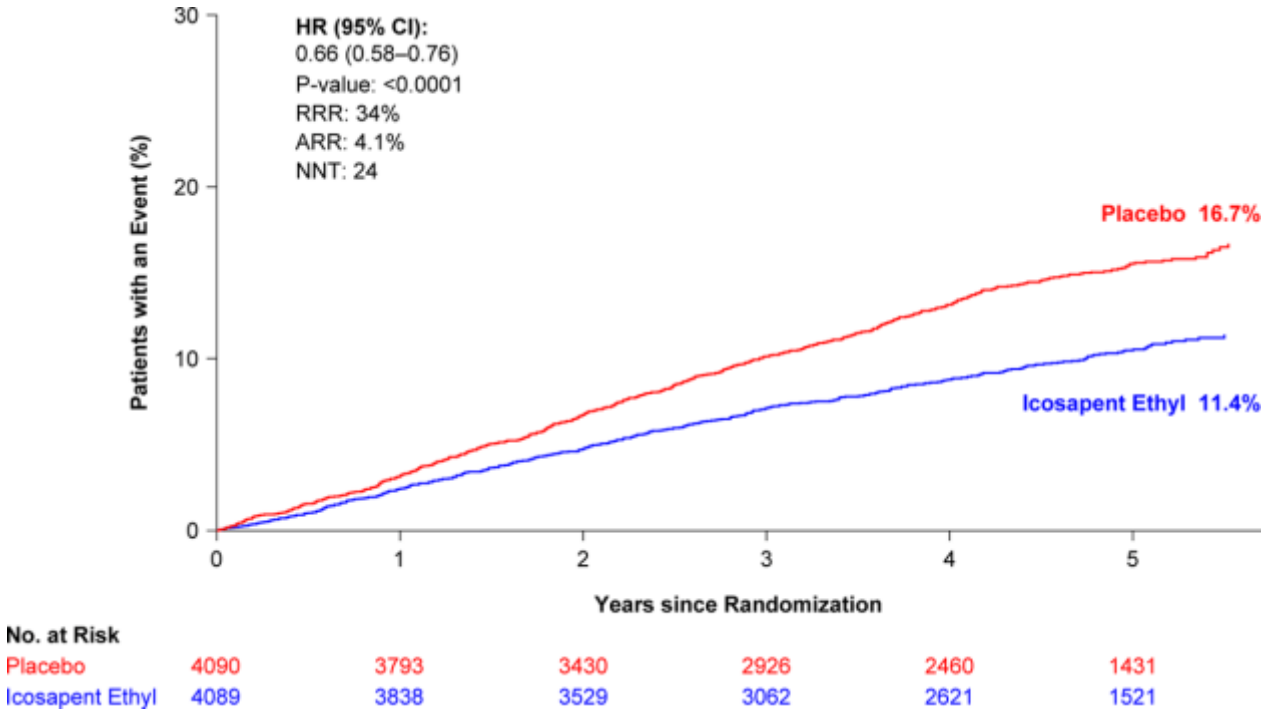
**Diabetes progression outcome:** new insulin initiation, increase in the number of glucose-lowering medication classes, incidence of 5 or more measurements of blood glucose of 200 mg/dL or greater, or a new diagnosis of ketoacidosis or uncontrolled diabetes

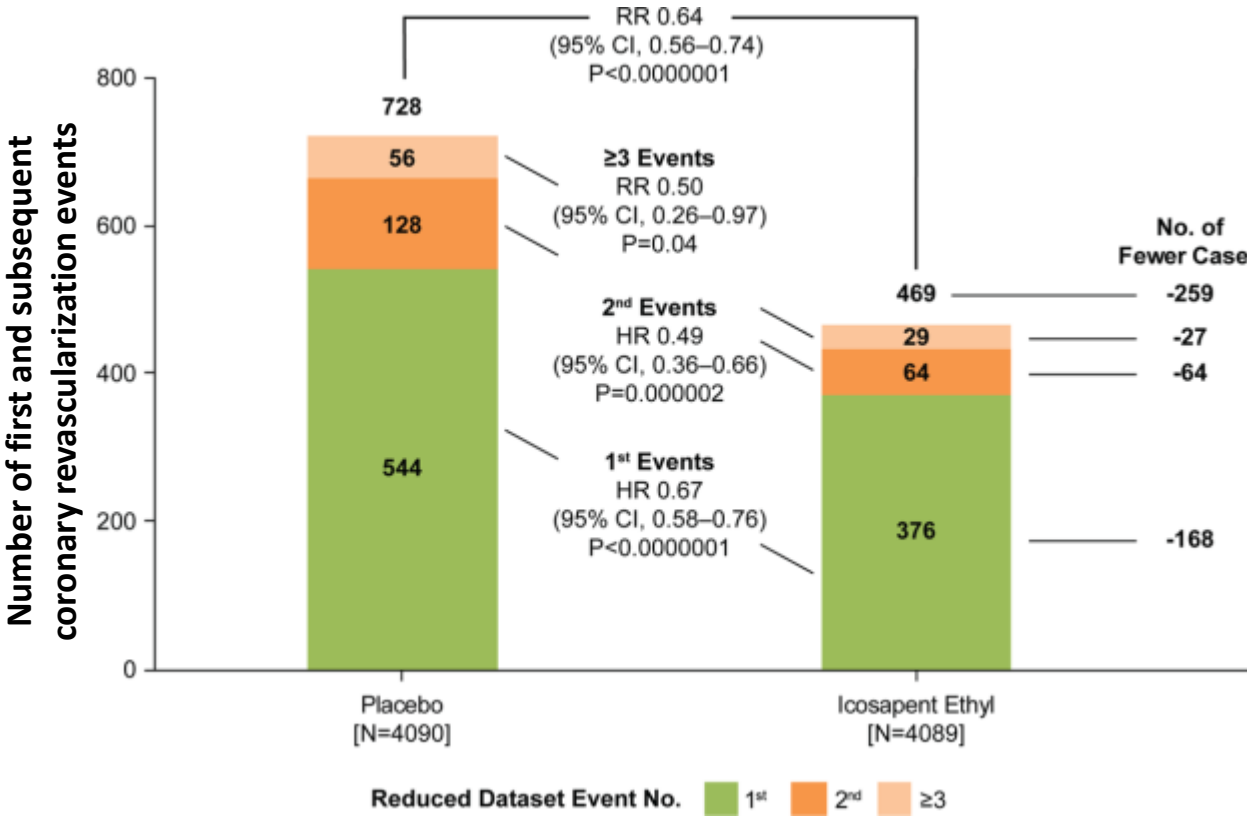
Mansi et al. JAMA Intern Med 2021

# Icosapent ethyl (omega3 FAs) reduce the need for first and subsequent coronary revascularizations (REDUCE-IT trial)

Statin-treated patients with elevated triglycerides and increased CV risk

**4 g n-3 PUFA (high purity EPA) daily**

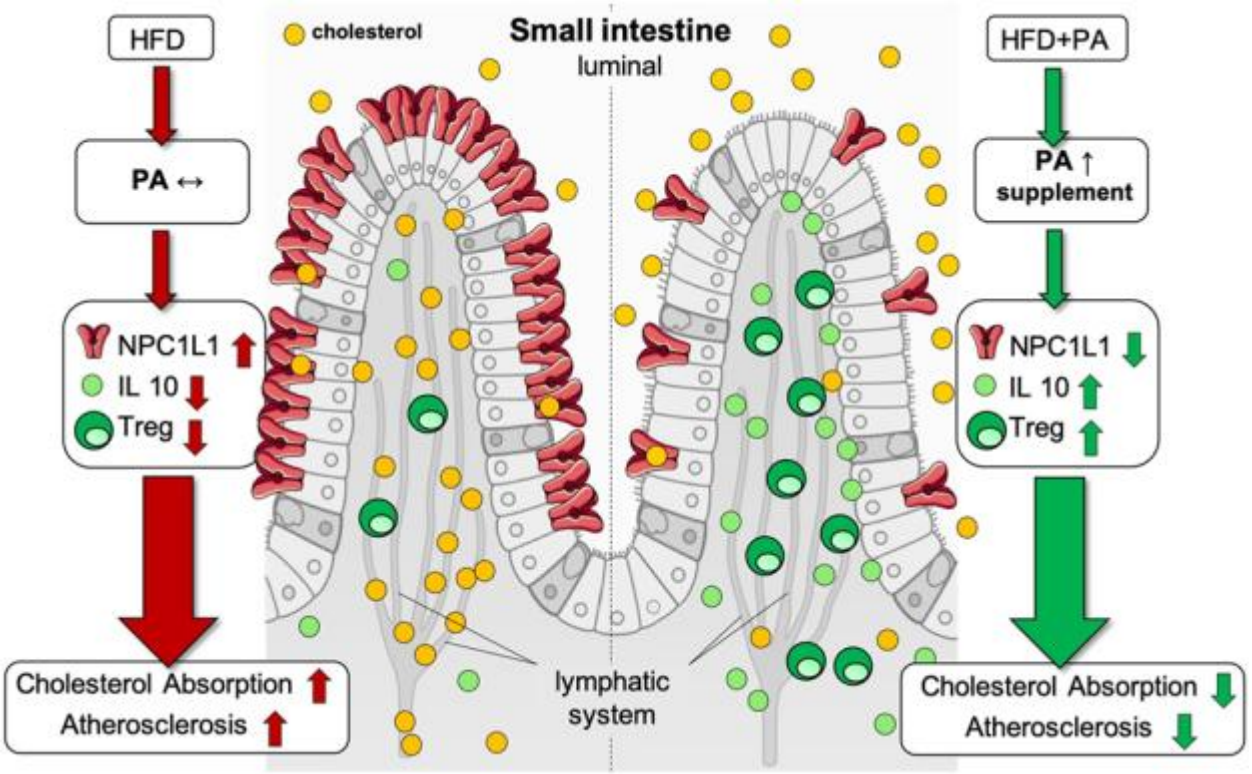



Peterson et al. Circulation 2021

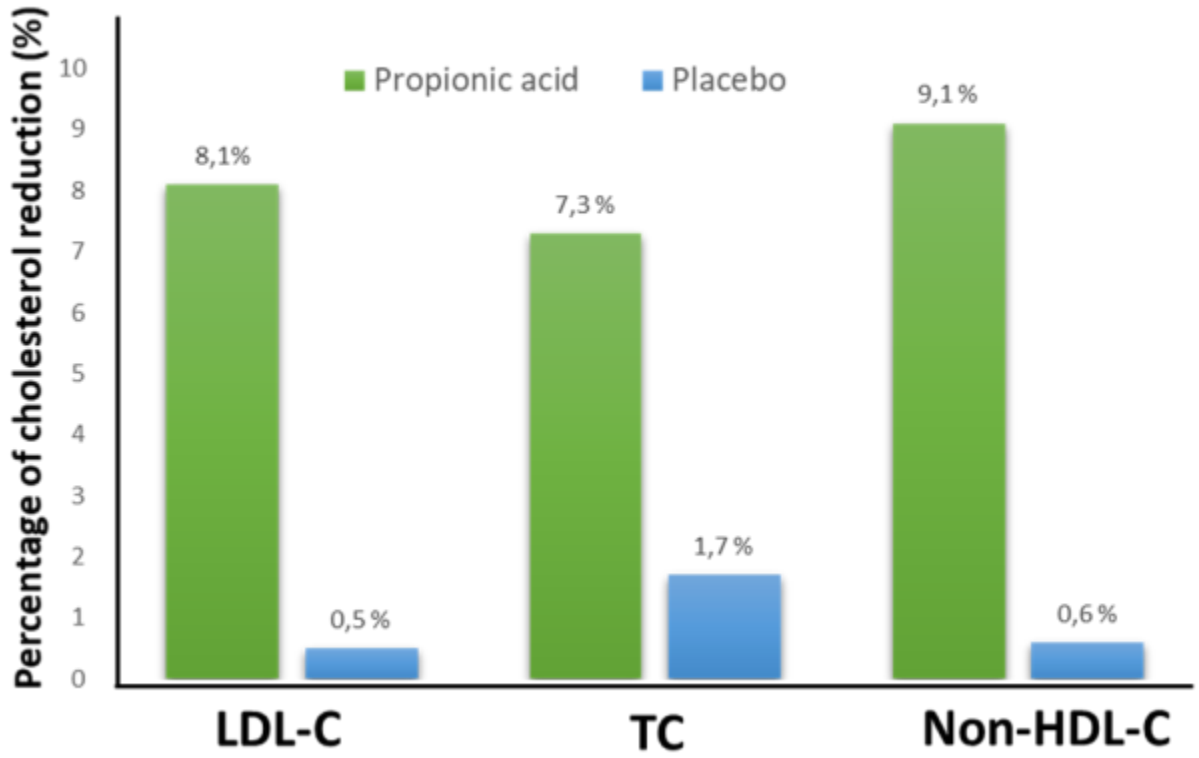
# Propionic acid affect gut microbiome and reduces LDL-C through an immunological pathway

gut microbiota metabolite (fatty acid)
target: intestinal cholesterol transporter NPC1L1




HFD, high-fat diet; IL-10, interleukin-10; NPC1L1, Niemann-Pick C1-like 1; PA, propionic acid; Treg, regulatory T cell

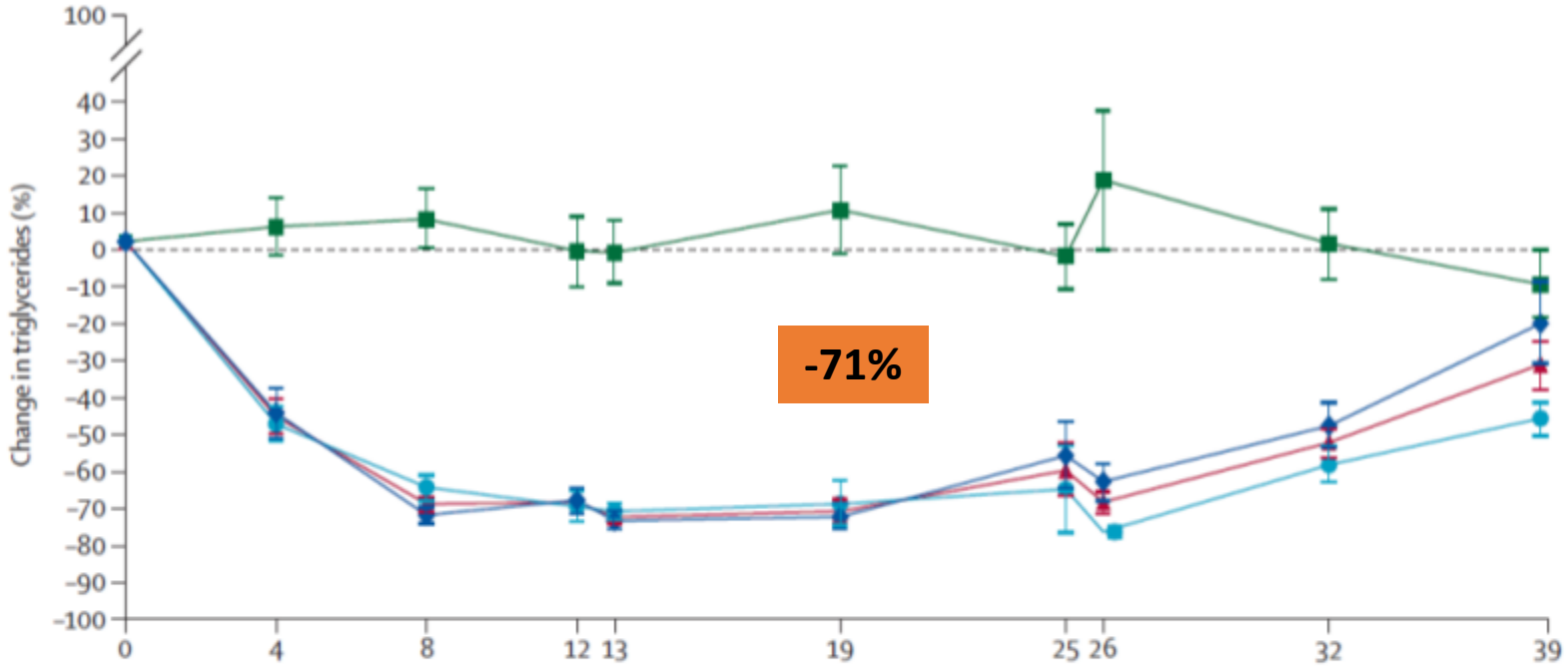
500 mg of Propionic acid twice daily in subjects with elevated baseline LDL cholesterol levels.




Haghikia et al. Eur Heart J 2021

# Volanesorsen decrease triglyceride levels in patients with multifactorial or familial chylomicronaemia

anti-sense RNA
target: hepatic apolipoprotein C-




| Number at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 38 | 37 | 36 | 30 36 | 35 | 29 35 | 30 | 32 |
| Volanesorsen total | 75 | 74 | 65 | 61 68 | 58 | 57 62 | 55 | 57 |
| Volanesorsen once per week | 25 | 25 | 24 | 24 25 | 25 | 25 25 | 25 | 25 |
| Volanesorsen once every 2 weeks | 50 | 49 | 41 | 37 43 | 33 | 32 37 | 30 | 32 |

C

Placebo at 3 months · Placebo at 6 months · Volanesorsen total at 3 months · Volanesorsen total at 6 months
Volanesorsen 300 mg once per week at 6 months · Volanesorsen 300 mg once every 2 weeks (after week 13) at 6 months

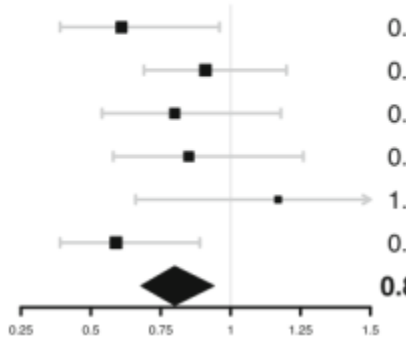
Gouni-Berthold et al. The Lancet 2021

# GATM polymorphism may be protective factor of statin induced myopathy

**Statin induced myopathy**

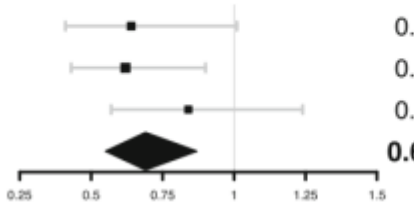
## rs9806699 G>A

| Study (Year) | Sample size Cases | Sample size Controls | MAF* Cases | MAF* Controls | OR (95% CI) | Weight (%) |
|---|---|---|---|---|---|---|
| Mangravite et al. (2013) | 72 | 220 | 0.21 | 0.30 | 0.61 (0.39–0.96) | 15.04 |
| Carr et al. (2014) | 150 | 587 | 0.28 | 0.30 | 0.91 (0.69–1.20) | 30.11 |
| Floyd et al. (2014) | 76 | 643 | 0.24 | 0.28 | 0.80 (0.54–1.18) | 16.95 |
| Luzum et al. (2015) | 306 | 80 | 0.25 | 0.28 | 0.85 (0.58–1.26) | 15.62 |
| Sai et al. (2016) | 52 | 86 | 0.78 | 0.75 | 1.17 (0.66–2.09) | 6.28 |
| Bai et al. (2018) | 51 | 705 | 0.60 | 0.72 | 0.59 (0.39–0.89) | 16.00 |
| **Overall (I–squared=17.5%, p=0.301)** | | | | | **0.80 (0.68–0.94)** | **100.00** |



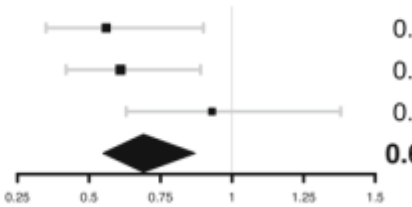

## rs1346268 T>C

| Study (Year) | Sample size Cases | Sample size Controls | MAF* Cases | MAF* Controls | OR (95% CI) | Weight (%) |
|---|---|---|---|---|---|---|
| Mangravite et al. (2013) (Marshfield) | 72 | 220 | 0.21 | 0.29 | 0.64 (0.41–1.01) | 26.42 |
| Mangravite et al. (2013) (SEARCH) | 100 | 4029 | 0.18 | 0.26 | 0.62 (0.43–0.90) | 43.99 |
| Floyd et al. (2014) | 76 | 643 | 0.24 | 0.27 | 0.84 (0.57–1.24) | 29.59 |
| **Overall (I–squared=0.0%, p=0.512)** | | | | | **0.69 (0.55–0.87)** | **100.00** |




## rs1719247 C>T

| Study (Year) | Sample size Cases | Sample size Controls | MAF* Cases | MAF* Controls | OR (95% CI) | Weight (%) |
|---|---|---|---|---|---|---|
| Mangravite et al. (2013) (Marshfield) | 72 | 220 | 0.19 | 0.29 | 0.56 (0.35–0.90) | 27.84 |
| Mangravite et al. (2013) (SEARCH) | 100 | 4021 | 0.17 | 0.25 | 0.61 (0.42–0.89) | 43.97 |
| Floyd et al. (2014) | 76 | 643 | 0.24 | 0.25 | 0.93 (0.63–1.38) | 28.18 |
| **Overall (I–squared=39.6%, p=0.191)** | | | | | **0.69 (0.55–0.87)** | **100.00** |

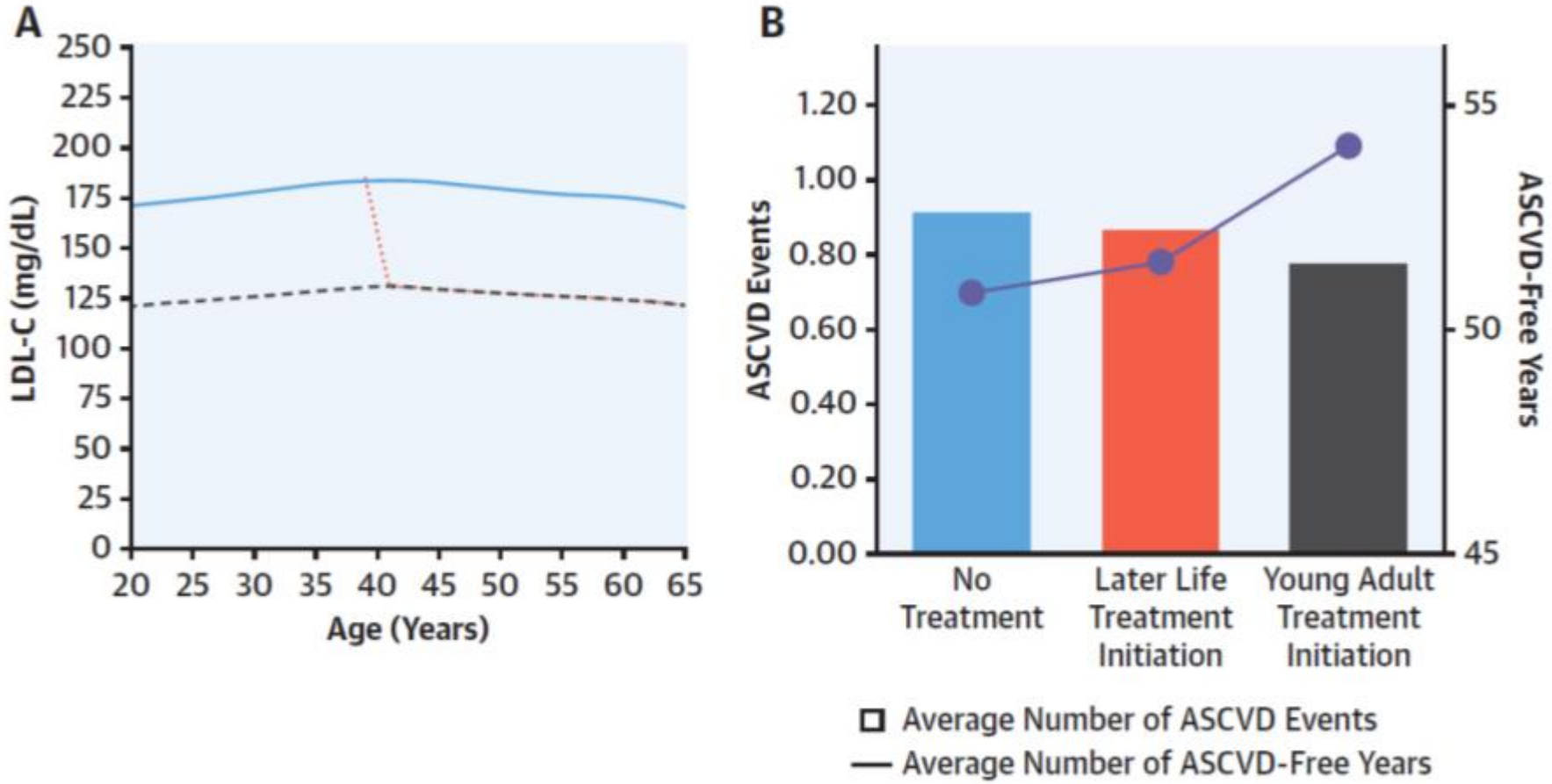



Polymorphism better

MAF= minor allele frequency

Liu et al. Eur J Clin Pharmacol 2021

# Statin treatment for LDL-C≥130mg/dl is cost effective for young adults

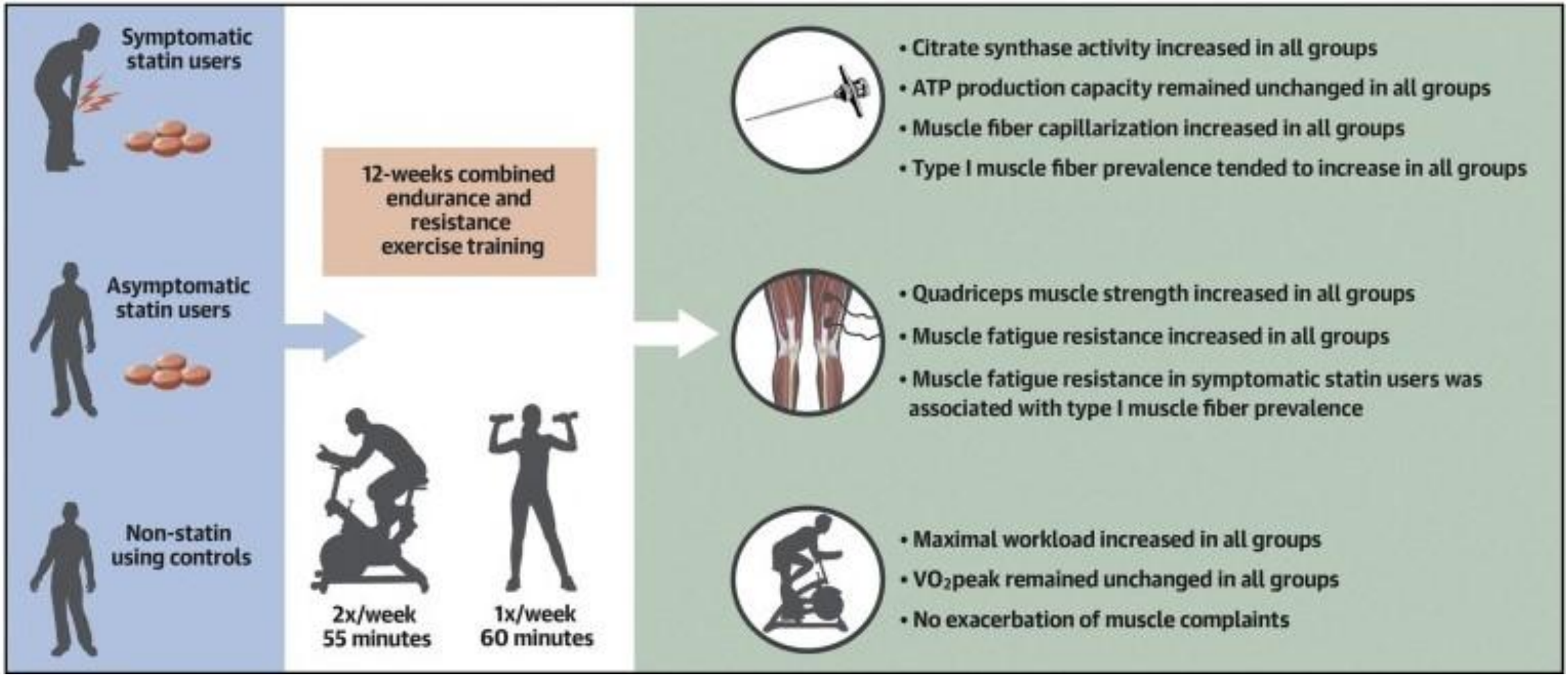



**Highly cost effective for young men**
**Intermediately cost-effective for young women**

**Statin treatment was more cost effective than intensive lifestyle intervention**

Kohli-Lynch et al. JACC 2021

# A moderate intensity exercise training program improves muscle performance without exacerbating muscle complaints in symptomatic statin users




Allard et al. J Am Coll Cardiol 2021

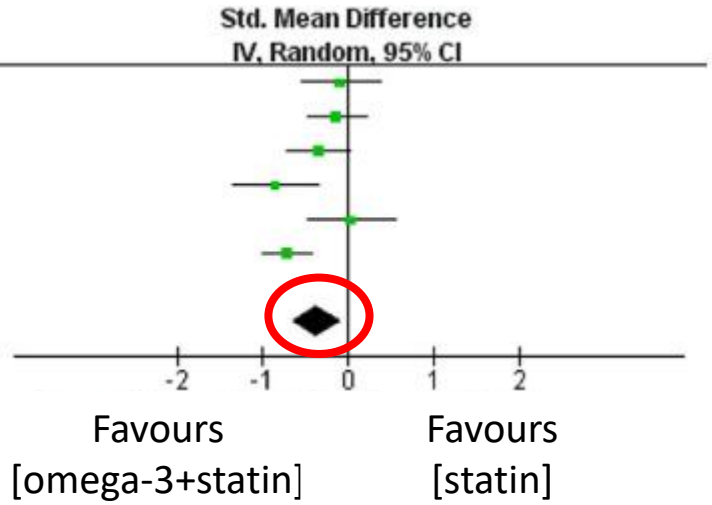
# Omega-3 combined with statins stabilizes and promotes coronary plaque regression compared with statin alone

## Total plaque volume change

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Ahn 2015 | -12.65 | 30.19 | 36 | -8.51 | 55.5 | 38 | 15.3% | -0.09 [-0.55, 0.37] |
| Alfaddagh (high-intensity statin) 2017 | 9.11 | 20.15 | 65 | 12.04 | 23.11 | 61 | 18.5% | -0.13 [-0.48, 0.22] |
| Alfaddagh (low-intensity statin) 2017 | 3.33 | 20.83 | 61 | 10.45 | 20.75 | 53 | 17.8% | -0.34 [-0.71, 0.03] |
| Budoff 2020 | -0.5 | 0.8 | 31 | 0.4 | 1.2 | 37 | 14.2% | -0.86 [-1.36, -0.36] |
| Niki 2015 | -0.5 | 3.7 | 29 | -0.6 | 2.8 | 30 | 13.9% | 0.03 [-0.48, 0.54] |
| Watanable 2017 | -8.76 | 10.61 | 97 | -1.62 | 9.32 | 96 | 20.3% | -0.71 [-1.00, -0.42] |
| **Total (95% CI)** | | | **319** | | | **315** | **100.0%** | **-0.36 [-0.64, -0.08]** |

Heterogeneity: Tau² = 0.08; Chi² = 14.43, df = 5 (P = 0.01); I² = 65%

Test for overall effect: Z = 2.55 (P = 0.01)

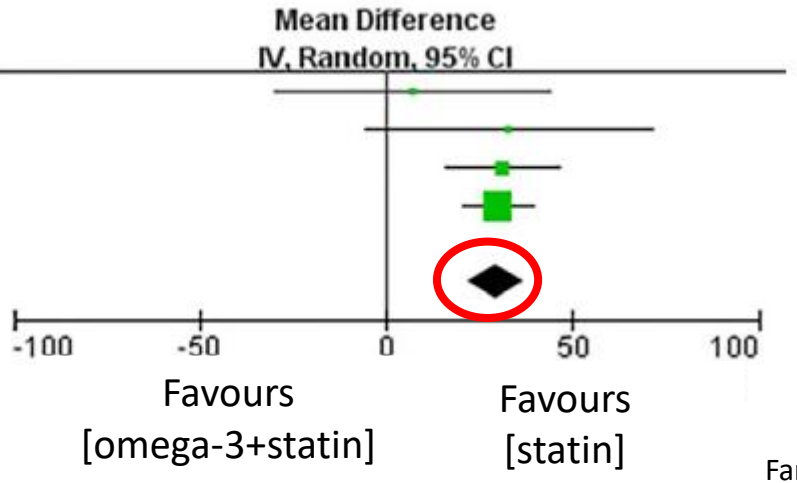



## Fibrous cap thickness change

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Kita (EPA) 2020 | 37.81 | 70.31 | 31 | 30.69 | 54.69 | 15 | 4.4% | 7.12 [-30.01, 44.25] |
| Kita (EPA+DHA) 2020 | 63.56 | 84.62 | 35 | 30.69 | 54.69 | 16 | 4.0% | 32.87 [-5.91, 71.65] |
| Nishio 2014 | 54.8 | 27.9 | 15 | 23.5 | 11.6 | 15 | 25.9% | 31.30 [16.01, 46.59] |
| Sugizaki 2020 | 50 | 15.87 | 21 | 20 | 15.87 | 21 | 65.7% | 30.00 [20.40, 39.60] |
| **Total (95% CI)** | | | **102** | | | **67** | **100.0%** | **29.45 [21.67, 37.23]** |

Heterogeneity: Tau² = 0.00; Chi² = 1.49, df = 3 (P = 0.69); I² = 0%

Test for overall effect: Z = 7.42 (P < 0.00001)



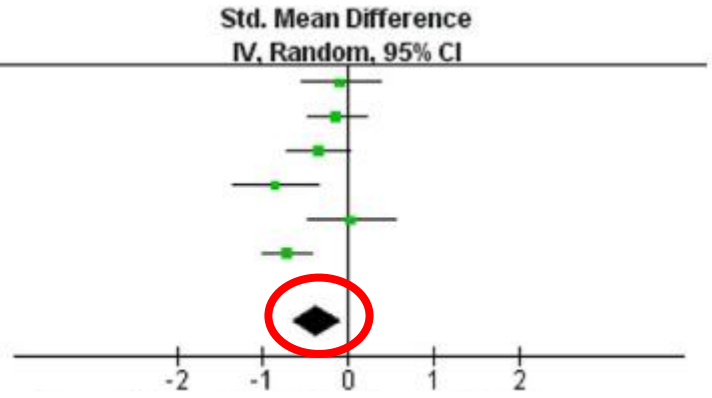

Fan et al. Am J Cardiol 2021

# EPA acts more beneficially on plaque progression than EPA & DHA

## Total plaque volume change

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Ahn 2015 | -12.65 | 30.19 | 36 | -8.51 | 55.5 | 38 | 15.3% | -0.09 [-0.55, 0.37] |
| Alfaddagh (high-intensity statin) 2017 | 9.11 | 20.15 | 65 | 12.04 | 23.11 | 61 | 18.5% | -0.13 [-0.48, 0.22] |
| Alfaddagh (low-intensity statin) 2017 | 3.33 | 20.83 | 61 | 10.45 | 20.75 | 53 | 17.8% | -0.34 [-0.71, 0.03] |
| Budoff 2020 | -0.5 | 0.8 | 31 | 0.4 | 1.2 | 37 | 14.2% | -0.86 [-1.36, -0.36] |
| Niki 2015 | -0.5 | 3.7 | 29 | -0.6 | 2.8 | 30 | 13.9% | 0.03 [-0.48, 0.54] |
| Watanable 2017 | -8.76 | 10.61 | 97 | -1.62 | 9.32 | 96 | 20.3% | -0.71 [-1.00, -0.42] |
| **Total (95% CI)** | | | **319** | | | **315** | **100.0%** | **-0.36 [-0.64, -0.08]** |

Heterogeneity: Tau² = 0.08; Chi² = 14.43, df = 5 (P = 0.01); I² = 65%
Test for overall effect: Z = 2.55 (P = 0.01)




## Fibrous cap thickness change

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
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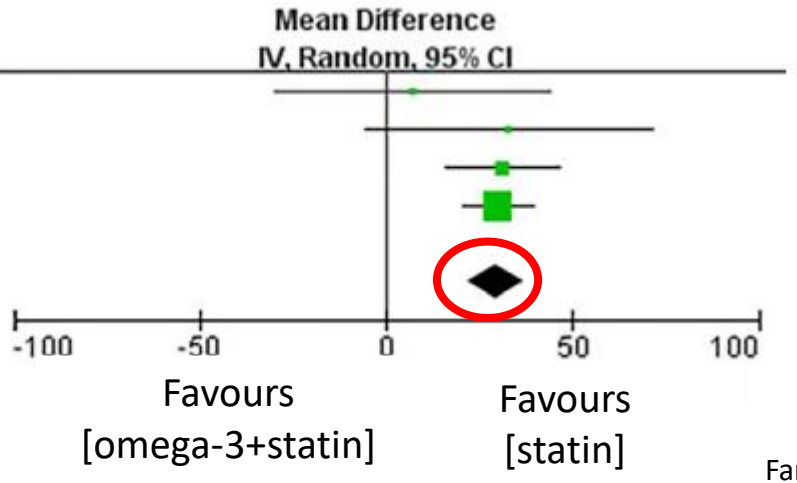
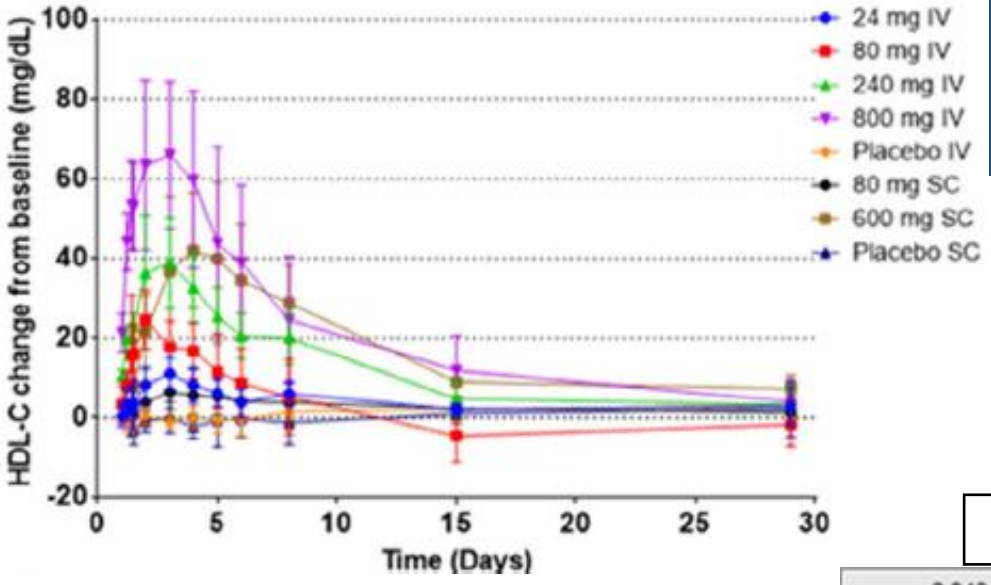



Fan et al. Am J Cardiol 2021

# MEDI6012 is safe and improves the lipid profile of patients

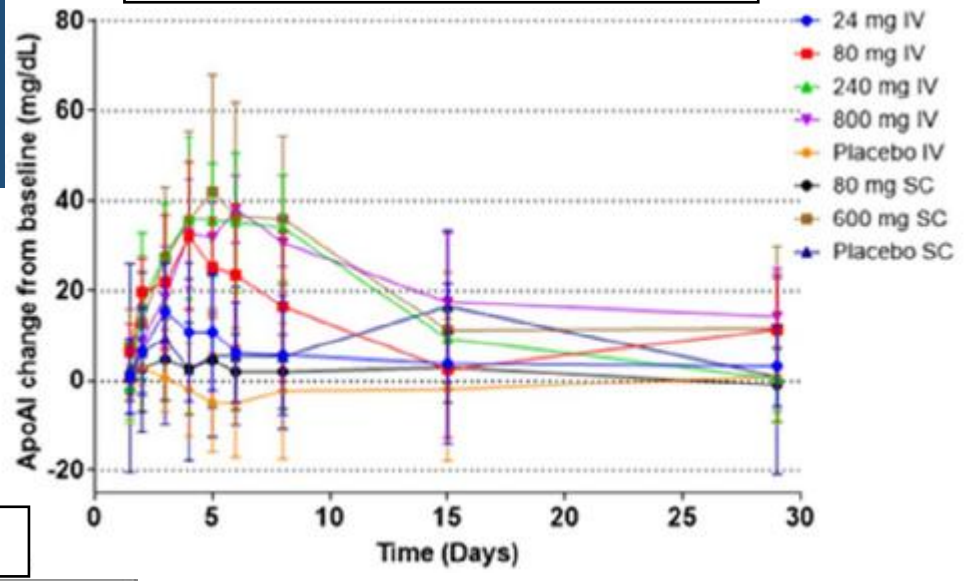
48 subjects with stable coronary heart disease on a statin

HDL-C change

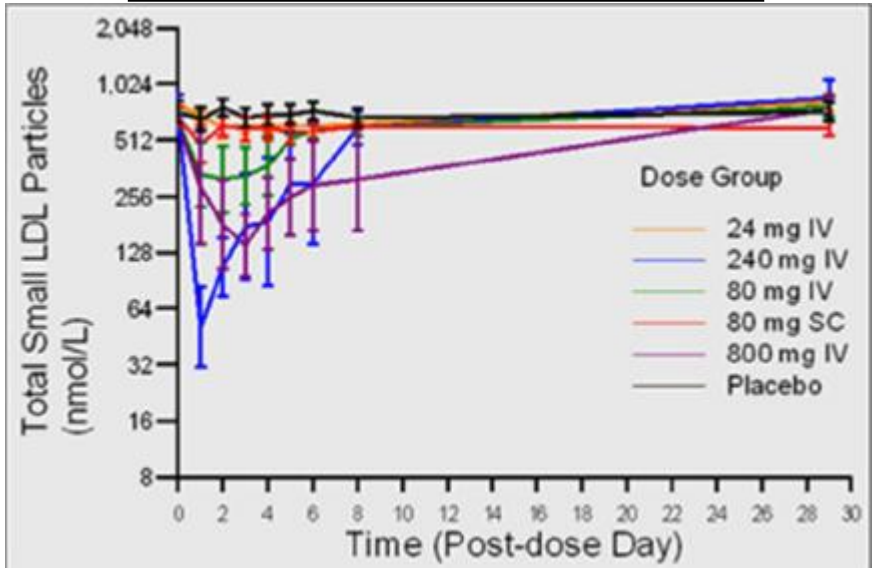



Recombinant human lecithin-cholesterol

ApoA1 change

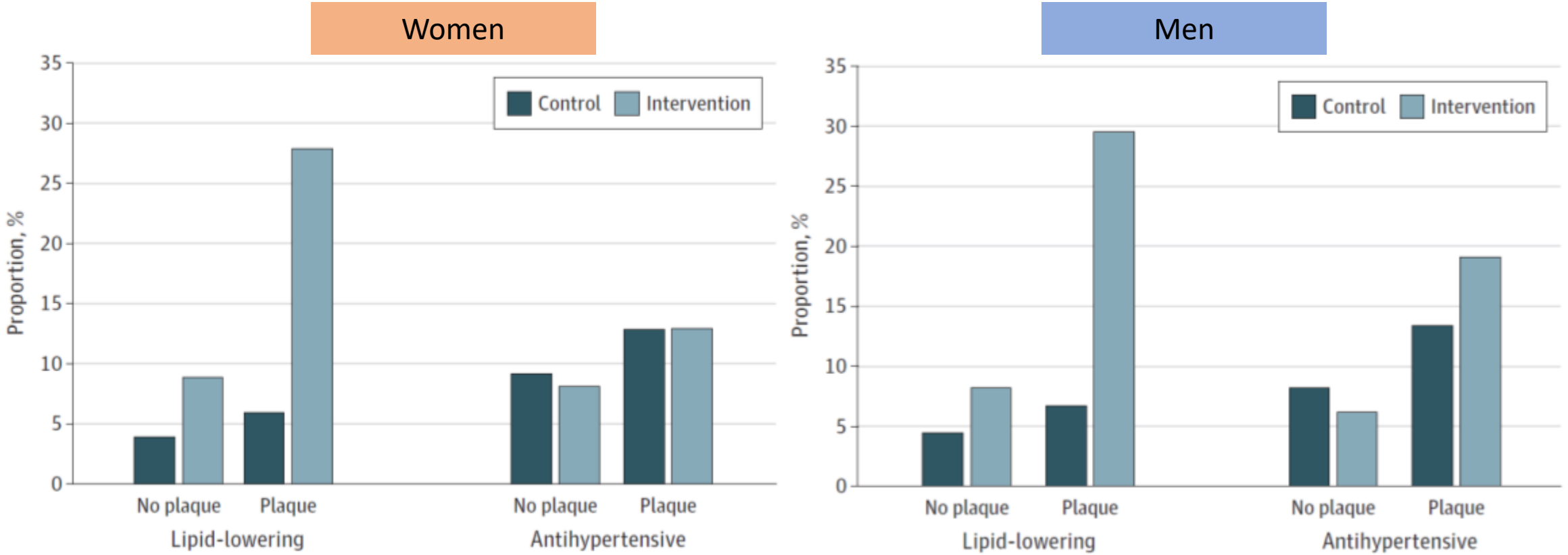



Small LDL particles




George et al. J Am Heart Assoc. 2021

# Information on carotid atherosclerosis can improve prescription of lipid-lowering drugs but not antihypertensive treatment




P<0.001 for both

RCT: including 3,532 participants low-moderate CVD risk
Carotid atherosclerosis: carotid intima-media thickness and carotid plaques

Sjölander et al. JAMA Net Open 2021

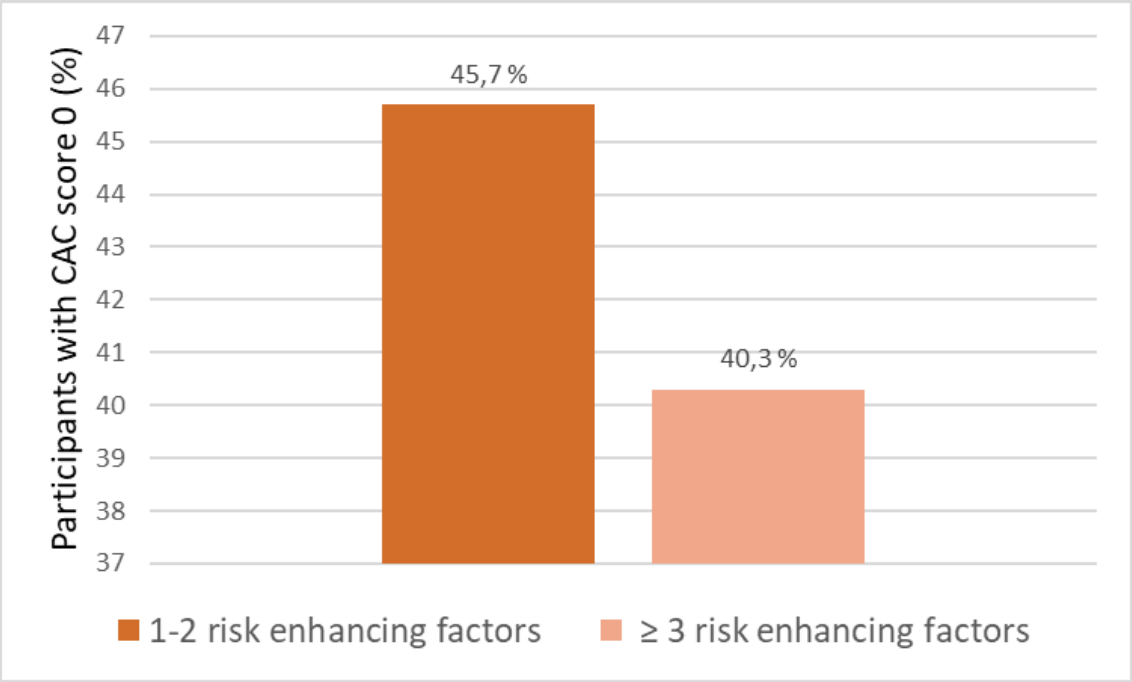
# CAC score improves reclassification of intermediate CV risk individuals who might benefit from statin initiation

**Multi-Ethnic Study of Atherosclerosis**
Prospective cross-sectional study
1688 participants
no clinical ASCVD or diabetes

→ **CAC score 0**: 42,8%

→ 12 years

→ <7.5 events per 1000 person-years for all individual risk-enhancing factors and combinations of risk-enhancing factors




CAC scoring classify more accurately than risk enhancing factors individuals with an intermediate risk of ASCVD who might benefit from statin therapy

Net Reclassification Improvement for CAC was 0.067

Risk enhancing factors: family history of premature ASCVD, premature menopause, metabolic syndrome, chronic kidney disease, lipid and inflammatory biomarkers, and low ABI

Patel et al. JAMA Cardiol 2021