Oral cholesterol lowering therapies: The basis of prevention

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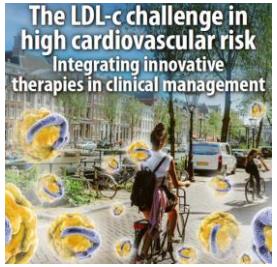
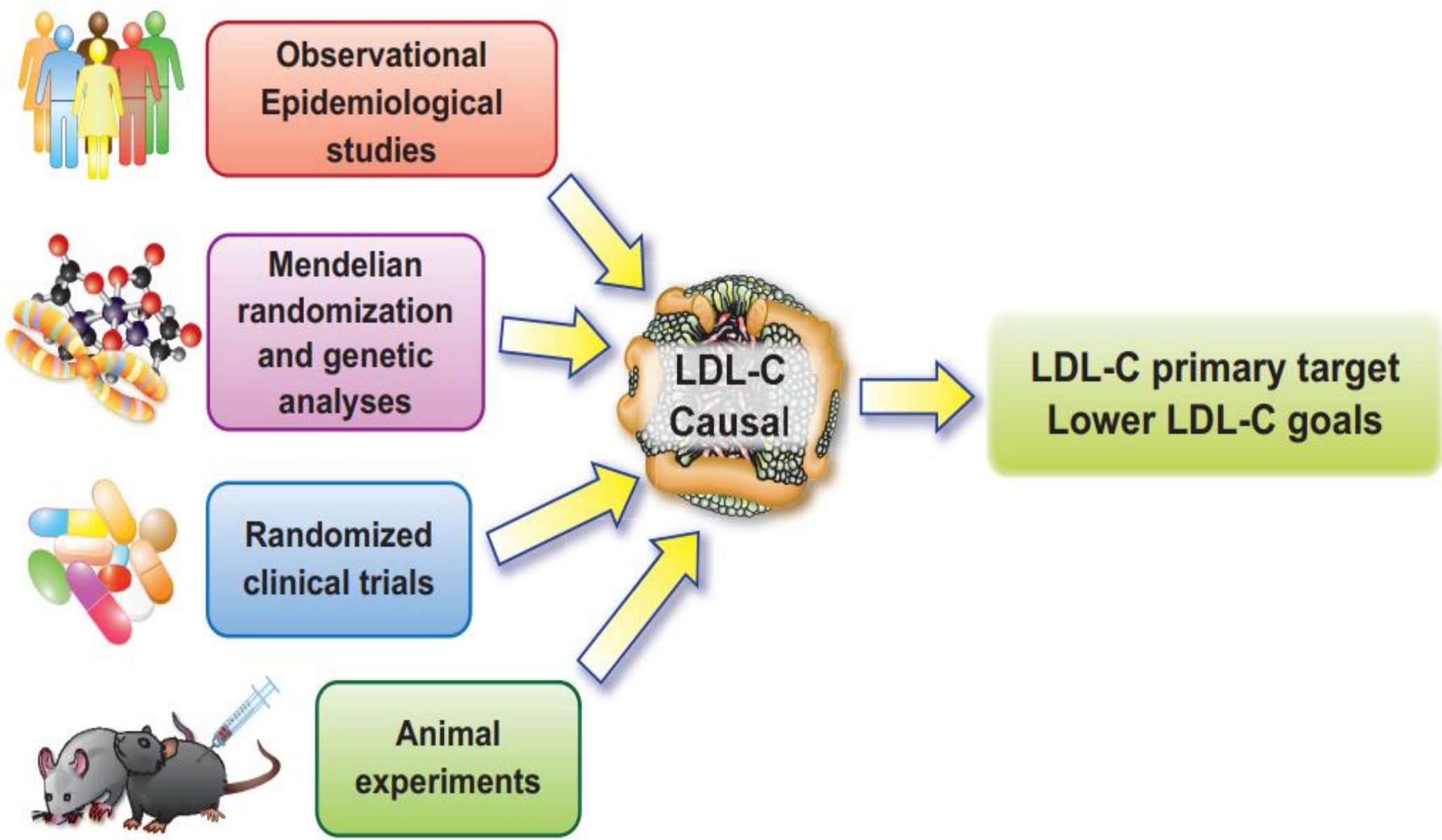
The LDL-c challenge in high cardiovascular risk - Integrating innovative therapies in clinical management



PHYSICIANS' ACADEMY FOR PACE-CME CARDIOVASCULAR EDUCATION

L Tokgözoğlu has received funding and support from Abbott, Amgen, AstraZeneca, Bayer, Daiichi Sankyo, Lilly, MSD, Novartis, Novo Nordisk, Pfizer, Sanofi, Servier and Ultragenyx



Tokgözoğlu, European Heart Journal (2022)

Interventions to reduce LDL-C

Lifestyle

Statins

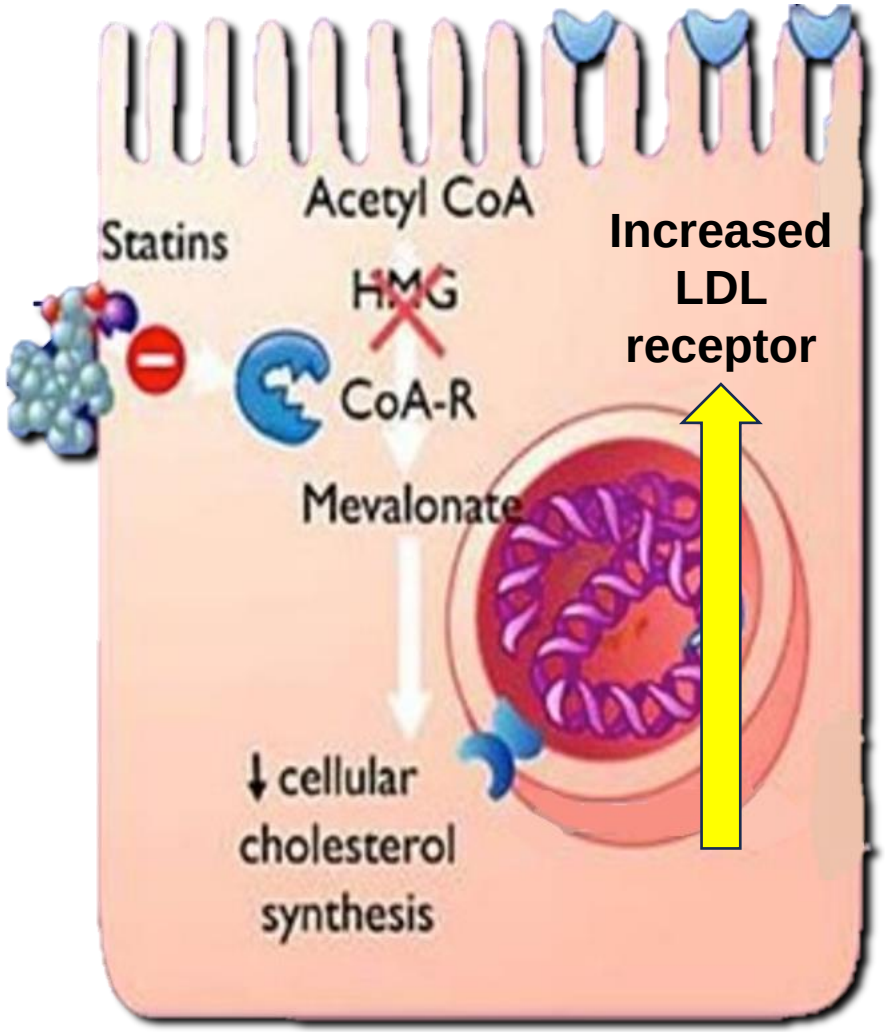
Combination Therapy

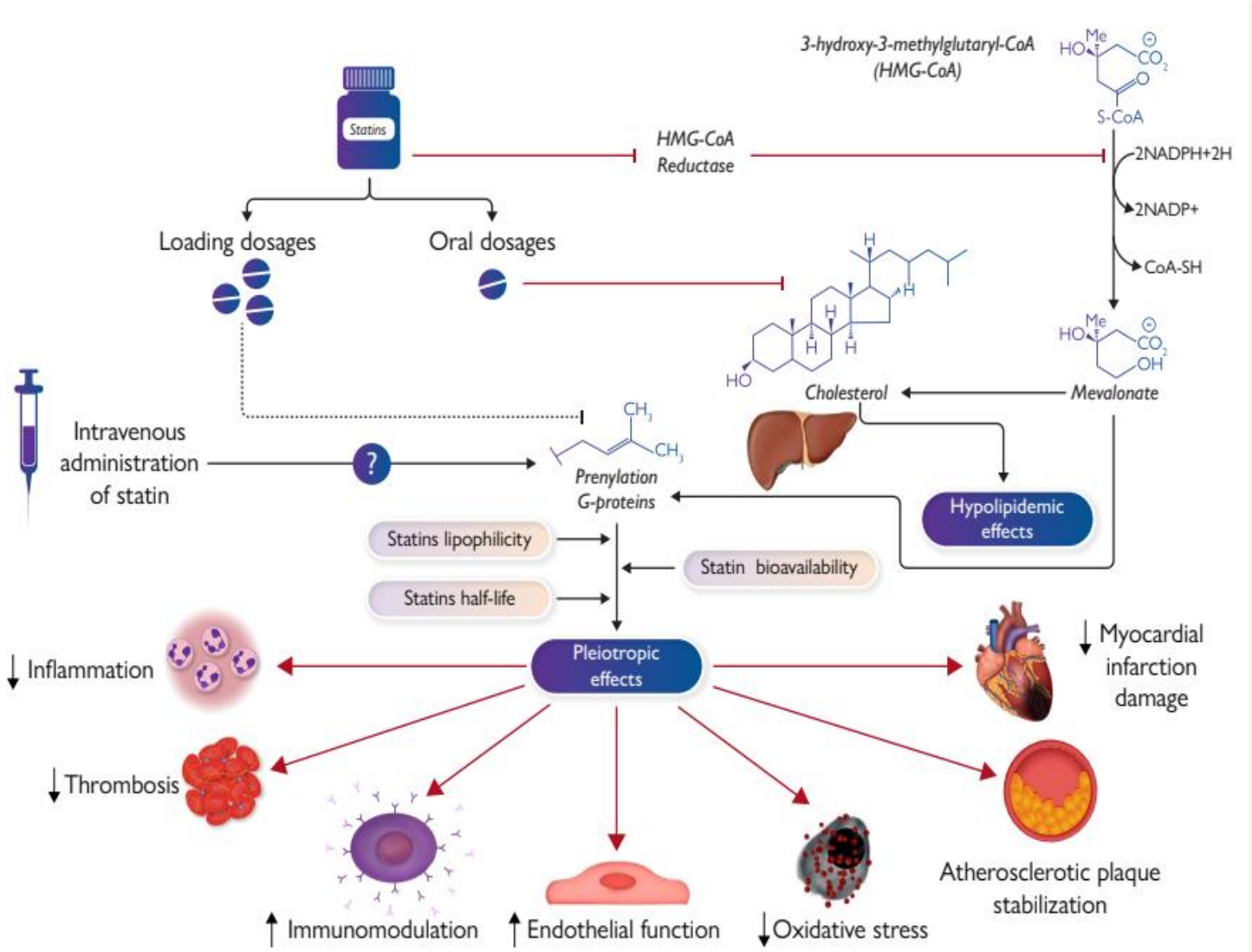
Oral:
Ezetimibe *, BAS *
Bempedoic acid *
Obicetrapib
Oral PCSK9 inhibitors
Lomitapide (only for HoFH)

***Therapies shown to decrease CV events**

Injectable:
PCSK9 monoclonal Ab *
Inclisiran
Evinacumab

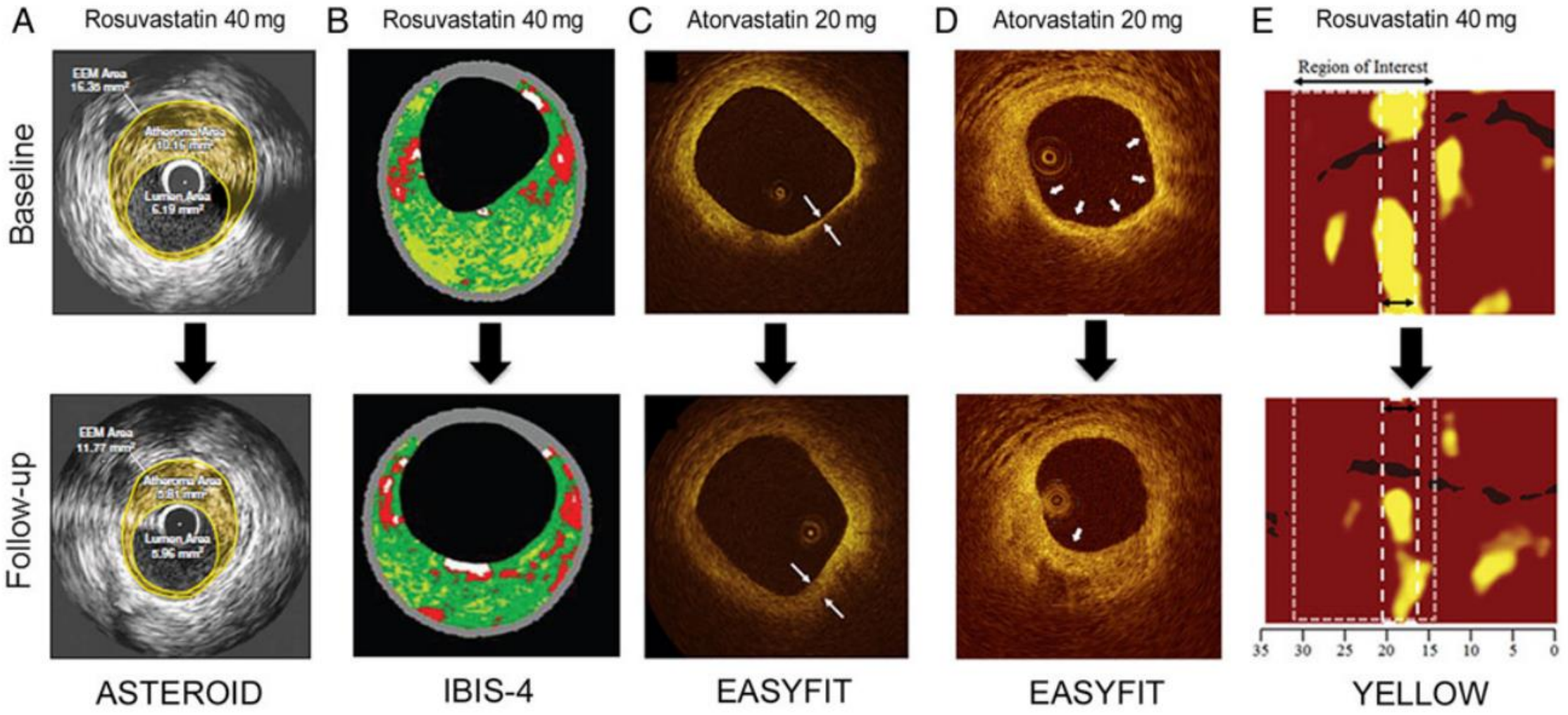
Effects of statins:





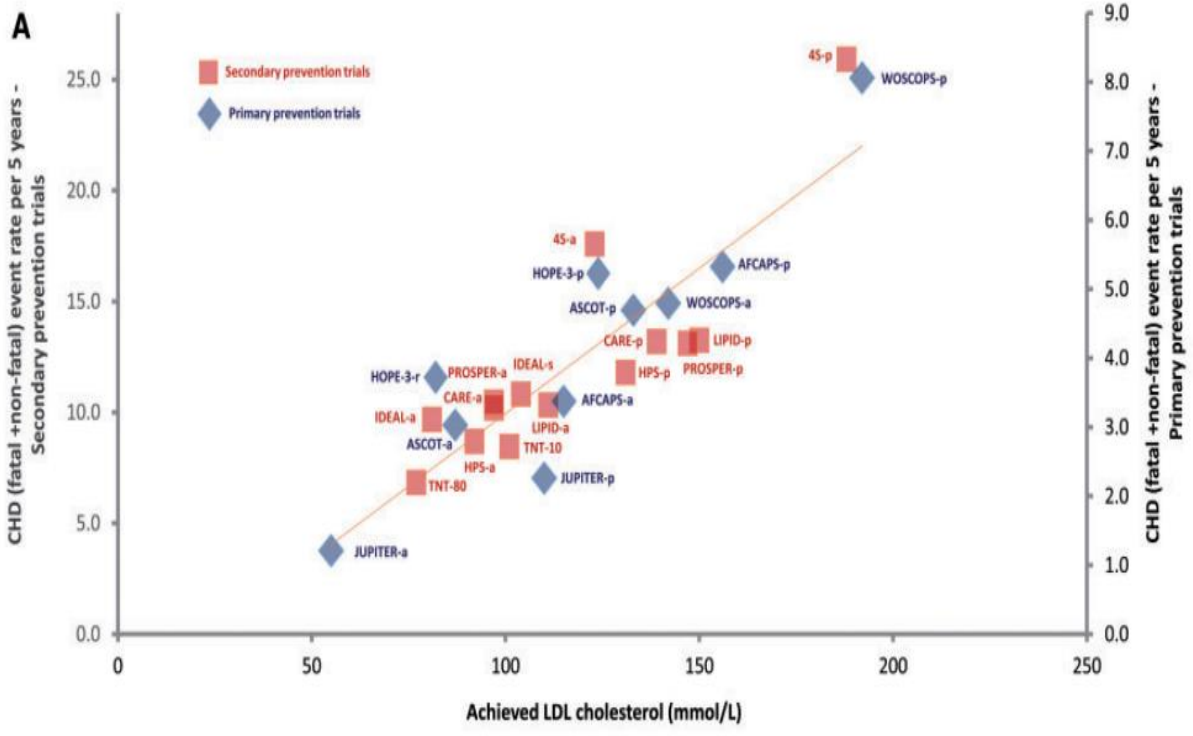
European Heart Journal (2023) 44, 2332–2334

Impact of statins on atherosclerotic plaque



European Heart Journal (2016) 37, 524–535

Linear relation between LDL-C reduction and CVD



- For each 1 mmol/L reduction in LDL cholesterol, statin therapy reduced:
  - Major vascular events by ~20%
  - Major coronary events by 25%
  - Coronary revascularisations by 25%
  - Ischemic stroke by ~20%

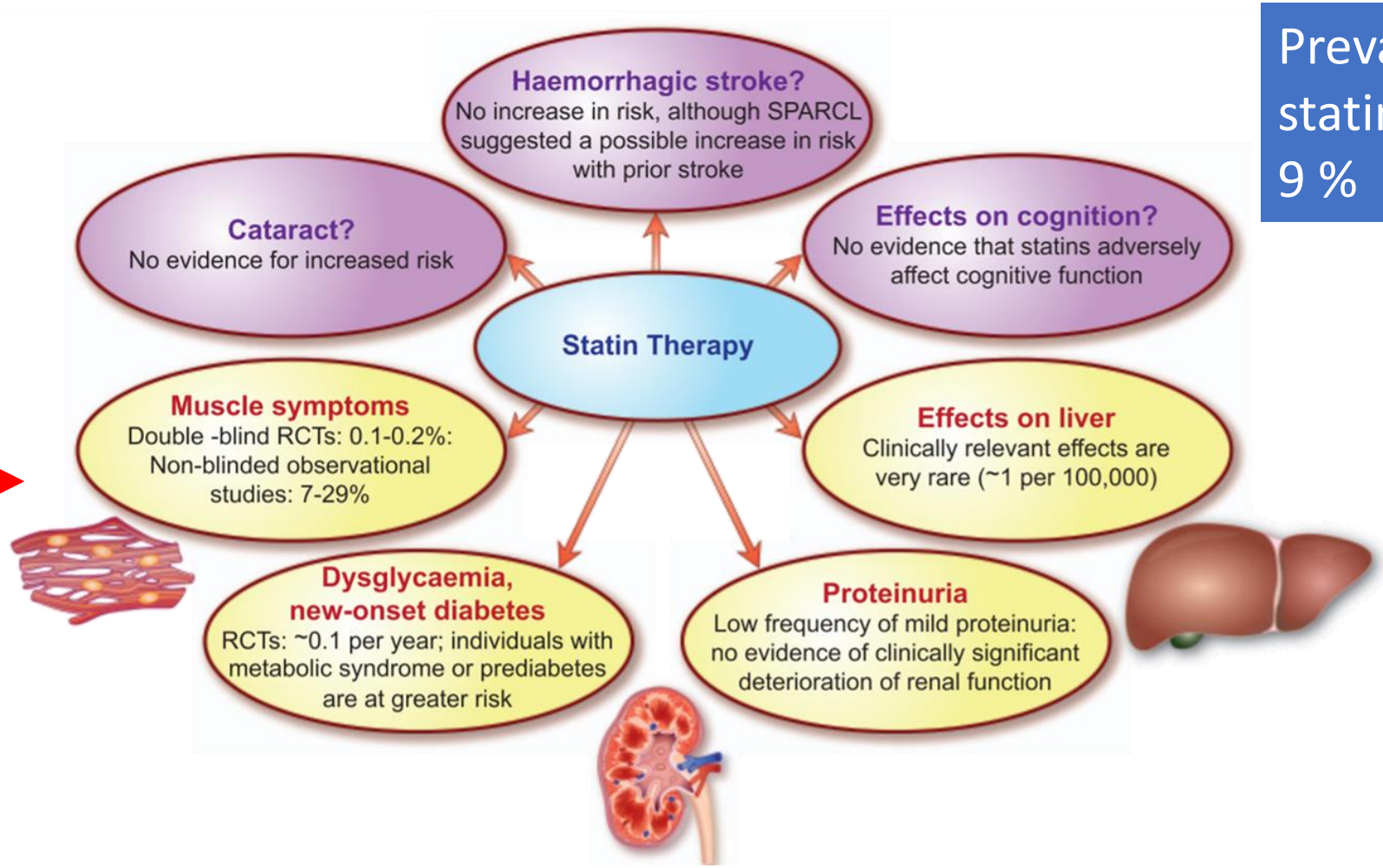
- High intensity statins lower LDL-C, by ≥ 50%
- But only 28% use HIS- Da Vinci Trial

Lancet. 2015;385:1397–1405
European Heart Journal (2017) 38, 2459–2472
European Journal of Preventive Cardiology (2021) 28, 1279–1289

CV benefits of statins outweigh the risk of adverse effects

Prevalance of statin intolerance: 9 %

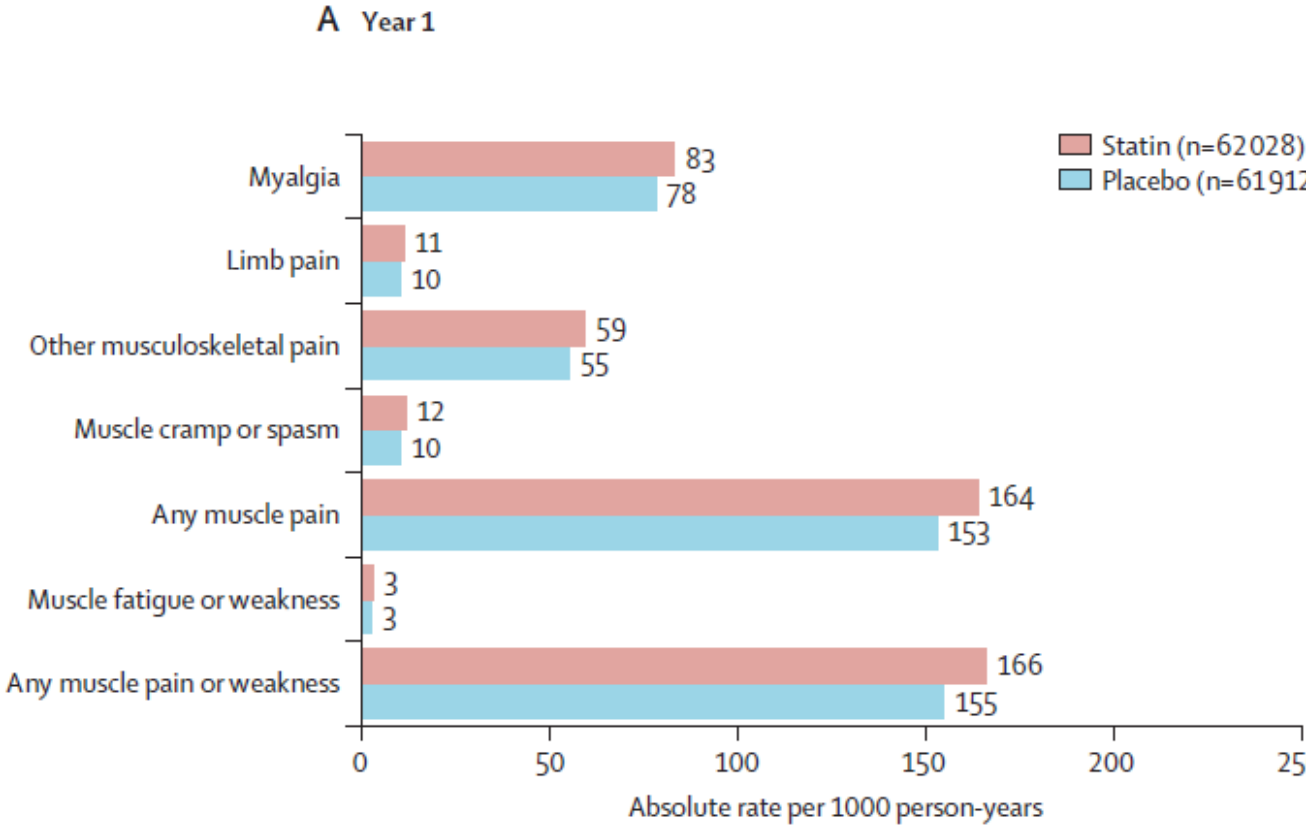
Decrease adherence

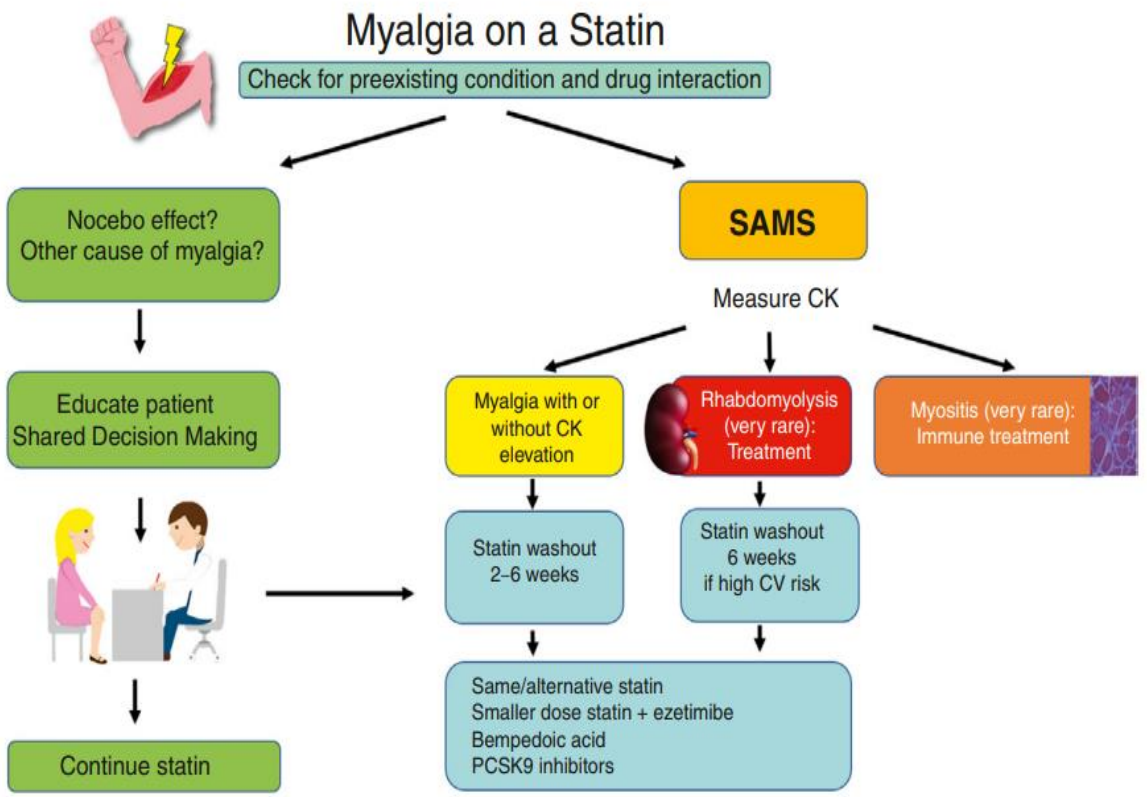


European Heart Journal, 2018;39:2526
European Heart Journal, 2022 ;43 3213–3223

Effect of statin therapy on muscle symptoms

Meta-analysis, 19 RCT, n > 150,000

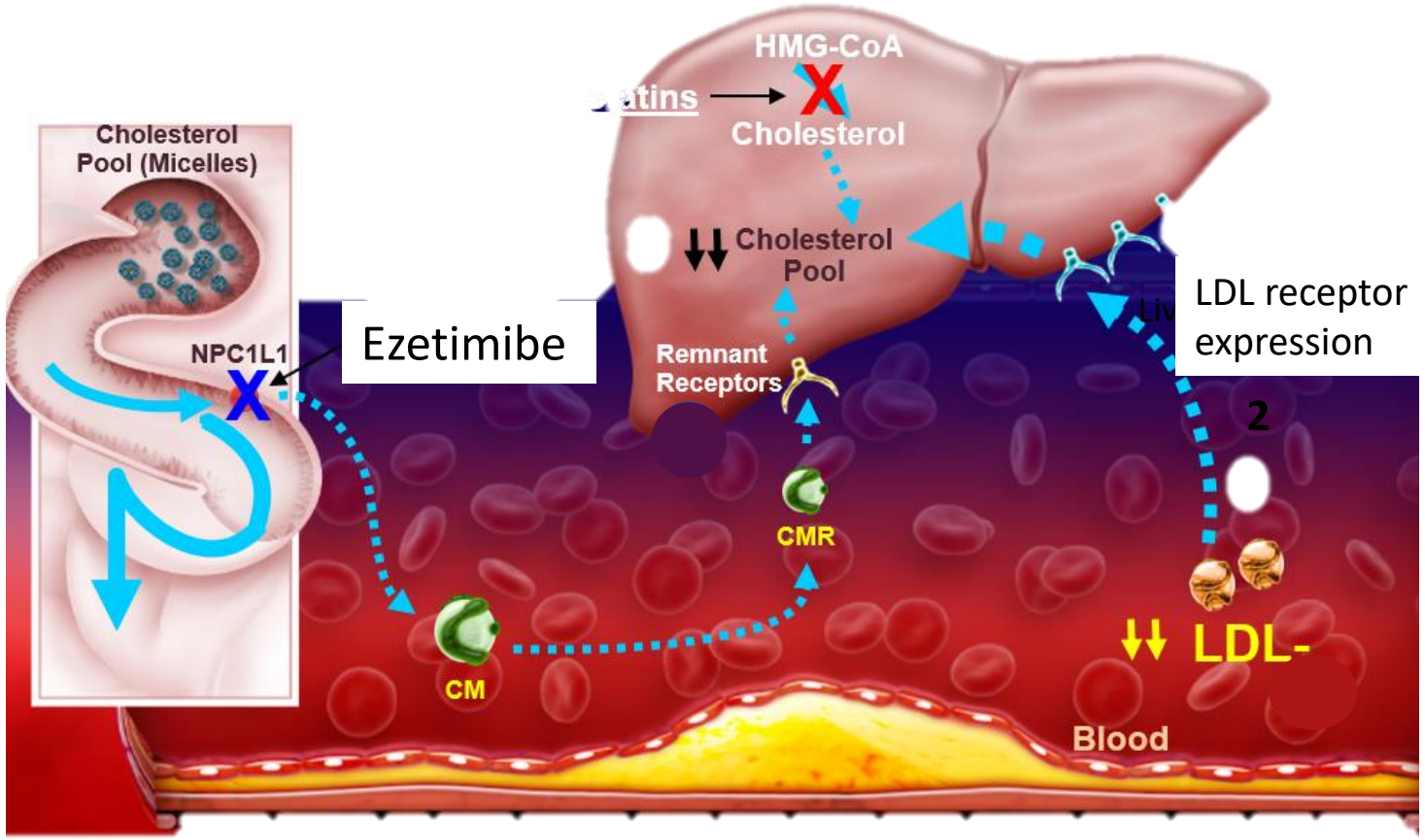




90% of all reports of muscle symptoms were not due to the statin!

Lancet 2022 10.1016/S0140-6736(22)01545-8
Clinical Lipidology: A Companion to Braunwald's Heart Disease, 3rd edition

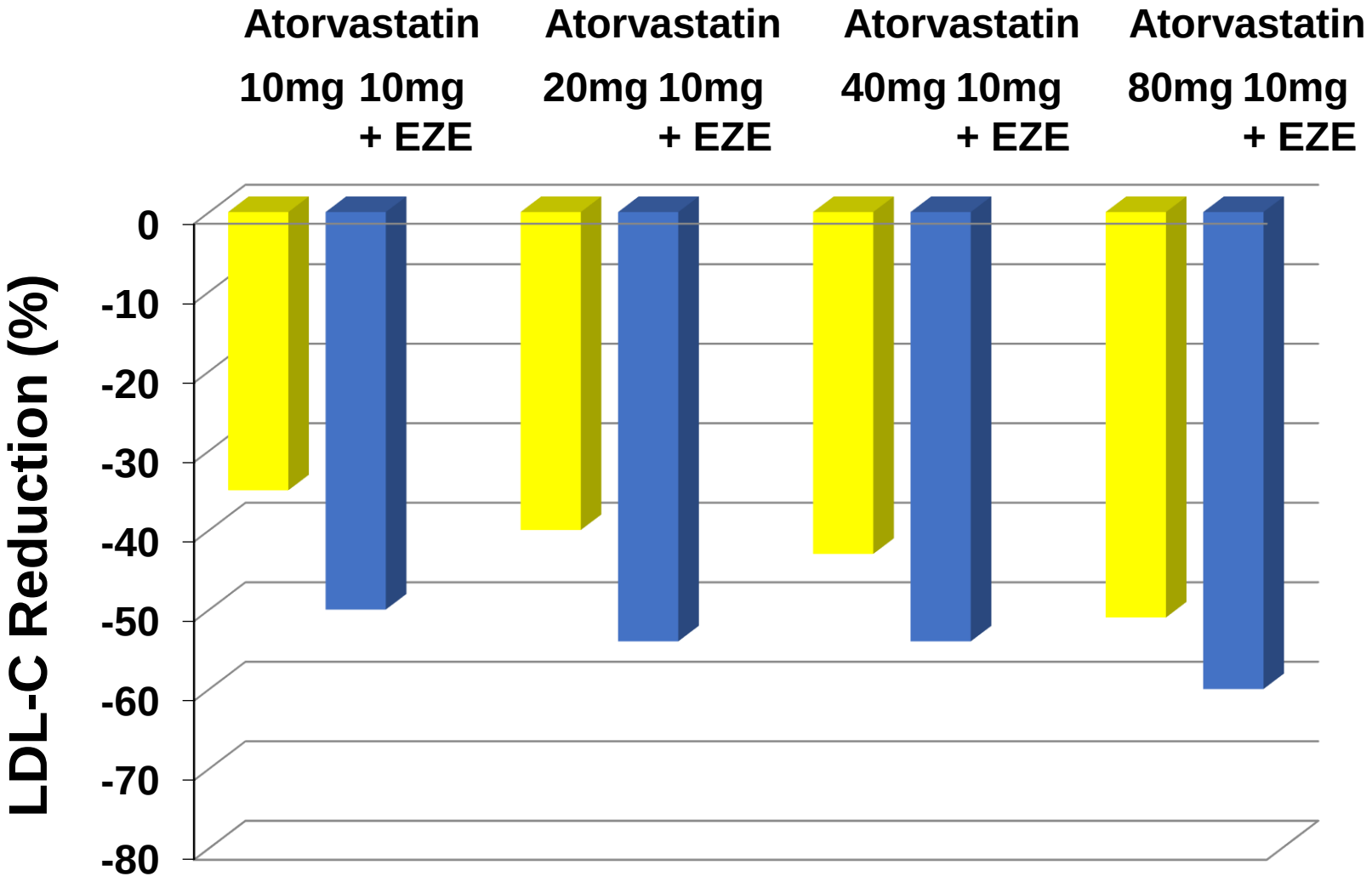
Ezetimibe:



- **Targets the Niemann–Pick C1–like 1 protein, reducing absorption of cholesterol from the intestine**
- **Lowers LDL-C 15-20%**
- **First choice in combination: cheap, safe**
- **First non-statin to improve CV outcomes in IMPROVE-IT**

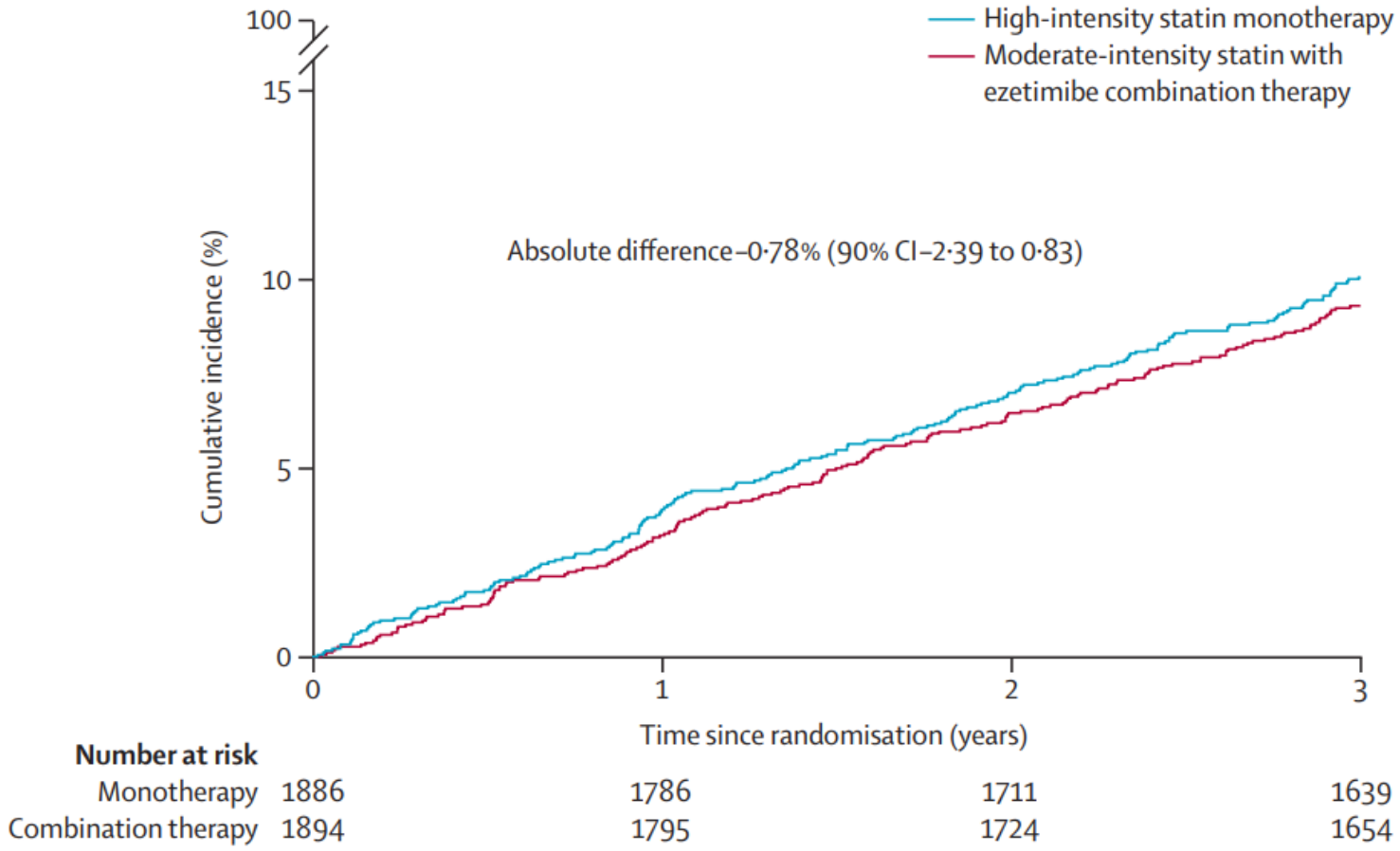
N Engl J Med 2015; 372:2387-2397

Ezetimibe + statin versus statin monotherapy



Int J Clin Pract 2004;58(7):653-8

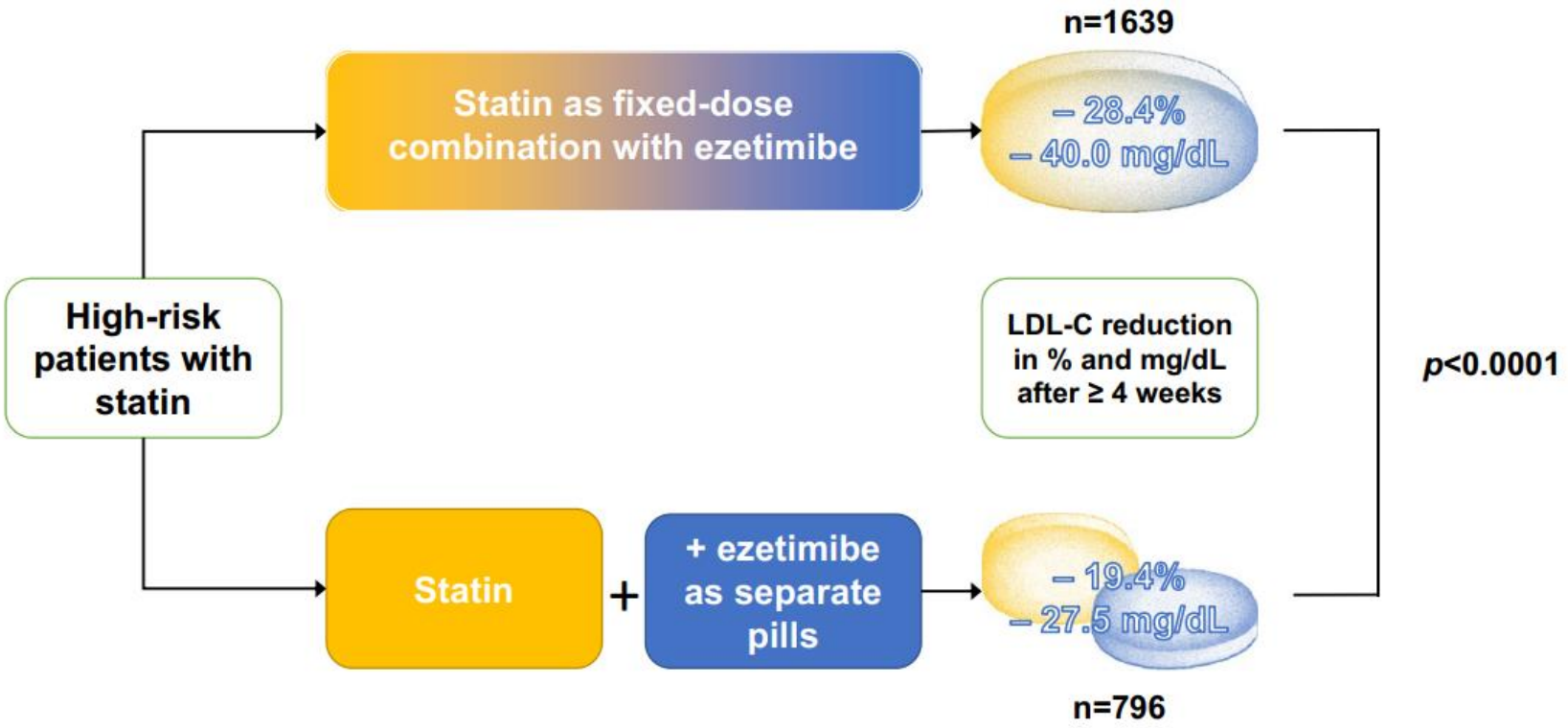
Efficacy and safety of moderate-intensity statin + ezetimibe combination vs high-intensity statin monotherapy in patients with ASCVD (RACING): n=3780



- Combination therapy was non-inferior to high-intensity statin monotherapy
- A higher proportion of patients on combination therapy achieved LDL below 70 mg/dL
- Lower intolerance-related drug discontinuation or dose reduction

Lancet 2022; 400:380-90

Effectiveness of fixed-dose statin/ezetimibe compared to separate pill combination on LDL-C

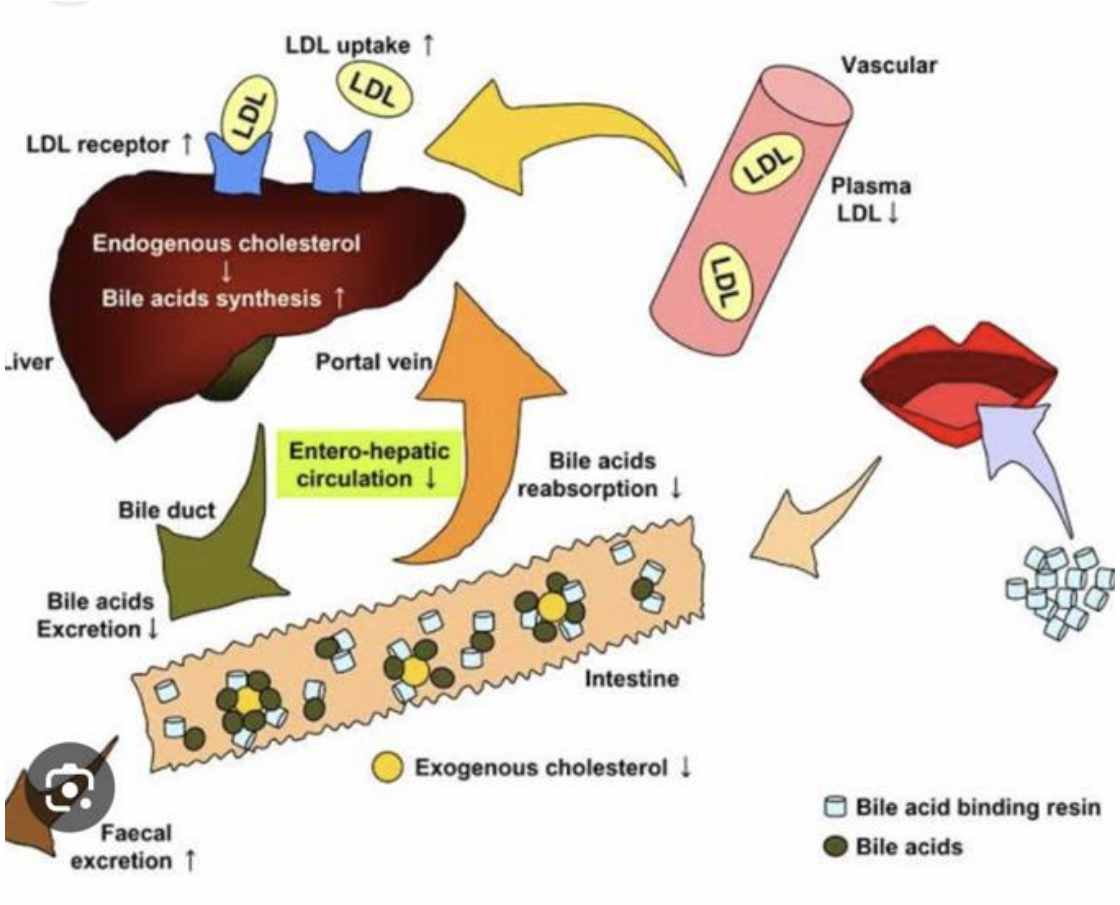


Retrospective analysis of 311,242 patients

Clinical Research in Cardiology (2022) 111:243–252

Bile acid sequestrants

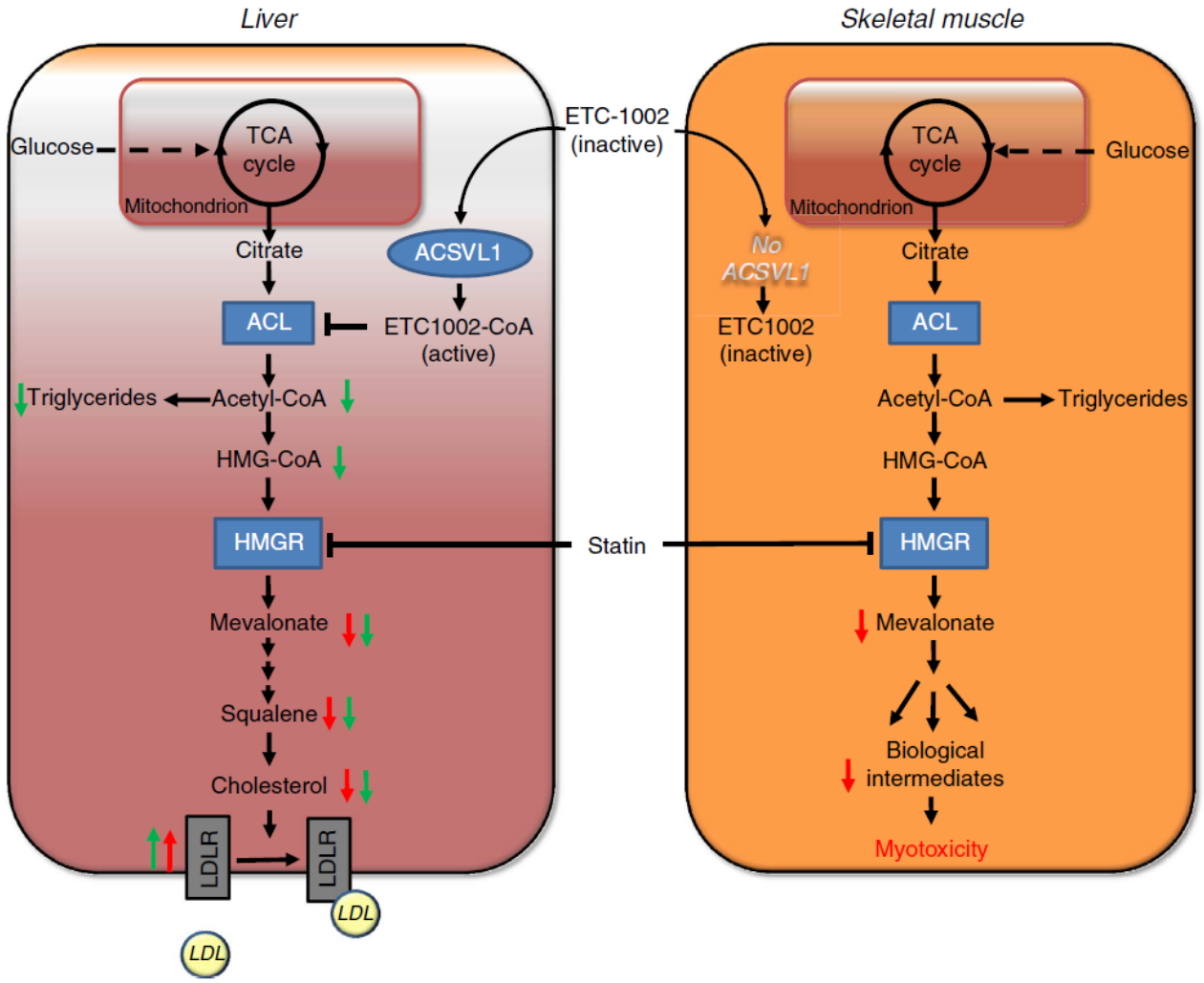
- **Colesevelam, cholestyramine, and colestipol, bind bile acids in the intestine disrupting the enterohepatic circulation of bile acids, and increase fecal excretion.**
- **LDL-C is lowered 12-20%**
- **Gastrointestinal side effects, fat soluble vitamin absorbtion decrease**
- **Not absorbed systemically therefore safe in children and in pregnant women**



Current Vascular Pharmacology 2008: 6(4):271-81

Bempedoic acid

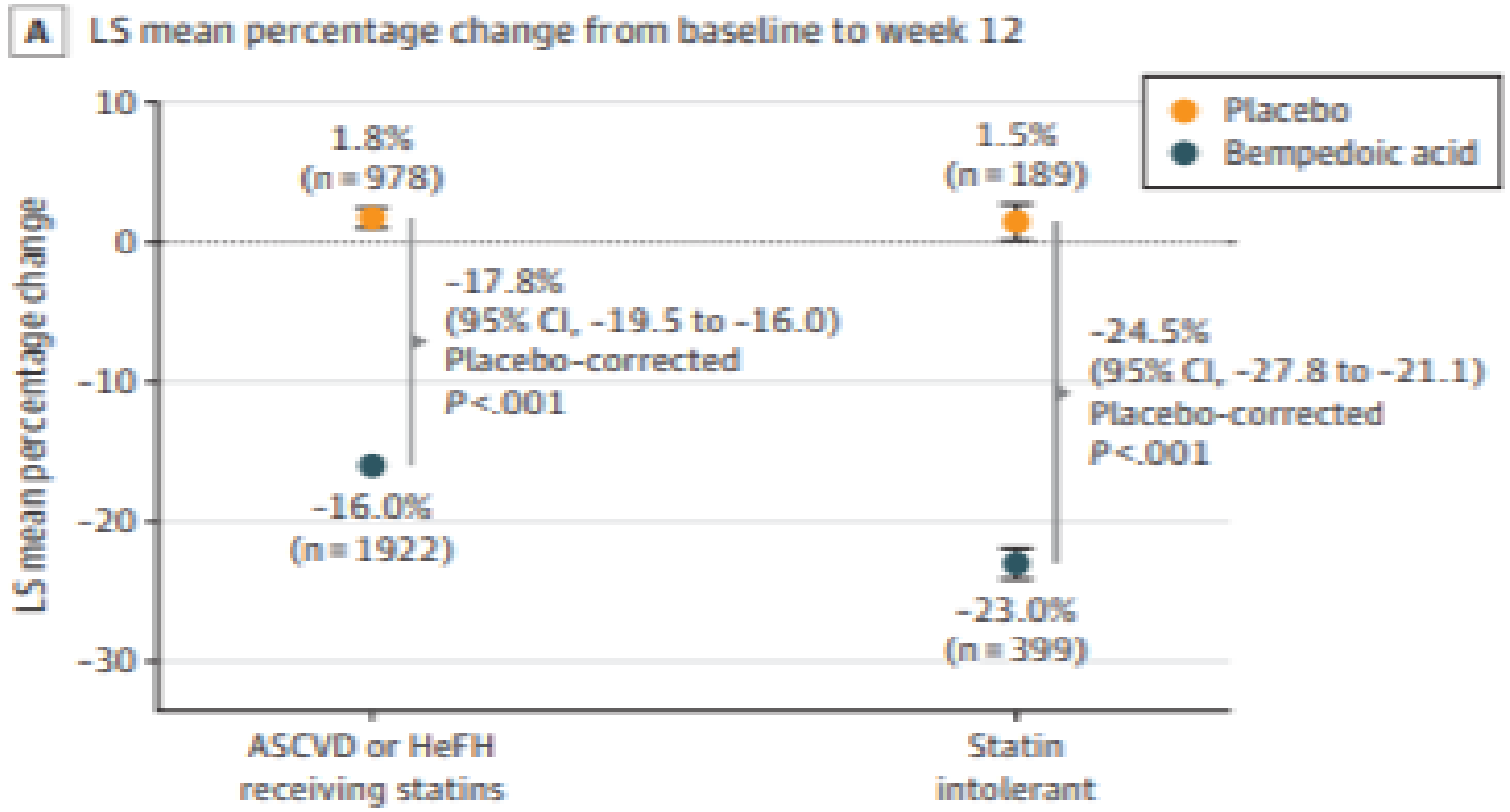
- **Inhibits ATP-citrate lyase an enzyme upstream of HMG-CoA in the cholesterol biosynthetic pathway**
- **Prodrug, the specific isozyme which converts BA into an active form is not present in skeletal muscle, lower muscular side effects**
- **Activates AMP-activated protein kinase**
- **Improves glucose tolerance**
- **Hs-CRP reduced 25 %**



Nature Communications 2016 DOI: 10.1038/ncomms13457

Bempedoic acid and LDL-C lowering: Pooled analysis of phase 3 studies

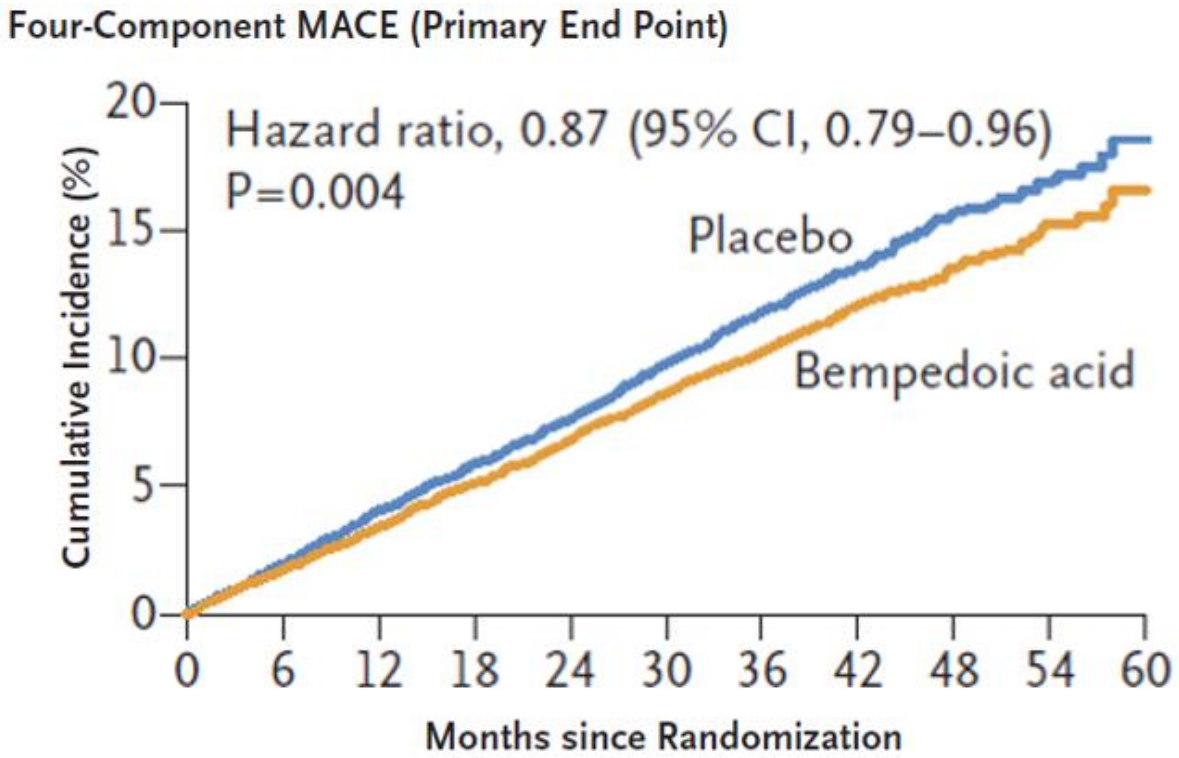
Figure 1. Changes in Low-Density Lipoprotein Cholesterol (LDL-C) Levels Associated With Bempedoic Acid Administration

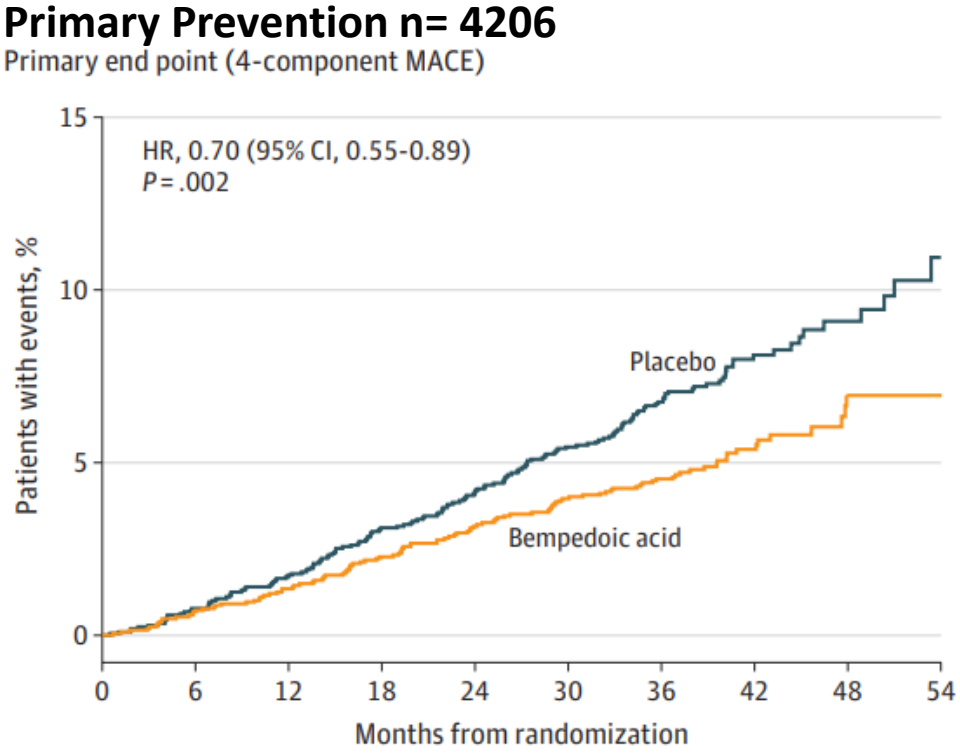


JAMA Cardiol. doi:10.1001/jamacardio.2020.2314

Bempedoic Acid: Cardiovascular Outcomes in Statin-Intolerant Patients

N=13,970; high and very high risk; unable or unwilling to take statins
bemepedoic acid monotherapy vs placebo; 40.6 months

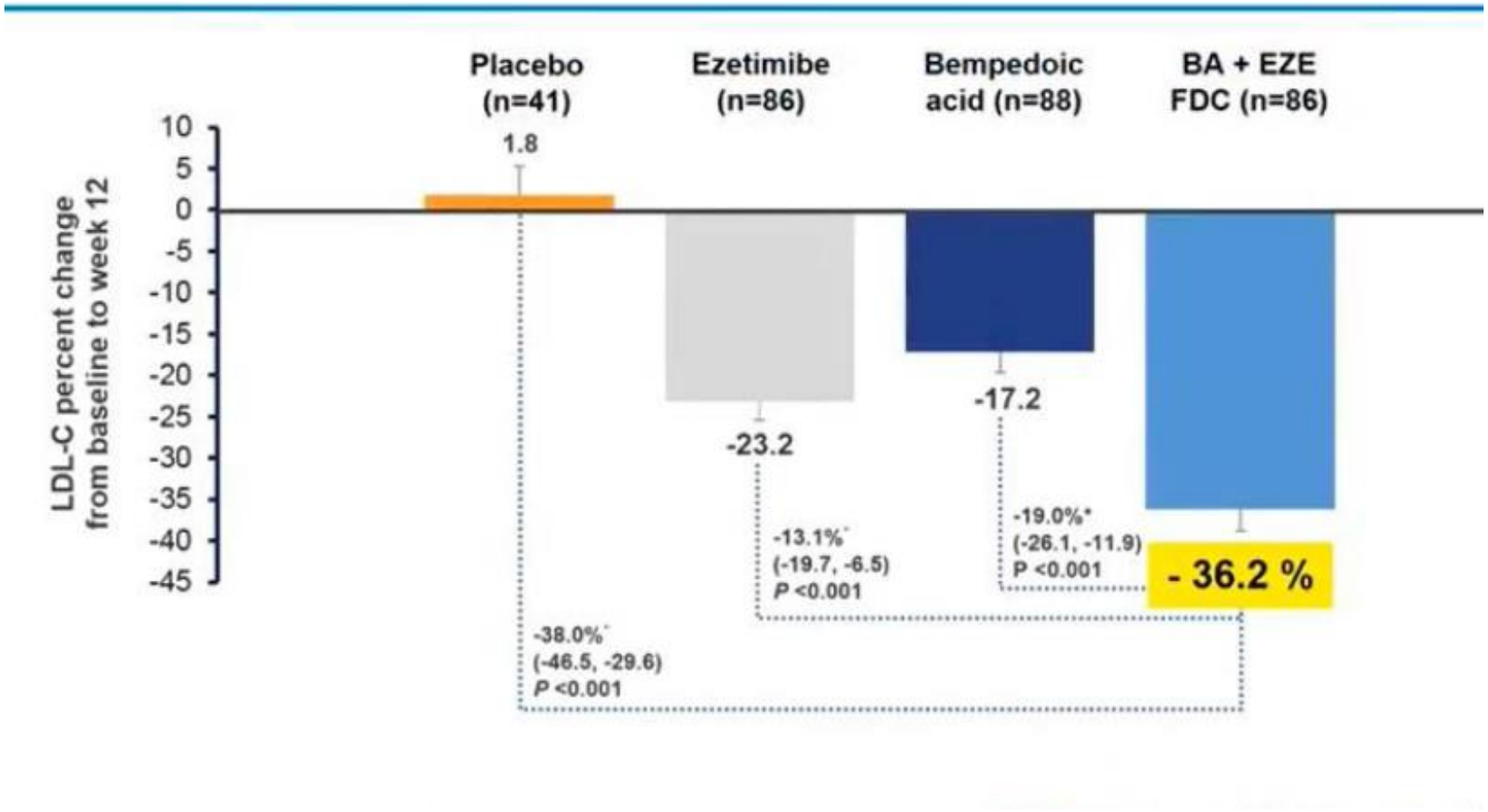




- **LDL-C reduced 22%**
- **MACE-4 reduced by 13%**
- **No increase in DM**
- **Gout, uric acid increased**

NEJM 2023; 388:1353-1364
JAMA 2023; 330(2):131-140

BA + ezetimibe fixed dose combination on top of maximally tolerated statins



Phase III RCT with the fixed-dose combination, bempedoic acid 180 mg, ezetimibe 10 mg or placebo added to stable background statin therapy for 12 weeks

European Journal of Preventive Cardiology 2020, Vol. 27(6) 593–603

Phase 2b Randomized Trial of the Oral PCSK9 Inhibitor MK-0616

- **Synthetic tricyclic peptide binding to PCSK9 1/100th size of MoAb**
- **Resistant to GI degradation**
- **Poorly absorbed, requires permeation enhancer sodium carbanate**

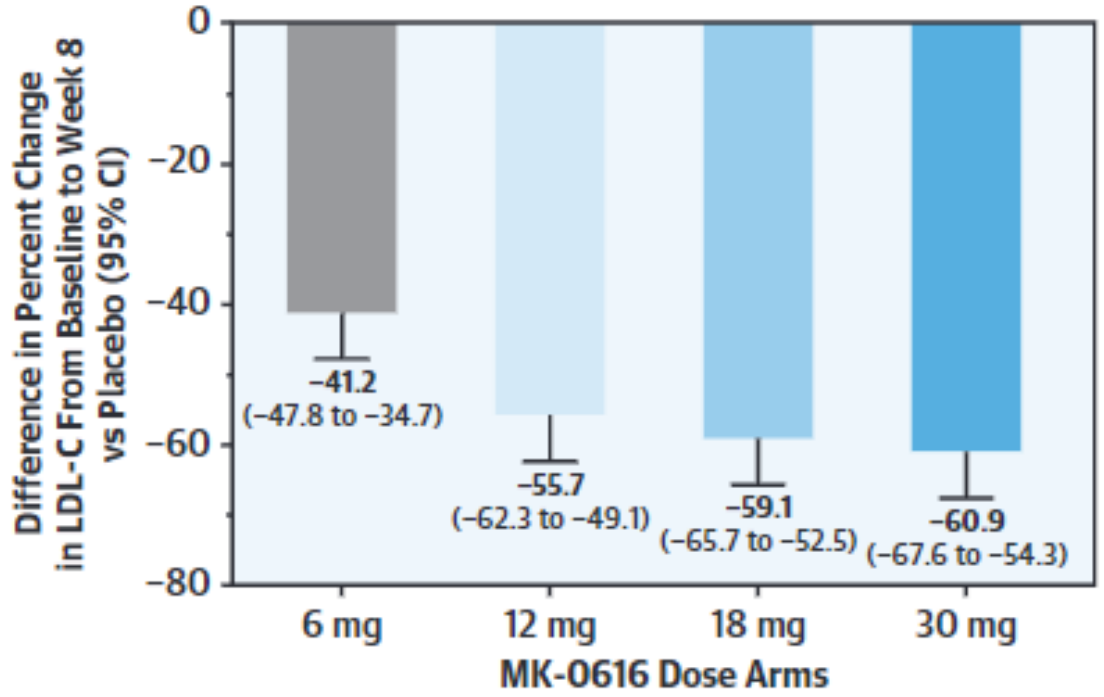
Baseline Participant Characteristics (*n = 381 Randomized Participants*)

Female: 49.3%
Mean LDL-C: 119.5 mg/dL

ASCVD Risk Category:
Clinical ASCVD: 38.6%
Intermediate/High ASCVD Risk: 56.4%
Borderline ASCVD Risk: 4.7%

Statin Intensity:
No Statin: 39.4%
Low-to-Moderate Intensity: 34.6%
High Intensity: 26.0%

Efficacy (*n = 380 Treated Participants*)



Key Points

- All doses of MK-0616 demonstrated statistically superior reductions in LDL-C vs placebo with up to 60.9% placebo-adjusted reduction from baseline values
- MK-0616 was well tolerated with no overall trends in AEs across treatment groups

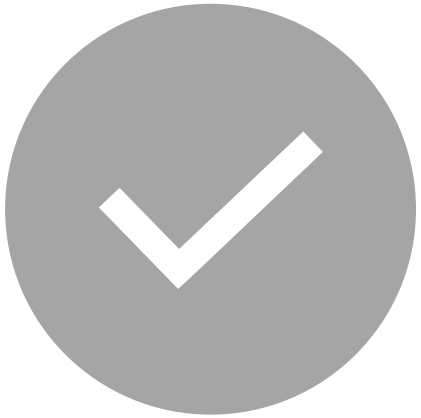
J Am Coll Cardiol 2023; 81 (16) 1553–1564

Oral therapy	Average LDL-C reduction
Low/Moderate-intensity statin	30%
Low-dose statin + ezetimibe	30-40%
Bempedoic acid + ezetimibe in statin naive	45%
High-intensity statin	50%
High-intensity statin + ezetimibe	65%
High-intensity statin + ezetimibe + bempedoic acid	70%

Inn Med 2022;63(12):1316-1322

Conclusion:

LOWERING LDL-C LEVELS IS THE MOST IMPORTANT PHARMACOLOGICAL INTERVENTION TO MITIGATE ATHEROSCLEROTIC CARDIOVASCULAR EVENTS



STATINS WILL STILL BE THE FIRST CHOICE IF TOLERATED

WITH THE NEW OPTIONS, SIGNIFICANT REDUCTIONS IN LDL-C ARE NOW POSSIBLE WITH COMBINATION ORAL THERAPIES