

# **Non-statin therapies for LDL- cholesterol lowering: ezetimibe and bempedoic acid**

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# Disclosures

- Organizations—National Lipid Association (NLA) (past president), President of the Foundation of the NLA (current); Chief Science Officer of the NLA (current)
- Guidelines—ACC/AHA 2013 Cholesterol Guideline, Endocrine Society Triglyceride Clinical Practice guideline, NLA Familial Hypercholesterolemia Recommendations
- Research contracts— Regeneron/Sanofi-Aventis, Amarin, Amgen, Pfizer, IONIS/Akcea, Regeneron, Novartis (all grants to medical school)
- Consulting—Novartis, Akcea, **Esperion**, 23andMe, Regeneron, Sanofi
- Editorial—Merck (Merck Manual)

# Background

- Statins decrease cardiovascular (CV) events
- Many patients at high CV risk have high LDL-C in spite of statin treatment
  - Insufficient response to high-intensity statins: ASCVD, very high baseline LDL cholesterol
  - Inability to take high enough doses of statins due to tolerability issues



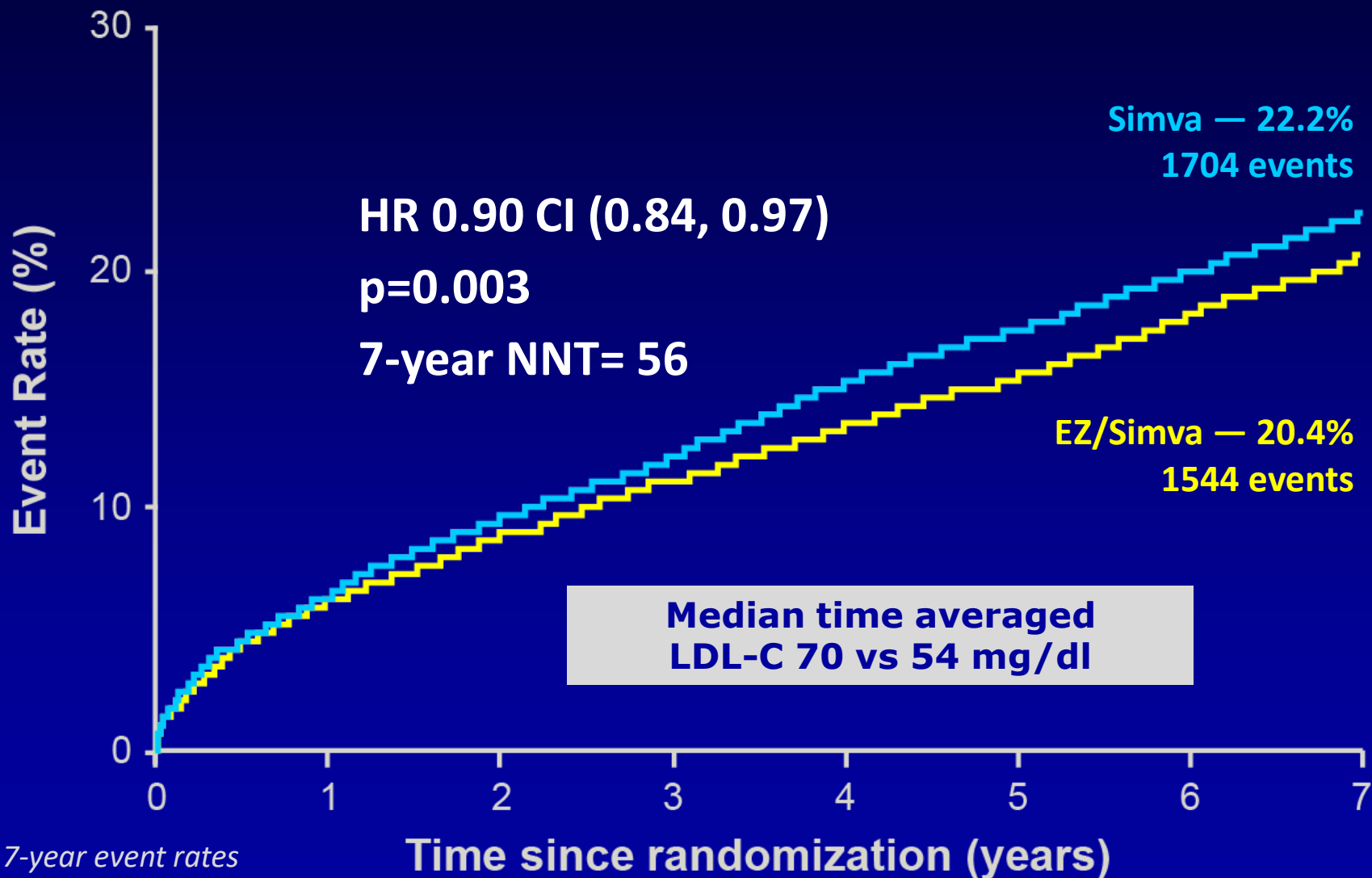
# Ezetimibe

- Cholesterol absorption inhibitor works at the enterocyte brush border—NPC1L1
- Lowers LDL cholesterol by about 15 to 20% (varies)
- Additive with statins
- Few side effects
- IMPROVE-IT CV outcomes trial
- Available as a generic

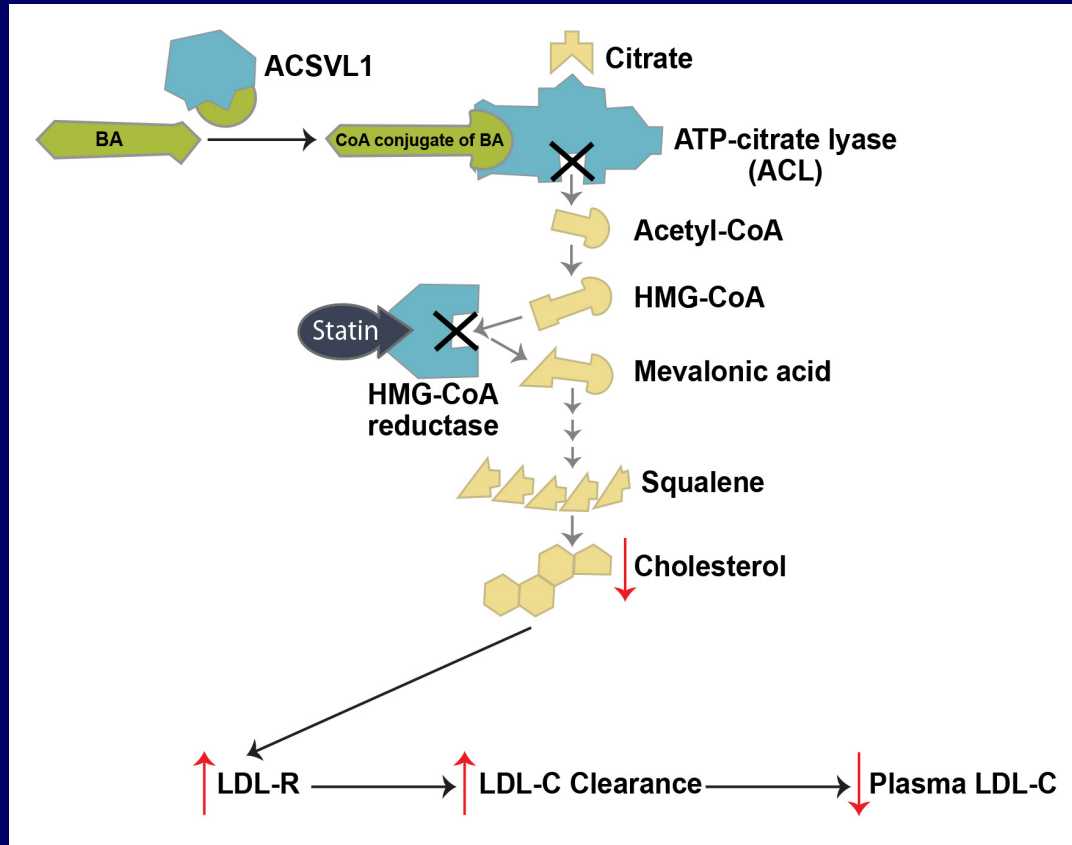


# Interpreting IMPROVE-IT

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



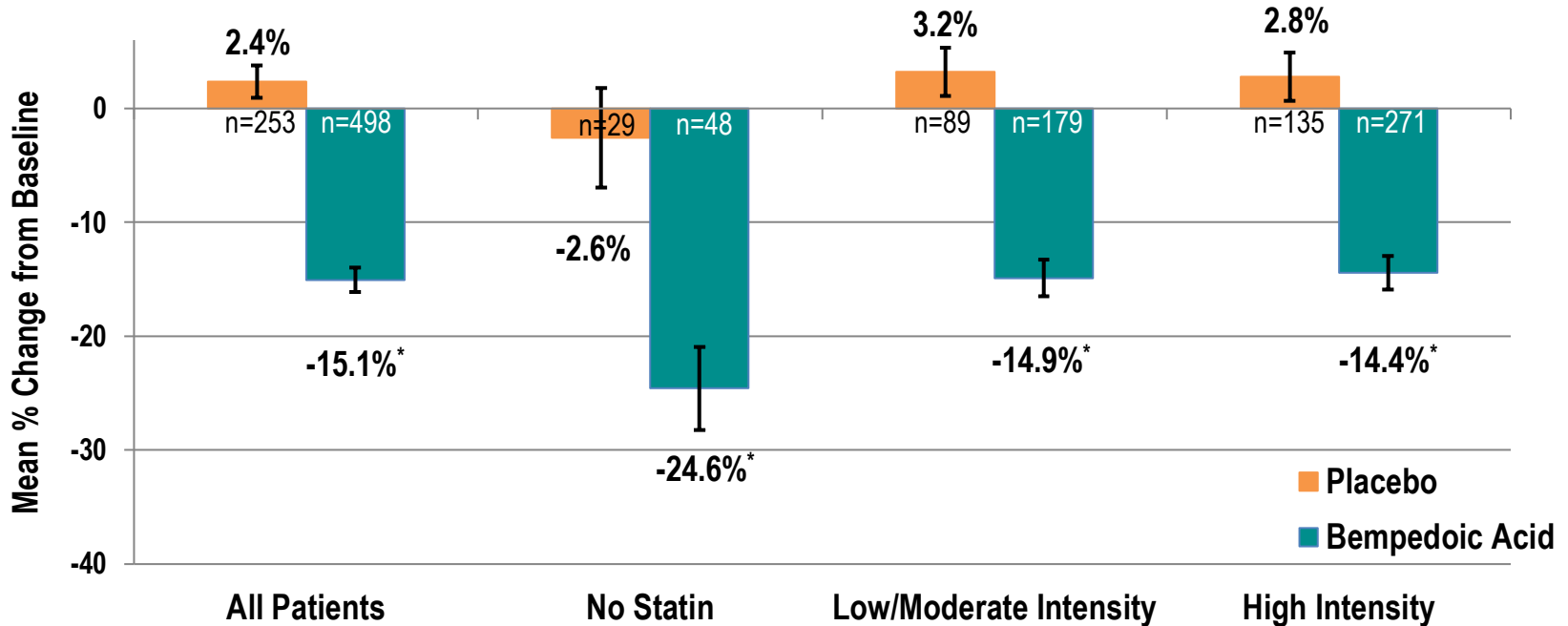
# Bempedoic Acid Mechanism of Action



- Bempedoic acid--prodrug activated in liver by very-long-chain acyl-CoA synthetase-1 (ACSVL1)
- Activated bempedoic acid acts in the same cholesterol synthesis pathway as statins
- Inhibits ATP-citrate lyase (ACL), enzyme upstream of HMG-CoA reductase
- Upregulates LDL receptors
- Activated bempedoic acid is not present in skeletal muscle

# CLEAR Wisdom Efficacy

Percent Change from Baseline to Week 12 in LDL-C (Background Statin Intensity)



\*P < .001 for all comparisons

Mean = least squares mean (standard error).

Goldberg, AC et al. Presented at ACC 2019

# Bempedoic acid

- Inhibitor of ATP citrate lyase
- 15 to 25% reduction in LDL-C levels—possibly more in patients not on statins
- Combination of bempedoic acid and ezetimibe lowers LDL-C about 35%
- Active in the liver only
- Overall good tolerance: uric acid increase, concern for tendon rupture
- Cardiovascular outcomes trial in progress





# Use of these non-statin therapies

- Patients on maximally tolerated statin above thresholds
- “Statin intolerant” patients
- Patients with familial hypercholesterolemia
- Patients averse to or intolerant of injectable therapies



Thank you!



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