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Update On LDL-C Lowering With Statins And Other Drugs Stabilizes And Shrinks Plaques And Decreases Morbid Vascular Events: Stopping Statins Increases Patients' Risk Of MI And Death

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Philips • Biotronik • Amgen • Medtronic Structural
• Consulting Fees/Honoraria	• Abbott Vascular • Boston Scientific Structural • PI CARDIA • MedAlliance

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Prevalence of ASCVD in the United States

In the United States, as of 2020, an estimated[1-4]

30.2 million were living with some form of ASCVD

19.03 million were receiving statin therapy for some form of ASCVD

15.17 million receiving statin therapy for some form of ASCVD were not at the ACC/AHA-recommended goal of LDL-C <70 mg/dL

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.
1. Wong ND et al. *J Clin Lipidol.* 2016;10(5):1109-1118; 2. Selvin E, Hirsch AT. *Atherosclerosis.* 2008;201(2):425-433; 3. Benjamin EJ et al. *Circulation.* 2019;139(10):e56-e528; 4. Choi CI, Brandt, N (2019). *Dyslipidemia/Atherosclerosis 2021-2030.* 2Q ed. Ser:2021:54-61.

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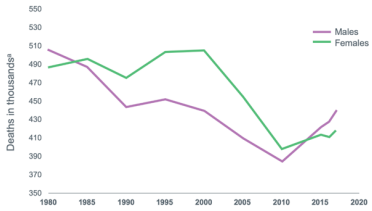
Cardiovascular disease deaths have increased in recent years in the US

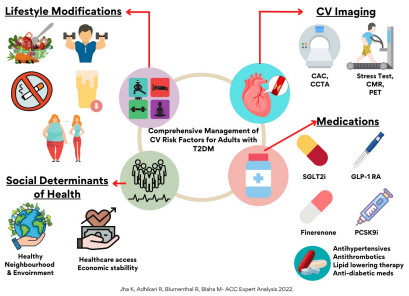
DEATHS ATTRIBUTABLE TO CARDIOVASCULAR DISEASE (US, 1980-2017)



*The data are from the US Centers for Disease Control and Prevention and represent the US population.

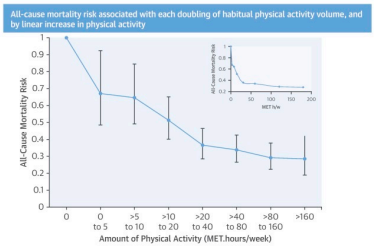
Step 1:
Lifestyle Modification

2022 AHA Statement on the Comprehensive Management of CV Risk Factors For Adults With T2DM



Jha K, Ashkiari R, Blumenthal R, Blaha M- ACC Expert Analysis 2022.

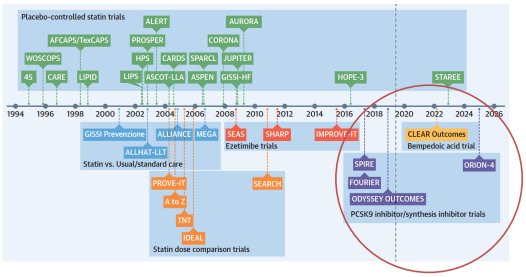
Physical Activity and Mortality in Stable CAD
Good but Not Enough



Stewart, R.A.H. et al. J Am Coll Cardiol. 2017;70(14):1689-700.

Pharmacotherapy

Key Trials in the Lipid Space



Available LDL Cholesterol Lowering Therapies

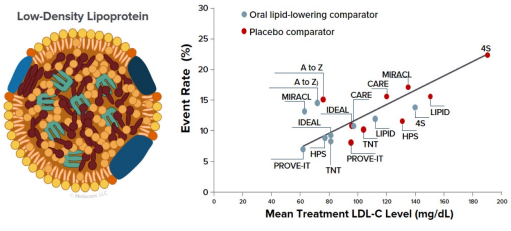
Name	Drug Target	Phase	Indication/In Use For	Effect on LDL-C	Known Safety Issues
Statins	HMGCR	Approved	All patients	20% to 50%	Rhabdomyolysis
Ezetimibe	NPC1L1	Approved	All patients	~23%	Not known
PCSK9i antibody	PCSK9	Approved	Secondary prevention; FH	~47%	Not known
Mipomersen	ApoB100 mRNA	Approved, FDA only	HoFH	26%	Liver toxicity, injection-site reactions, flu-like symptoms
Lomitapide	MTP	Approved, with registry	HoFH	40% to 50%	Liver toxicity, GI side effects
Bempedoic acid	ACL	Approved	Statin-intolerance; 3rd agent after statin/ezetimibe	17% to 21%	Gout, tendon rupture
Inclisiran	PCSK9 mRNA	Approved	NA	~50%	Mild injection-site reactions
Evinacumab	ANGPTL3	Approved	HoFH	~49%	Elevated liver enzymes

ACL = ATP citrate lyase; ANGPTL3 = angiopoetin-like 3 protein; apoB = apolipoprotein B; CETP = cholesteryl ester transfer protein; FDA = Food and Drug Administration; HMGCR = 3-hydroxy-3-methylglutaryl-coenzyme reductase; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein; MTP = microsomal triglyceride transfer protein; NPC1L1 = Niemann-Pick-like protein 1C1; PCSK9i = proprotein convertase subtilisin kexin type 9 inhibiting.

CRT24

Nurmohamed NS, et al. J Am Coll Cardiol. 2021;77(12):1564-75

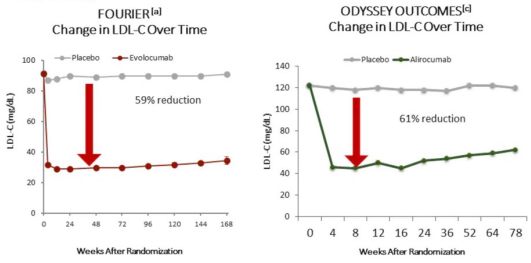
LDL Is the Causative Agent in Atherosclerosis and Lowering LDL-C Decreases Events



Raymond C, et al. Clev Clin J Med. 2014;81:11-19; Cholesterol Treatment Trialists' (CTT) Collaboration. Lancet. 2010;376:1670-1681.

Results of PCSK9 Inhibitors on LDL-C Levels
FOURIER and ODYSSEY OUTCOMES

- PCSK9 inhibitor use in high-risk patients reduced LDL-C levels from baseline by 50% to 60%[a,b]



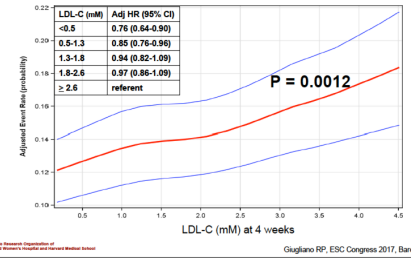
a. Sabatine M, et al. *N Engl J Med.* 2017;376:1713-1722; b. Steg PG, et al. *N Engl J Med.* 2018;379:2097-2107; c. Robinson JG, et al. *N Engl J Med.* 2015;372:1489-1499.

LDL-C lower is better

fourier

CV Death, MI, Stroke, UA, or Coronary Revasc

LDL-C (mM)	Adj HR (95% CI)
<0.5	0.76 (0.64-0.90)
0.5-1.3	0.85 (0.76-0.96)
1.3-1.8	0.94 (0.82-1.09)
1.8-2.6	0.97 (0.86-1.09)
≥ 2.6	referent



Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017

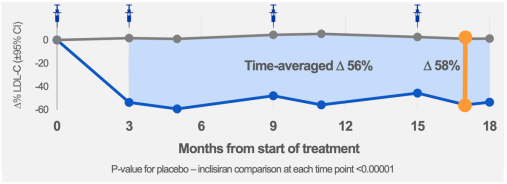
RNA Based Therapy to reduce LDL

Two injections a year

ORION-10: Efficacy

Durable and potent with consistent effect over 18 months

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

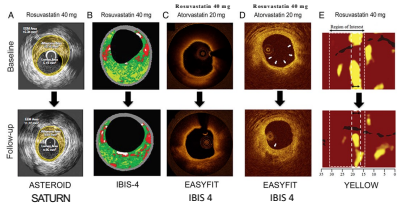


P-value for placebo – inclisiran comparison at each time point <0.00001

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

Can we modify high risk plaques by Statins and PCSK9?

Updated according to Koskinas KC, Räber L. Eur Heart J 2016

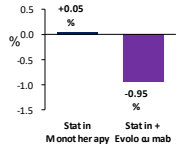


ASTEROID SATURN	IBIS-4	EASYFIT IBIS 4	EASYFIT IBIS 4	YELLOW
Plaque volume Regression LDL-C < 1.8mmol/L	Stabilization of necrotic core	Fibrous cap thickening Reduction of inflammation		Reduction of lipid content

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: GLAGOV

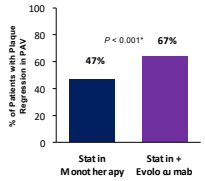
Nicholls et al. JAMA 2016. 316(22):2373-2384

1° Endpoint PAV @18months



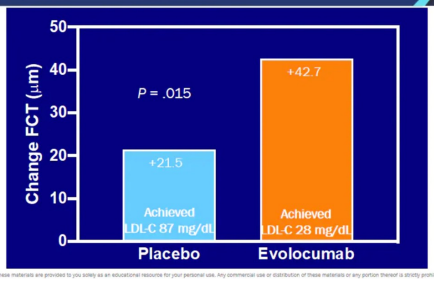
Δ -1.0% (-1.8 to -0.64), p<0.001

Regressors according to PAV



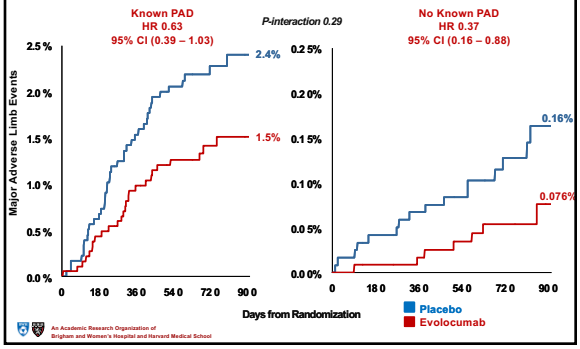
HUYGENS Primary Endpoint

Minimum Fibrous Cap Thickness



Nicholls S, et al. Presented at: ESC Congress 2021 – The Digital Experience; August 27-30, 2021. Late breaking presentation.

Major Adverse Limb Events in Patients with and without Known PAD



Discontinuing Statin Associated with Cardiovascular Events

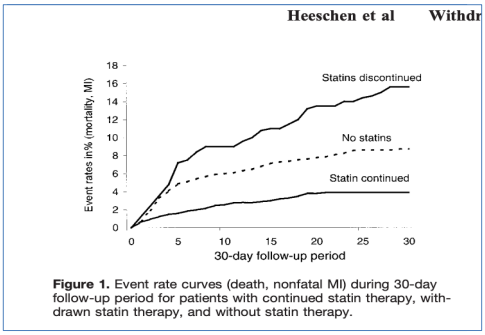
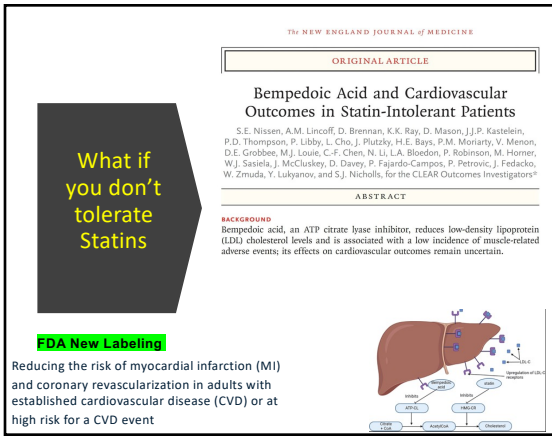


Figure 1. Event rate curves (death, nonfatal MI) during 30-day follow-up period for patients with continued statin therapy, with-drawn statin therapy, and without statin therapy.

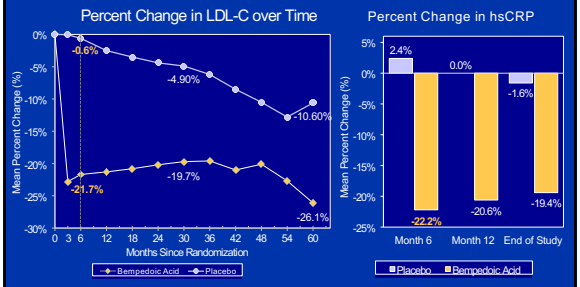
What if you don't tolerate Statins



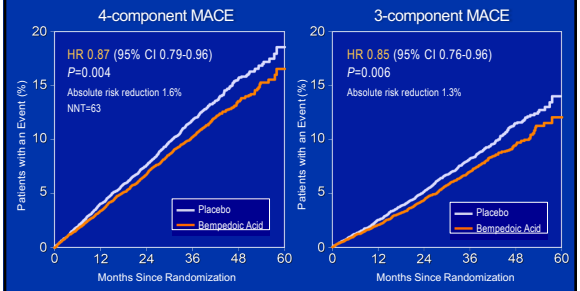
FDA New Labeling

Reducing the risk of myocardial infarction (MI) and coronary revascularization in adults with established cardiovascular disease (CVD) or at high risk for a CVD event

Effect of Trial Regimens on LDL-C and hsCRP



Primary and First Key Secondary Cardiovascular End Points

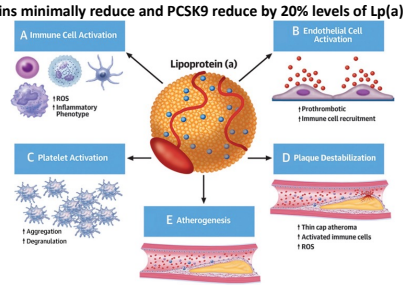


Lipoprotein(a) The new Kid in the Block

Why we care?

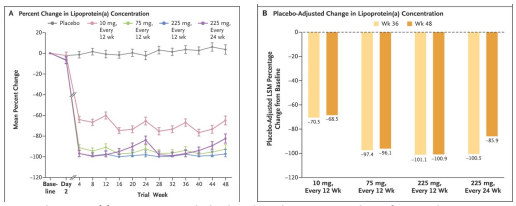
One in 5 have high levels of Lp(a)

Statins minimally reduce and PCSK9 reduce by 20% levels of Lp(a)



Rosenson RS et al. J Am Coll Cardiol 2021; 78:434-436.

Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease



Percent Change in Lp(a) Concentration and Placebo-Adjusted Mean Percent Change from Baseline in the Lp(a) Concentration with Olpasiran at Weeks 36 and 48

O'Donoghue ML, Rosenson RS, et al. N Engl J Med 2022. DOI:10.1056/NEJMoa2211023

Phase 2 Trial of Zerlasiran: Multiple doses of an siRNA Targeting Lipoprotein(a) over 60 weeks

Steven E. Nissen MD MACC

Qiuqing Wang, MS; Stephen J. Nicholls MBBS PhD; Ann Marie Navar, MD PhD; Kausik K Ray, MD, MPhil; Gregory G. Schwartz MD, PhD; Michael Szarek, PhD; Erik S.G. Stroes, MD, PhD; Roland Troquay, MD; Jannick A.N. Dorresteijn, MD PhD; Henry Fok, MBBS, PhD; David A. Rider, PhD; Steven Romano, MD; Kathy Wolski, MPH; and Curtis Rambaran MBBS MD

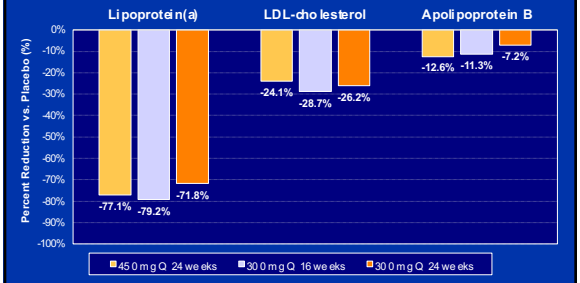
Disclosure

Consulting: Many pharmaceutical companies

Clinical Trials: AbbVie, Arrowhead, AstraZeneca, Bristol Myers Squibb, Encarda, Eli Lilly, Esperion, Medtronic, New Amsterdam, Novartis, Silence Therapeutics.

Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor a tax deduction is received.

Mean Time-Averaged Changes after Zerlasiran : Baseline to 60 Weeks



Take home points and Final Punch

- **LDL is the garbage of lipid metabolism**
- **Lifestyle management is welcome but not sufficient to reduce LDL-C and CVD events**
- **Data from large randomized studies: Furrier, Odyssey, and Orion 10 supports that dropping LDL-C reduce cardiovascular events including in patients with PAD**
- Statin and PCSK9 reducing the lipid core within the plaque and Shrink it per intravascular imaging by OCT IVUS and NIRS
- Discontinuation of these drugs results with increase of events
- Elevated Lp(a) is a common independent atherosclerotic CVD risk factor that should be measured.
- If you have high LDL-C and not taking these agents you are in denial

Thank you for your attention