Novel Lipid Therapies in Cardiovascular/Stroke Reduction

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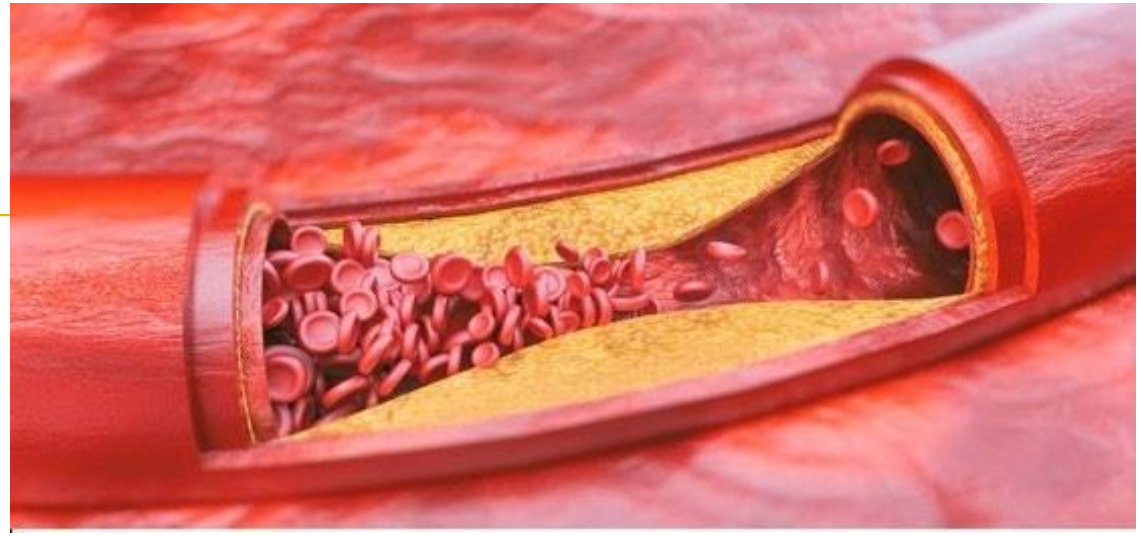
Disclosures

- Speaker’s Bureau: Esperion, Amgen
- Advisory Board: Esperion, Novartis, Amgen
- Honoraria: Medscape
- Consulting Fees: Amgen, Novartis

Objectives

- Real life: 68 year old Hispanic male with ASCVD
- Approach to managing secondary prevention in very high risk patients.
- Assess Pharmacologic Non-Statin Options for Reducing LDL-C.
- Review evolving data on plaque morphology with PCSK9 inhibitors.
- Assess parallel Risk Reduction
- Review triglycerides as risk

Patient Case: Jose´



68-year-old Hispanic male with ASCVD

HPI:

- NSTEMI in his early 60s
- Complicated by HFrEF (LVEF 35%)
- Hospitalized when diagnosed with HFrEF but not since then

Medical History:

- HTN
- HL
- DM II
- SIHD (NSTEMI)
- HFrEF (LVEF 35%)
- CKD (G3A2)

Social History:

- Denies smoking (quit after MI)
- Denies alcohol
- Does not Exercise
- Low Sodium Diet
- Lives with wife who prepares meals

Allergies: NKDA

FH: premature ASCVD

Medications:

- Sacubitril/Valsartan 97/103 mg BID
- Lisinopril 20 mg BID
- Metoprolol Succinate 200 mg QD
- Furosemide 20 mg QD
- Spironolactone 25 mg QD
- Metformin 1000 mg BID
- Insulin Glargine 25U QD
- Atorvastatin 20 mg (myalgia on 40mg)
- Ezetimibe 10 mg

Patient Case: Jose´

68-year-old Hispanic male with ASCVD

Physical Exam:

- BP 138/84 (home BP average is 135/83 mm Hg)
- HR 58 beats/min
- Height 68 inches, weight 220 lbs (dry weight)
- BMI 33.4 kg/m^2
- no signs or symptoms of fluid overload

LIPID PANEL

Test Name	Units	Ref. Range	Result	
			3 months ago	Today
TOTAL CHOLESTEROL	mg/dL	0-200	185	180
HDL-C	mg/dL	40-60	35	40
TRIGLYCERIDES	mg/dL	0-150	250	225
LDL-C	mg/dL	0-130	100	95

Echo: LVEF 35% **HbA1c:** 8.9% to 9.1%

Comprehensive Metabolic Panel

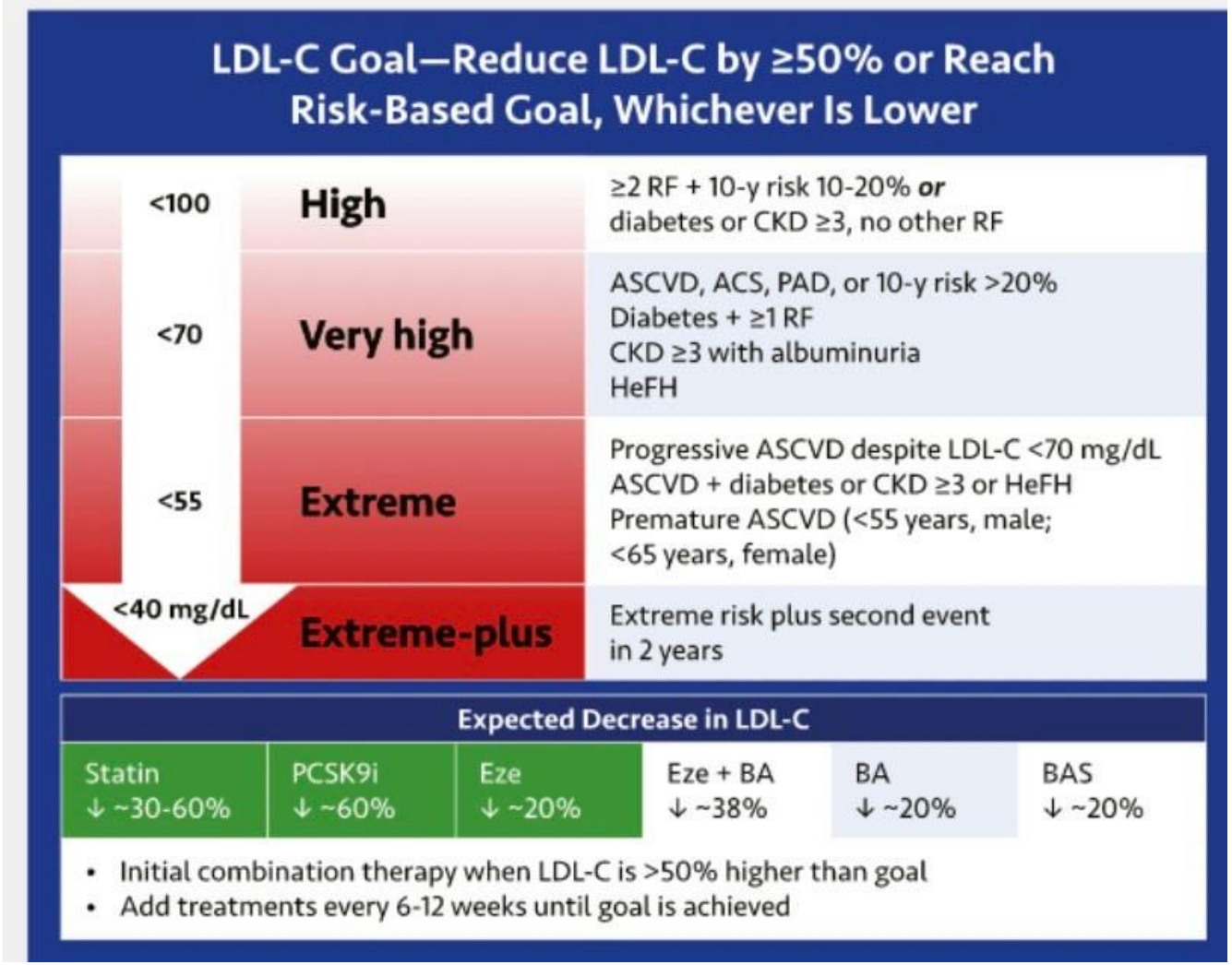
Test Name	Units	Ref. Range	Result	
			3 months ago	**Today**
NA	mmol/L	133-145	141	141
K	mmol/L	3.5-5.0	4.7	4.8
CL	mmol/L	96-108	100	102
BUN	mg/dL	6-23	20	21
CREAT	mg/dL	0.6-1.1	1.48	1.43
GLU R	mg/dL		169	174
CA	mg/dL	8.4-10.2	8.7	9.0
AST	U/L	0-47	33	31
ALP	U/L	39-117	90	50
PROT TOT	g/dL	6.8-8.8	8.1	7.2
BILI T	mg/dL	0.0-1.0	0.5	0.6
CO2	mmol/L	22-29	25	26
ALT	U/L	0-47	30	32
ALB	g/dL	3.4-5.0	3.8	4.0
Uric Acid	mg/dL	4.0-6.0	6.0	6.1
eGFR	mL/min/1.73m^2		51	53

SPOT URINE ALBUMIN/CR

			3 months ago	Today
ALBUMIN/CREATININE	mg/G	0-30	45	50

Management of Lipids in Diabetes, Cardiorenal, and Metabolic Diseases

Monitor Lipids Every 6-12 Weeks Until Individual Target Is Achieved



Proven ASCVD benefits in CVOTs

• IPE, EPA, or EPA+DHA.

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; BA = bempedoic acid; BAS = bile acid sequestrant; CKD ≥3 = stage 3 chronic kidney disease; CVOT = cardiovascular outcome trial; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; Eze = ezetimibe; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; IPE = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol; OM3 = prescription-strength omega-3 fatty acid; PAD = peripheral artery disease; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; Pio = pioglitazone; RF = major risk factors (ie, advancing age, elevated non-HDL-C, elevated LDL-C, low HDL-C, diabetes, hypertension, CKD, cigarette smoking, family history of ASCVD); TG = triglyceride.

Handelsman et al. J Diabetes Complications. 2022; 36(2):108101

Guideline Recommendations Endorse Even Lower LDL-C Goals

2018 AHA/ACC guidelines[1]	2019 ESC/EAS guidelines[2]	2019 ADA guidelines[3]	2017 AACE/ACE guidelines[4]
Clinical ASCVD	LDL-C reduction	Diabetes and ASCVD	Very high CV risk†
LDL-C reduction	**≥50%**	LDL-C reduction to	LDL-C reduction to
≥50%	AND	**<70** mg/dL	**<70** mg/dL
Very high-risk ASCVD*	High CV risk	(**1.8** mmol/L)	(**1.8** mmol/L)
LDL-C reduction to	LDL-C reduction to		Extreme CV risk‡
<70 mg/dL	**<70** mg/dL		LDL-C reduction to
(**1.8** mmol/L)	(**1.8** mmol/L)		**<55** mg/dL
	Very high CV risk		(**1.4** mmol/L)
	LDL-C reduction to		
	<55 mg/dL		
	(**1.4** mmol/L)		

AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACE, American College of Endocrinology; ACS, acute coronary syndrome; ADA, American Diabetes Association; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. †Very high risk includes established or recent hospitalization for ACS, coronary, carotid, or peripheral vascular disease, 10-year risk >20%, diabetes or CKD 3/4 with 1 or more risk factor(s), and HeFH. ‡Extreme risk includes progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL, established clinical CVD in patients with DM, CKD 3/4, or HeFH, and history of premature ASCVD (<55 male, <65 female).

1. Grundy SM et al. *Circulation*. 2019;139:e1082-e1143; **2.** Mach F et al. *Eur Heart J*. 2020;41(1):111-188; **3.** Chamberlain JJ et al. *Ann Intern Med*. 2018; 168(9):640-650; **4.** Jellinger PS, et al. *Endocr Pract.* 2017;23(suppl 2):1-87.

Table 4. Very High-Risk* of Future ASCVD Events (Table view)

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation[S4.1-40])
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)[S4.1-15,S4.1-17]
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

Grundy SM et al. *Circulation*. 2019;139:e1082-e1143

ASCVD/Stroke Lipid Management

ALWAYS assess your ASCVD risk in patients to determine risk category.

Depending on baseline LDL-C and risk category, establish LDL-C goal

Utilize all tools in toolbox to achieve treatment goals.

Therapies for Lipid Management: LDL-C and Beyond

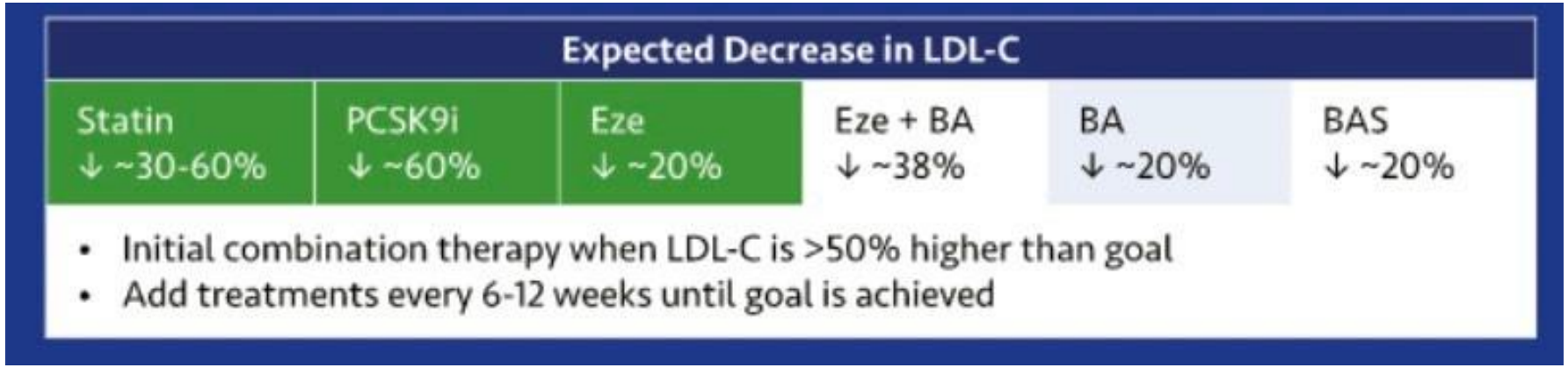
Lipid-Lowering therapies

Traditional therapies

- HMG-CoA reductase inhibitors (statin)
- Cholesterol absorption (NPC1L1) inhibitors (ezetimibe)
- Bile acid sequestrants (cholestyramine)

Recent therapies

- PCSK9 mAb inhibitors (Repatha, Praluent)
- ATP citrate lyase inhibitors (Nexletol)
- siRNA for PCSK9 mRNA (Leqvio)
- Icosapent Ethyl (Vascepa) - Triglycerides

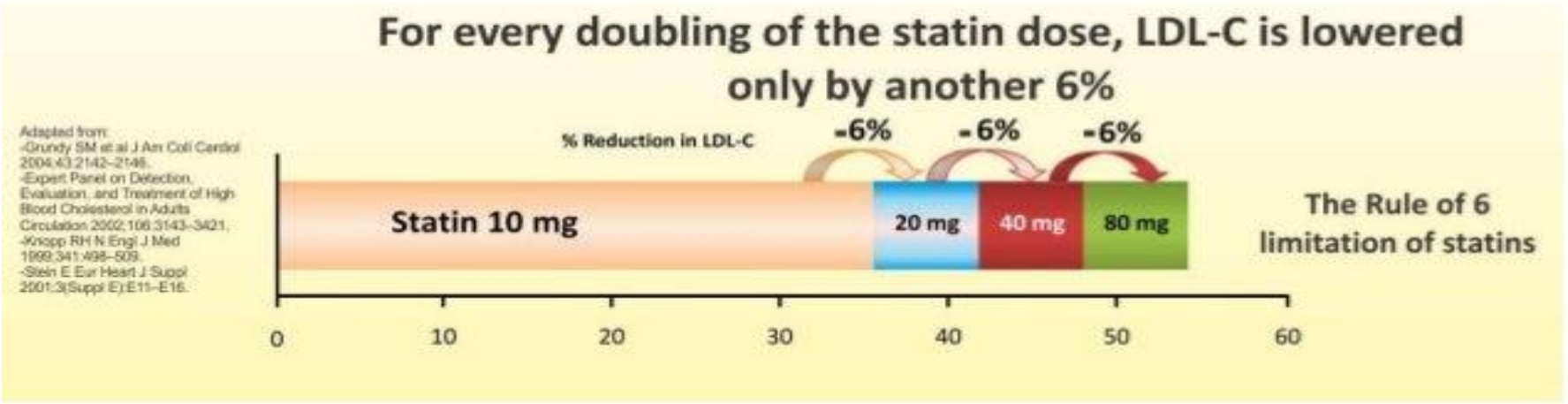


ASCVD, atherosclerotic cardiovascular disease; ATP, adenosine triphosphate; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C, low-density lipopro
monoclonal antibody; NPC1L1, Niemann-Pick C1-Like 1; PCSK9, proprotein convertase subtilisin/kexin type 9.
Hegele RA et al. *Circ Res*. 2019;124(3):386-404.

Non-statin treatment	How it lowers LDL cholesterol	How it's taken	Side effects to be aware of *	Added ASVCD risk reduction
Ezetimibe	Works by blocking the body's ability to absorb cholesterol in the gut	By mouth, usually once daily	Diarrhea, stomach pain, muscle or joint pain, runny or stuffy nose, feeling tired	In some patients, adding ezetimibe to statin therapy lowered cardiovascular events. Can lower cholesterol about 17% monotherapy, up to 30% in combo with statin therapy.
Bempedoic acid	Partly blocks the production of cholesterol in the liver	By mouth, once daily	Muscle spasms, back pain, pain in hands or feet. Increase in uric acid., so those with gout have increased episodes.	A study is being done to determine if bempedoic acid lowers cardiovascular risk in patients at risk for cardiovascular disease events who cannot take statin therapy.
PCSK9 inhibitors	Works by helping the body get rid of LDL cholesterol from the blood by blocking a protein in the liver (called proprotein convertase subtilisin kexin 9, or PCSK9)	Given under the skin by self injection, 1-2 times a month or monthly billing through the pharmacy benefits	Skin reactions at the site of injection, allergic reactions, headache, influenza	In some patients, adding a PCSK9 inhibitor to statin therapy (with or without ezetimibe) lowered cardiovascular events and reduced LDL cholesterol by 50-70%.For HeFH, about 40%.
Inclisiran	Works by increasing the number of LDL receptors on the liver by decreasing production of PCSK9 in the liver through siRNA	Given under the skin by the provider's office every 6 months billing through the buy and bill medial benefits.	Skin reactions at the site of injections, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremity and dyspnea. These were generally mild, and none were severe or persistent	Adding siRNA, inclisiran, to low fat diet and max tolerated statin, lowers cholesterol approximately 50%. A study is being done to determine if incllisiran lowers cardiovascular risk in patients with HeFH and/or ASCVD.

Remember the Rule of 6's in Statins

Coronary Artery Disease Risk
Statins monotherapy limitations



Lipid Lowering Agents

PCSK9 mAB inhibitors

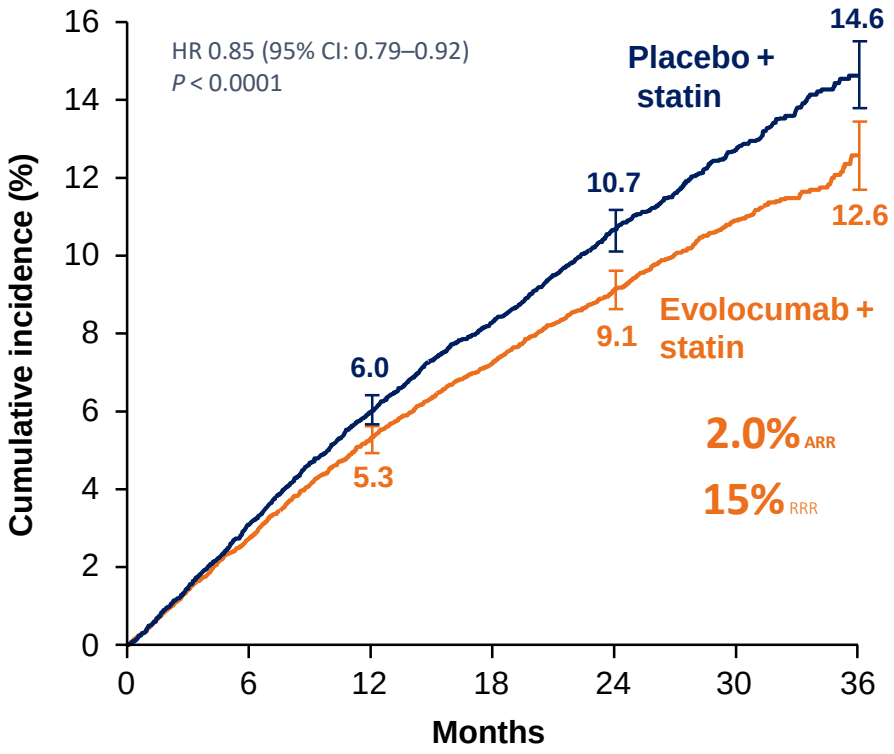
Evolocumab

Alirocumab

Evolocumab Outcomes Trial (FOURIER): Evolocumab Significantly Reduced CV Events

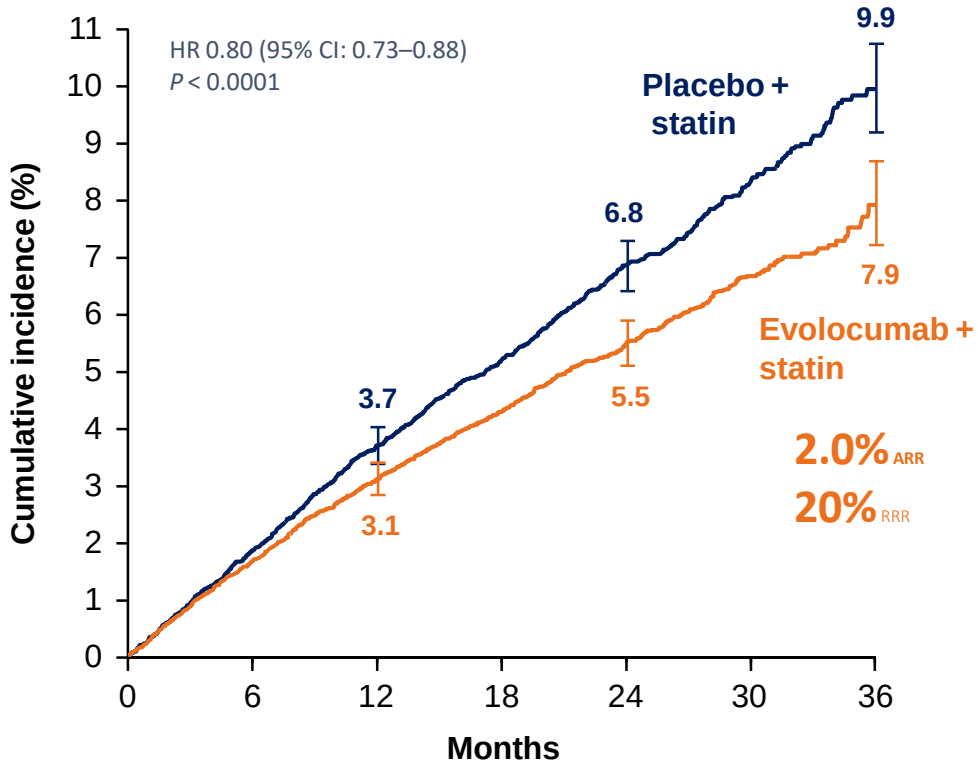
Composite of CV Death, MI, Stroke, Hospitalization for UA, or Coronary Revascularization

Primary Composite Endpoint



Composite of CV Death, MI, or Stroke

Key Secondary Composite Endpoint



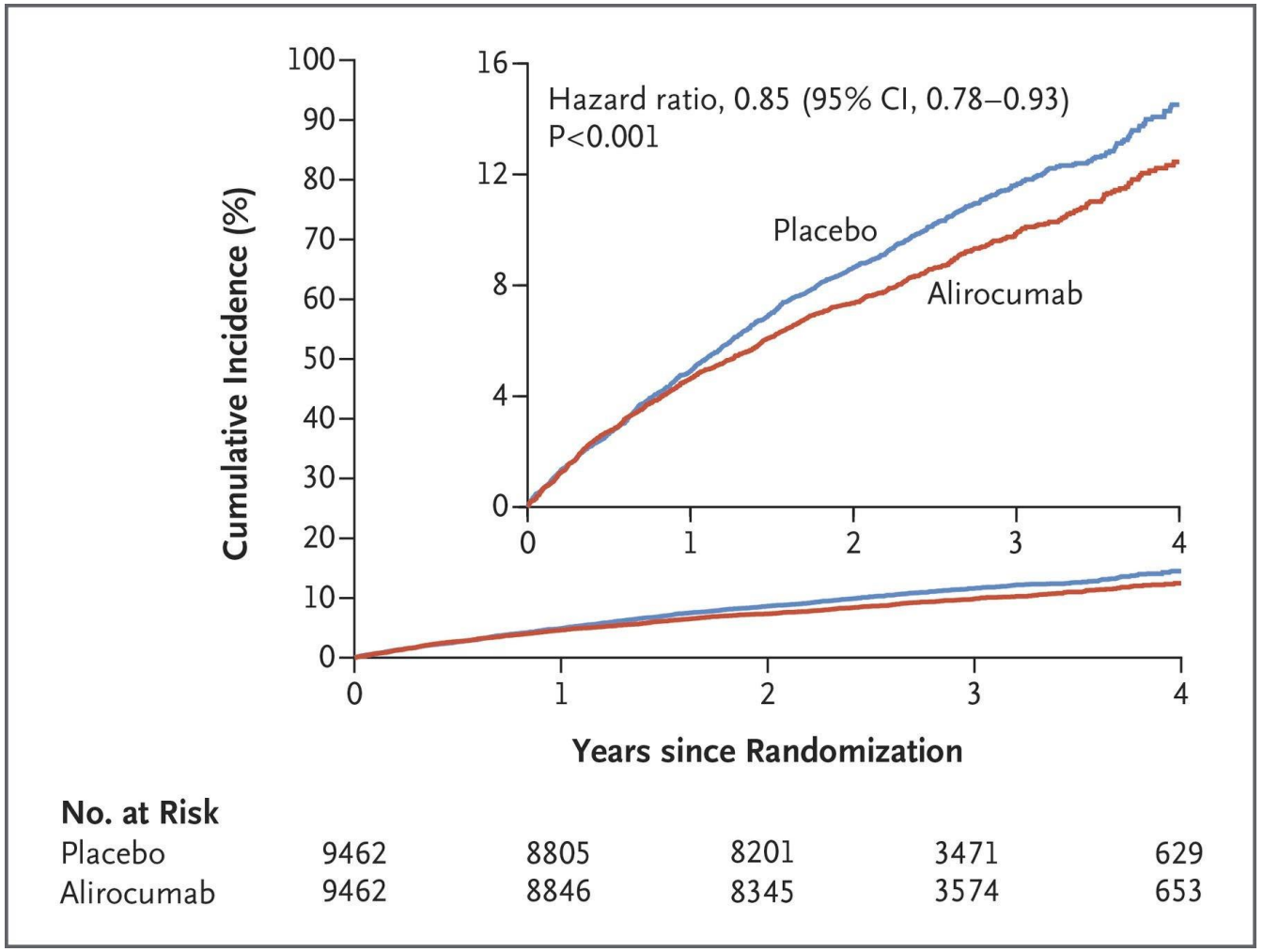
*Not statistically significant

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; RRR, relative risk reduction; UA, unstable angina.

1. Repatha® (evolocumab) Prescribing Information, Amgen.
2. Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-1722.

Alirocumab Outcomes Trial (ODYSSEY-OUTCOMES): Alirocumab Significantly Reduced CV Events

Composite of CV Death, MI, Stroke, UA requiring hospitalization



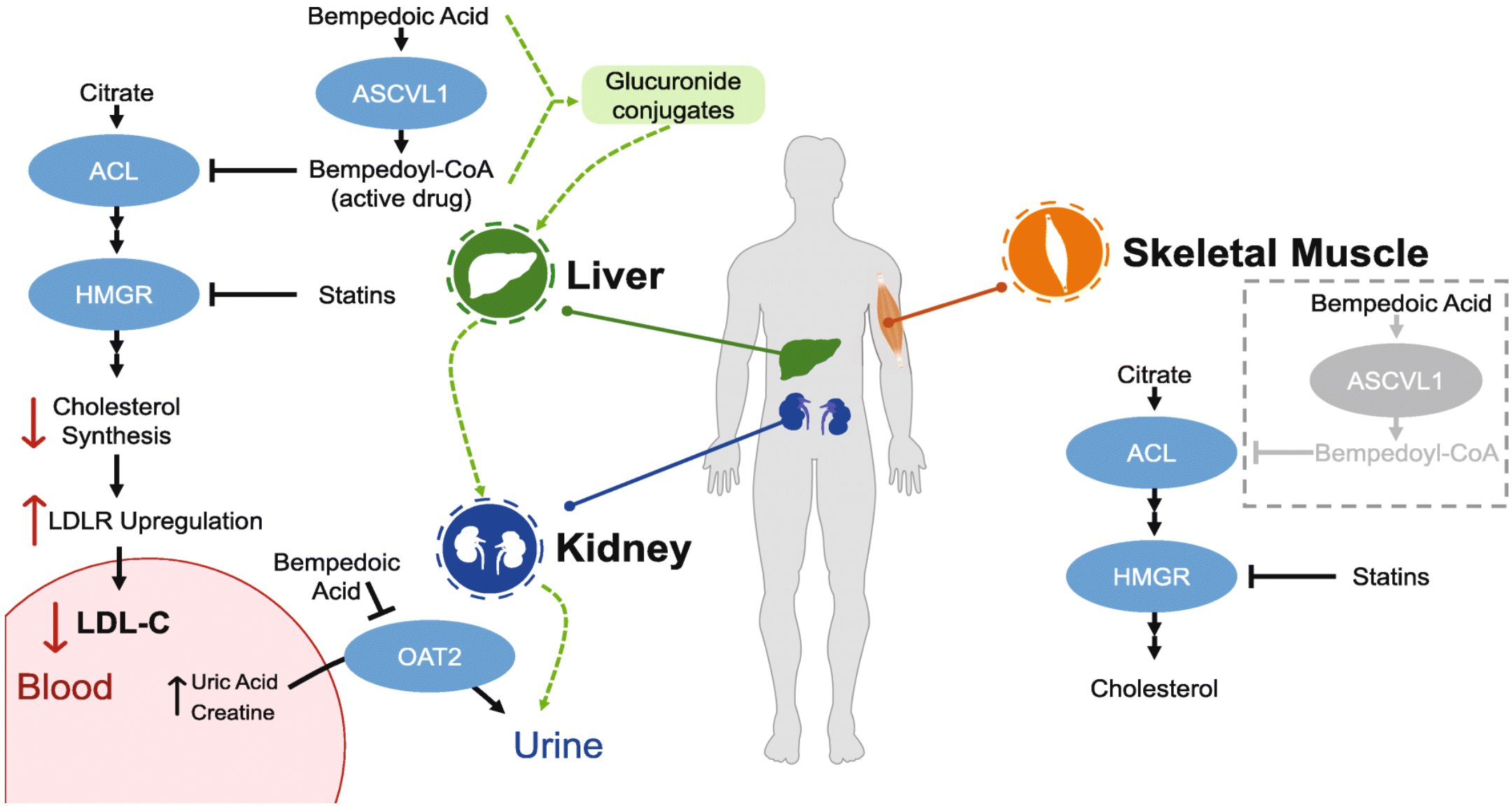
1. Schwartz GG, et al. *N Engl J Med*. 2018; 379:2097-2107

ATP Citrate Lyase Inhibitors

Bempedoic Acid

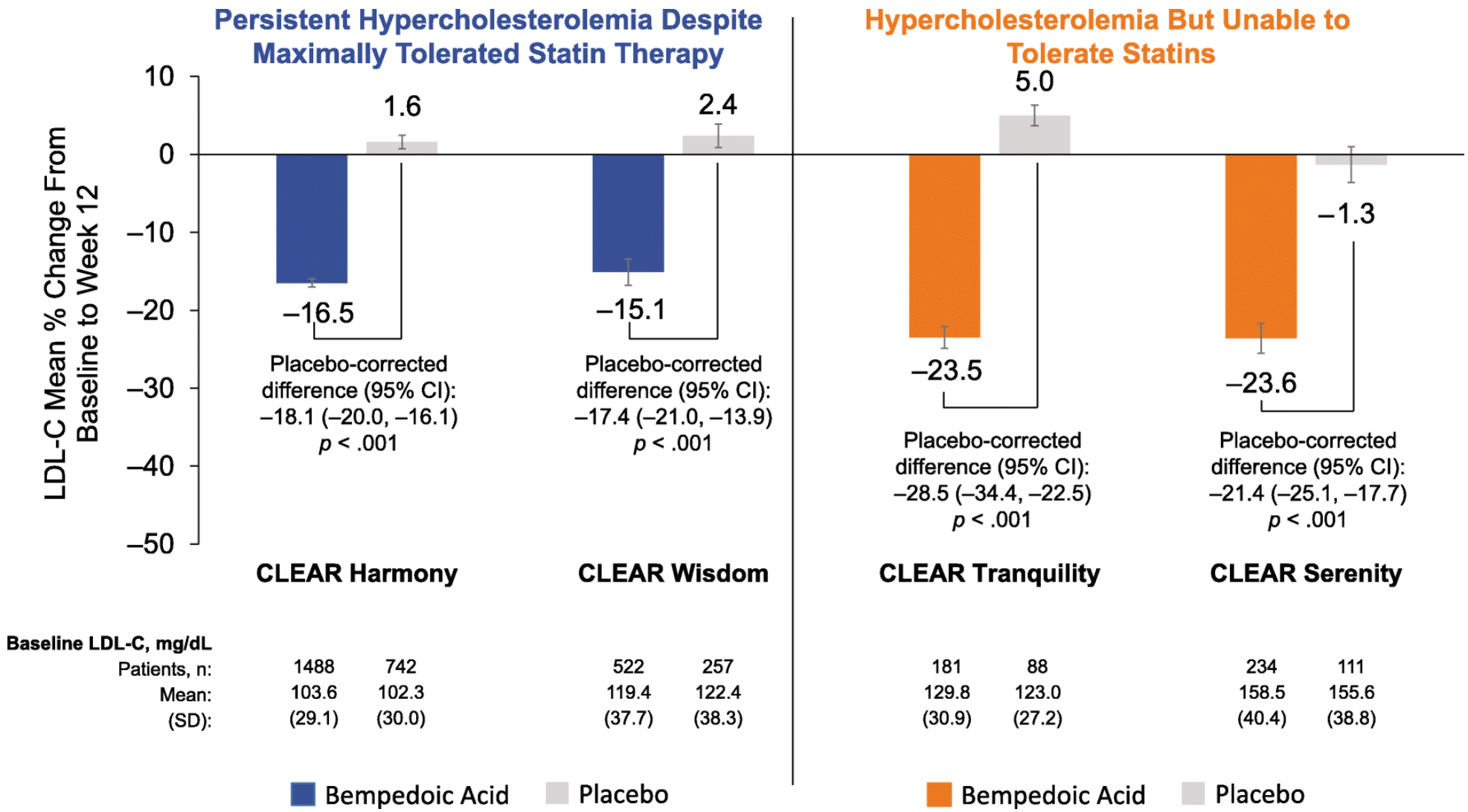
Bempedoic Acid + Ezetemibe

Mechanism of Action: Bempedoic Acid



Ballantyne, C.M., Bays, H., Catapano, A.L. *et al.* Role of Bempedoic Acid in Clinical Practice. *Cardiovasc Drugs Ther* **35,** 853–864 (2021). https://doi.org/10.1007/s10557-021-07147-5

Clinical Efficacy: Bempedoic Acid



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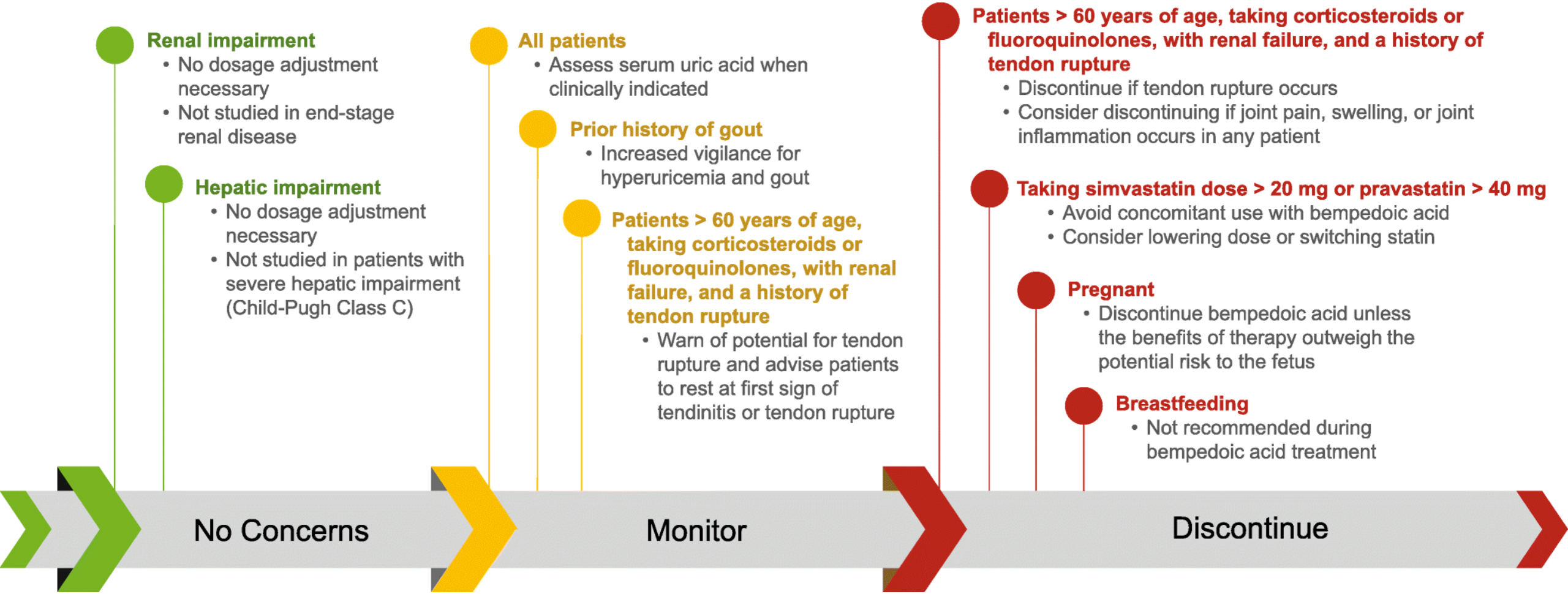
Monitoring: Bempedoic Acid



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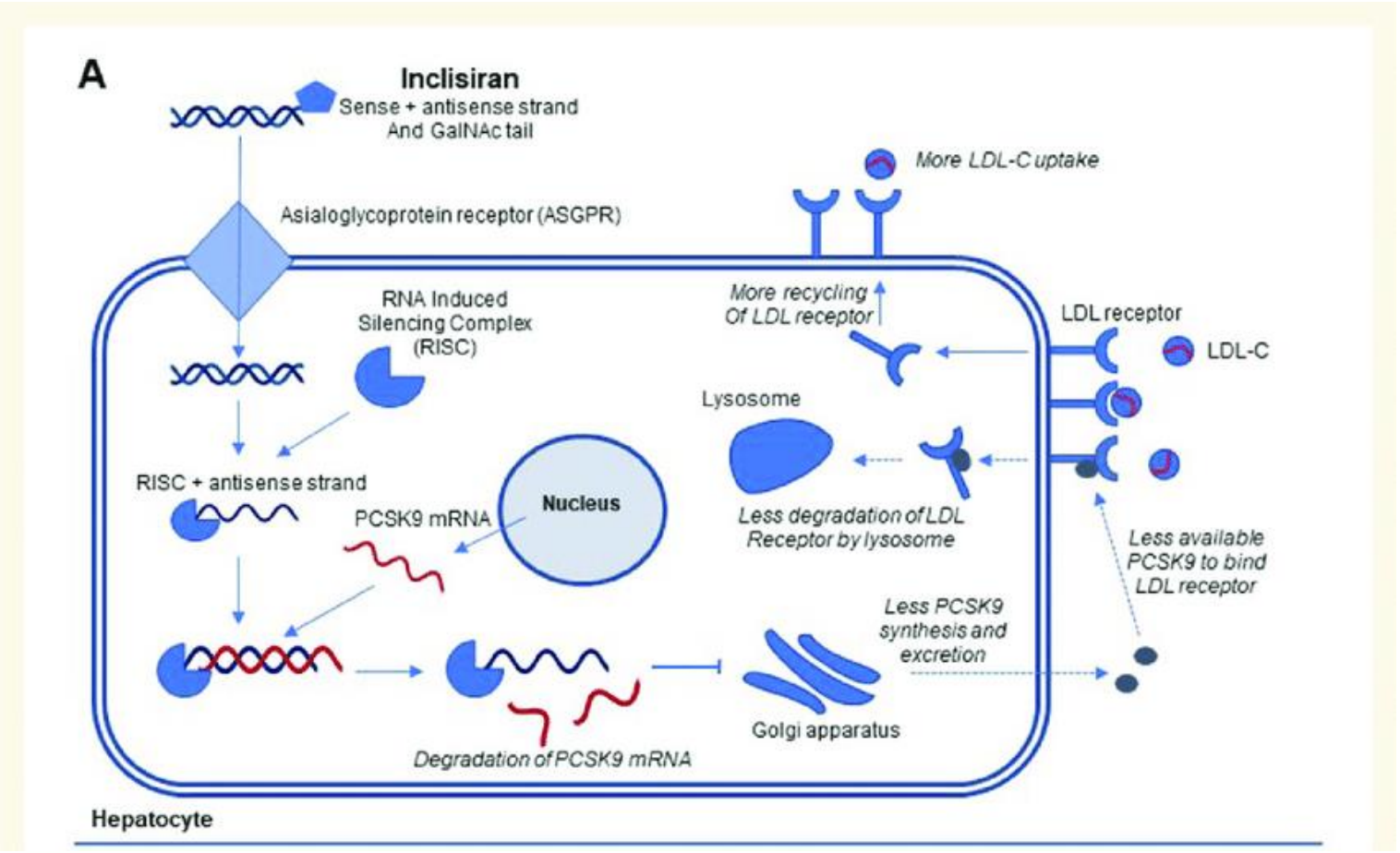
siRNA for PCSK9 mRNA

Inclisiran

Mechanism of Action: Inclisiran



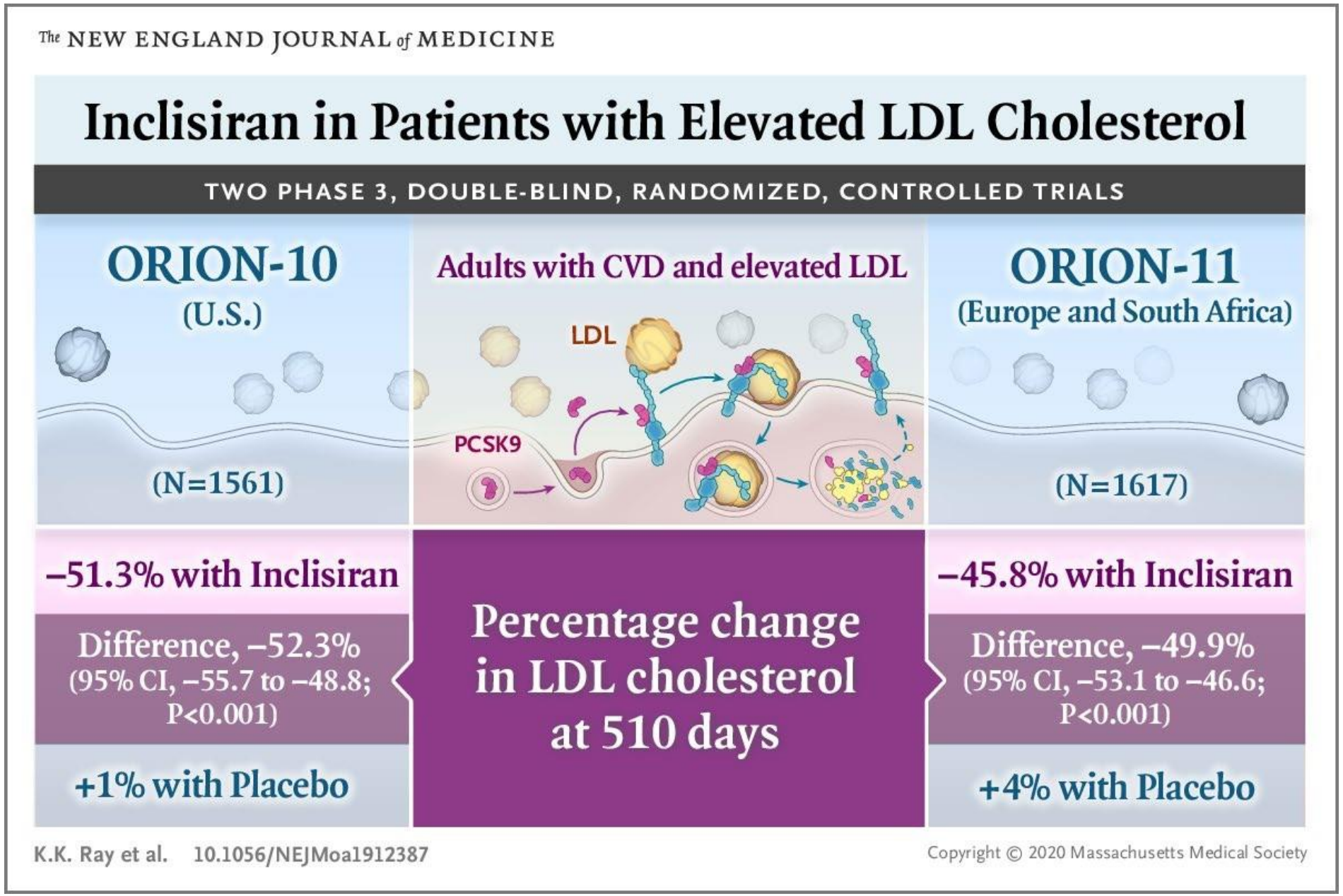
Inclisiran specifically works in the liver

- Harnesses the body's process of RNA interference in cytoplasm
- Conjugated with GalNAc for specific uptake by hepatocytes.
- Target: PCSK9 mRNA, which is subject to degradation in the cytoplasm and not in nucleus.
- LEQVIO plasma levels decline within 24 hours and are undetectable within 48 hours.

Prevents production of PCSK9 protein[1] → Greater hepatic uptake of circulating LDL-C[1] → Reduction of LDL-C levels in the bloodstream[1]

Arjen J Cupido, John J P Kastelein, Inclisiran for the treatment of hypercholesterolaemia: implications and unanswered questions from the ORION trials, *Cardiovascular Research*, Volume 116, Issue 11, 1 September 2020, Pages e136–e139, https://doi.org/10.1093/cvr/cvaa212

Clinical Efficacy: Inclisiran

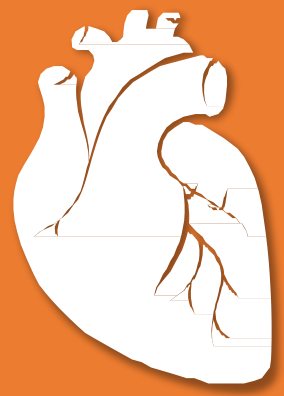


What about Triglycerides?

Inclisiran

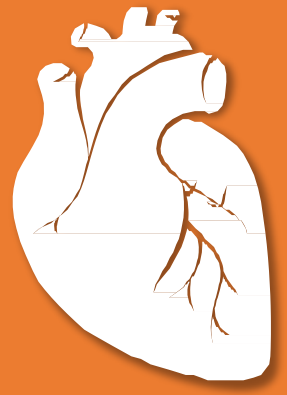
Parallel Risk-Reduction Pathways

LDL



LDL-C<70 mg/dL
LDL-C<55 mg/dL

TRIGLYCERIDES



TG<135 mg/dL

Management of Lipids in Diabetes, Cardiorenal, and Metabolic Diseases

Monitor Lipids Every 6-12 Weeks Until Individual Target Is Achieved

Management of Hypertriglyceridemia

Reduce risk of ASCVD	
All patients with elevated TG	Low-fat, moderate-CHO diet and other lifestyle + max-tolerated statin
Patients with TG 135-499 mg/dL + ASCVD or diabetes + 2 RF	Add IPE
Others with TG <500 mg/dL	Consider adding fibrate, OM3,[a] or niacin
Reduce risk of pancreatitis	
All patients with TG >500 mg/dL	Low-fat, moderate-CHO diet and other lifestyle + max-tolerated statin Add fibrate, OM3,[a] or niacin
Patients with insulin resistance	Consider adding pioglitazone
Patients with acute, severe hypertriglyceridemia	Consider insulin

Expected Decrease in TG				
Statin ↓ ~20-30%	Fibrate ↓ ~30-50%	OM3[a] ↓ ~30-40%	Niacin ↓ ~20-30%	Pio ↓ ~10-15%

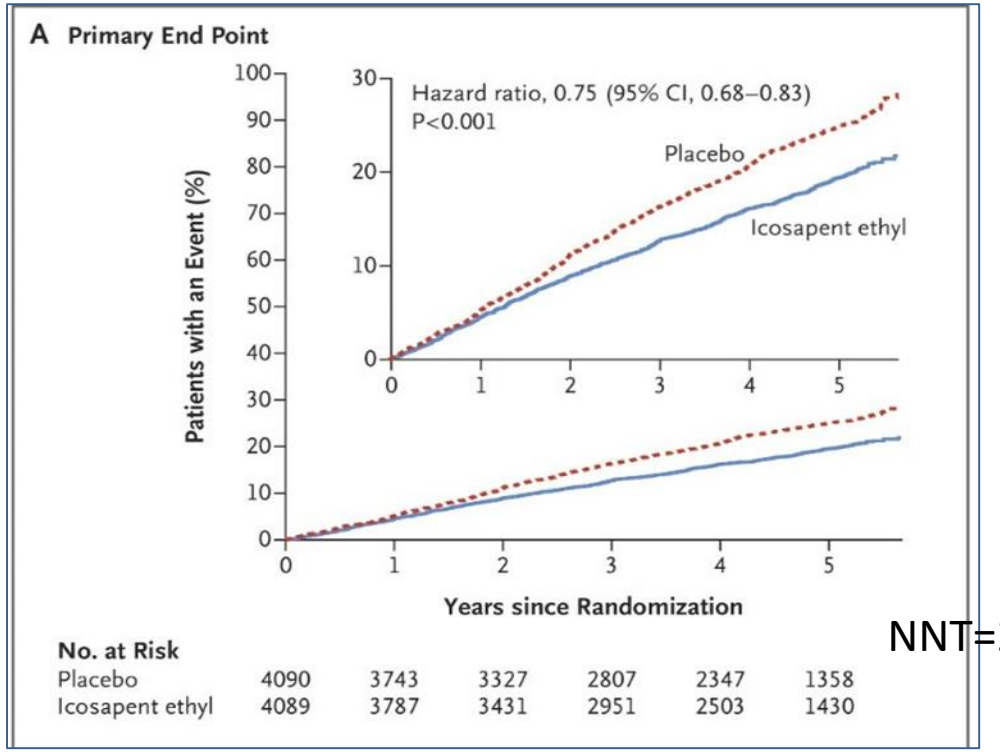
Proven ASCVD benefits in CVOTs

[a] IPE, EPA, or EPA+DHA.

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; BA = bempedoic acid; BAS = bile acid sequestrant; CKD ≥3 = stage 3 chronic kidney disease; CVOT = cardiovascular outcome trial; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; Eze = ezetimibe; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; IPE = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol; OM3 = prescription-strength omega-3 fatty acid; PAD = peripheral artery disease; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; Pio = pioglitazone; RF = major risk factors (ie, advancing age, elevated non-HDL-C, elevated LDL-C, low HDL-C, diabetes, hypertension, CKD, cigarette smoking, family history of ASCVD); TG = triglyceride.

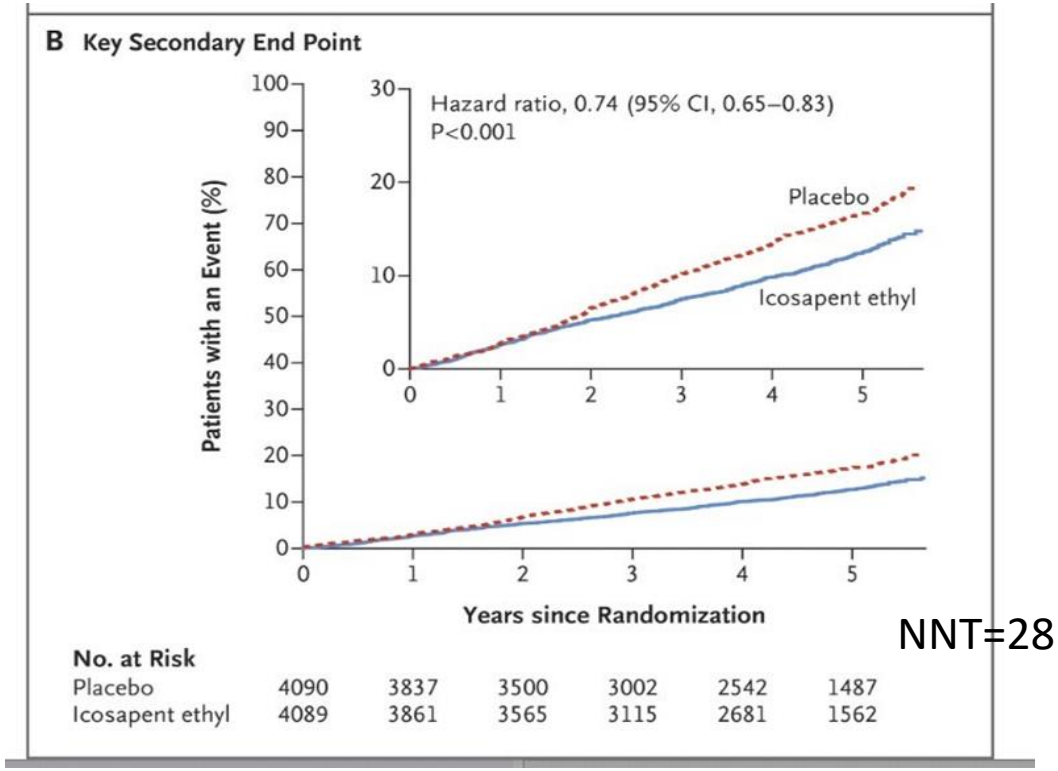
Significant Reduction in MACE with IPE on background of well controlled LDL-C

CVD/MI/Stroke/Coronary Revascularization/UA



NNT=21

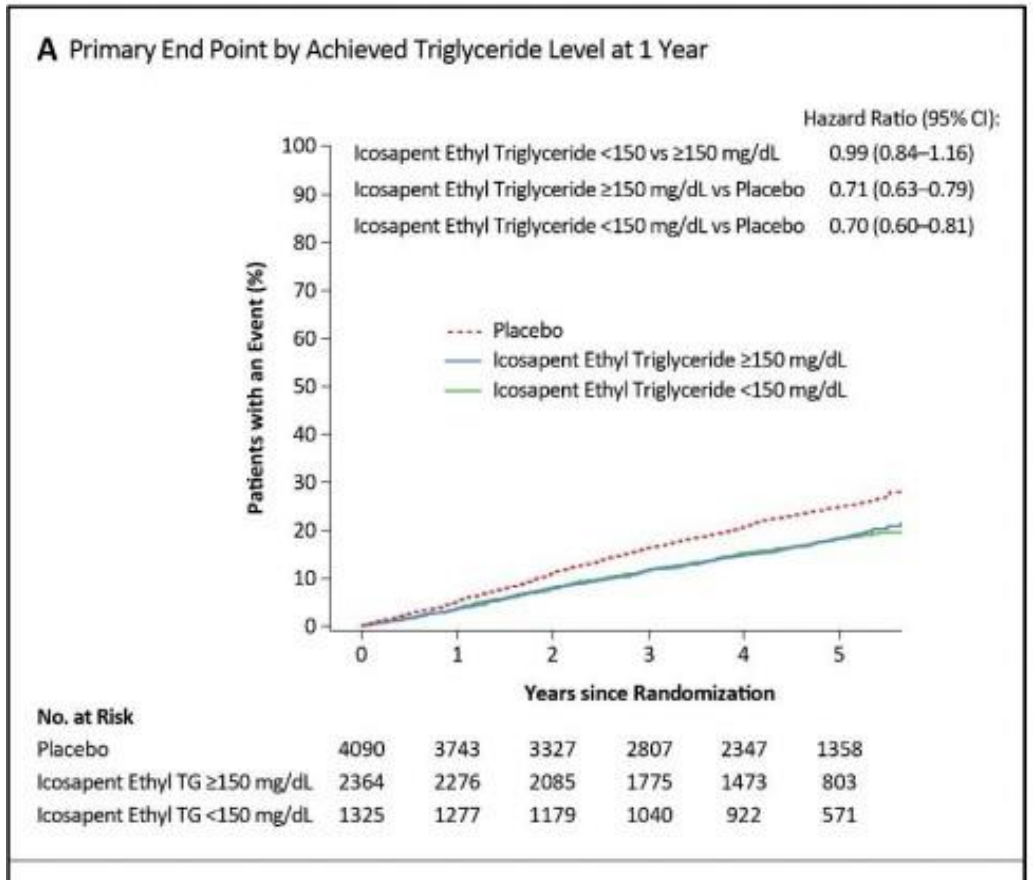
CVD/MI/Stroke

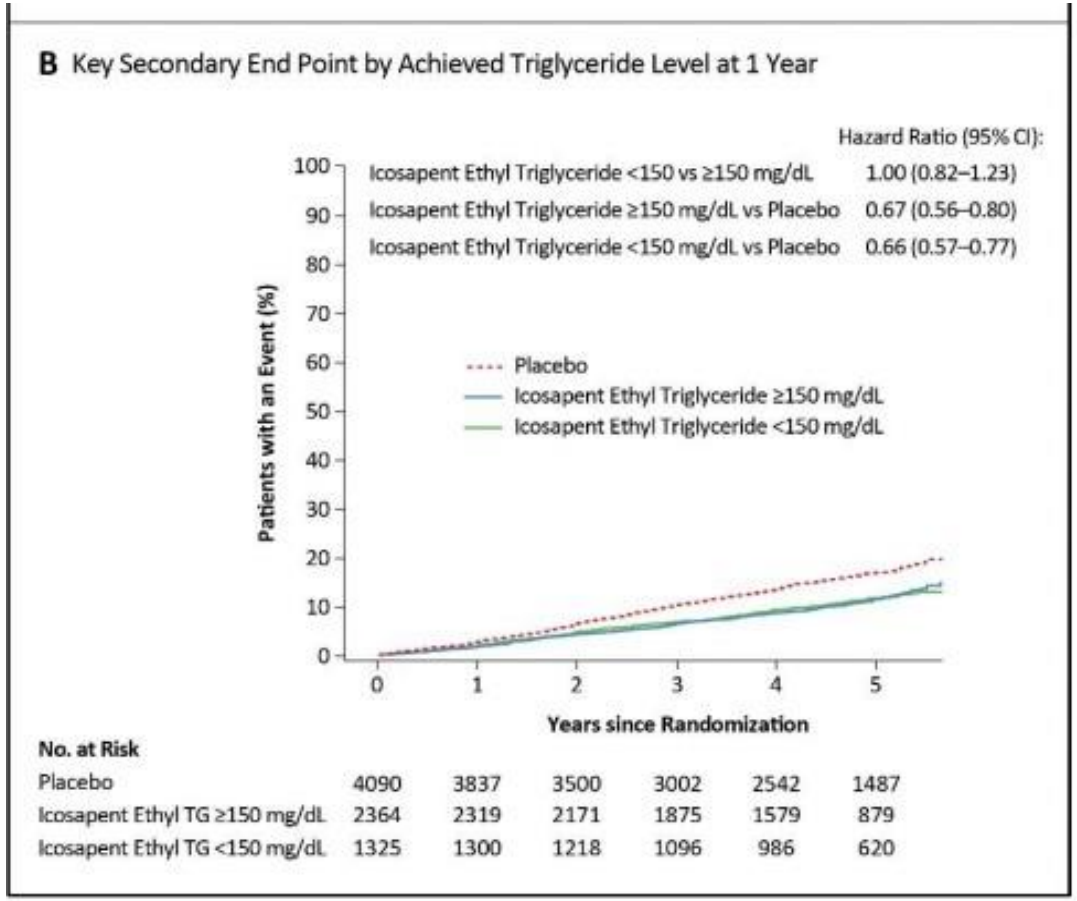


NNT=28

Bhatt et al. NEJM. REDUCE-IT.

Effects Similar Regardless of On-Treatment TGs





Bhatt et al. NEJM. REDUCE-IT.

Back to Our Patient…

- ”Extreme Risk” (ASCVD + DM + CKD Stage 3a). Already on maximal statin (ATV 20) and ezetimibe. Current LDL-C 95 mg/dL. Triglycerides 225 mg/dL.
- LDL-C goal <55 mg/dL. LDL-C goal 50%
- For LDL-C, start PCSK9i.
- Start IPE 2 grams BID.

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Summary

There is a dose-dependent relationship between LDL-C and MACE.

Secondary prevention patients are undertreated with respect to LDL-C treatment targets.

Combination lipid lowering therapy can be helpful in reducing LDL-C and in some cases with CV outcomes data, reducing CV risk.

Treat early, treat aggressively.

Piedmont HEART

Take-Home Messages

- Secondary prevention patients should be assessed into average risk, very high risk or extreme risk patients.
- LDL-C targets should include target LDL-C based on guidelines and risk
- When LDL-C treatment goals cannot be achieved with statin alone, non-statin therapies such as PCSK9 inhibitors/ezetimibe (which have CV outcomes data) or bempedoic acid/inclisiran (LDL-C reduction but no outcomes data yet).
- LDL-C and TG should be considered parallel risk-reduction pathways and if TG>135 mg/dL, IPE should be added.
- Risk reducing effects of IPE appear to be independent of achieved on-treatment TGs.

Questions

1. **What pharmacological agent is <u>indicated</u> for the patient who can not tolerate multiple statin medications with HLD, HTN, and LDL of 130, but wants to reduce cardiovascular risk?**
   a. PCSK9i
   b. Ezetimibe
   c. No agents are currently indicated for statin intolerance
   d. Inclisiran

2. **For very high risk ASCVD patients with diabetes, all current guidelines recommend achieving target LDL target to be < 70mg/dL?**
   a. True
   b. False

3. **What pharmacological agents have been shown to reduce cardiovascular/stroke events?**
   a. Icosapent Ethyl and PCSK9i
   b. Inclisiran and ezetimibe
   c. Bempendoic acid and PCSK9i
   d. PCSK9i and fenofibrates