NON STATIN LIPID LOWERING THERAPY

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Treatment of Dyslipidemia is Important..!!!

CV benefits of lipid lowering

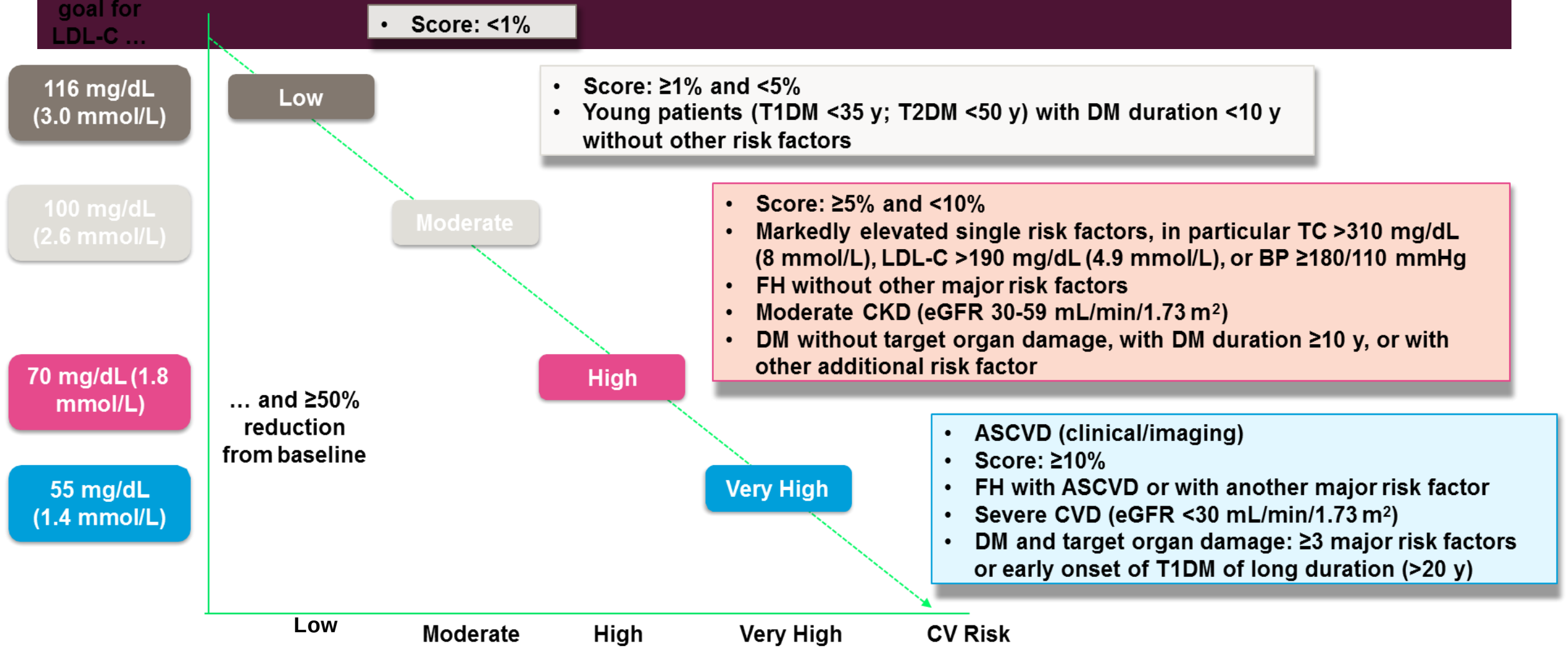
Cholesterol Treatment Trialists' (CTT) collaborators – Meta-analysis

Reduction of 1 mmol per liter (38.7 mg per deciliter) in LDL cholesterol levels yields a consistent 23% reduction in the risk of major coronary events over 5 years

N Engl J Med 2015; 372:2448-2450

TREATMENT GOALS FOR LDL-C ACROSS CATEGORIES OF TOTAL CARDIOVASCULAR DISEASE RISK[1]

2019 ESC/EAS Guidelines for the Management of Dyslipidemias



1. Mach F et al. *Eur Heart J.* 2020;41:111-188.

Updated Risk Stratification Approach Recommended by Lipid Association of India

Risk factors/markers

Major ASCVD risk factors

1. Age ≥45 years in males and ≥55 years in females
2. Family history of premature ASCVD
3. Current cigarette smoking or tobacco use
4. High blood pressure
5. Low HDL-C

Other high-risk features

1. Diabetes with 0-1 other major ASCVD risk factors and no evidence of target organ damage
2. CKD stage 3B or 4
3. Familial hypercholesterolemia (other than familial homozygous hypercholesterolemia)
4. Extreme of a single risk factor
5. Coronary calcium score >300 HU
6. Non-stenotic carotid plaque
7. Lipoprotein (a) ≥50 mg/dL

Moderate risk non-conventional risk factors

1. Coronary calcium score 100–299 HU
2. Increased carotid IMT
3. Lipoprotein (a) 20–49 mg/dL
4. Impaired fasting glucose*
5. Increased waist circumference**
6. Apolipoprotein B≥110 mg/dL
7. hsCRP ≥2 mg/L***

Risk group

Low-risk	Moderate risk	High-risk	Very high-risk	Extreme risk	
				Category A	Category B
0-1 major ASCVD risk factor and life-time CVD risk <30%	• 2 major ASCVD risk factors • Low risk group with ≥1 moderate risk non-conventional risk factor • Life-time CVD risk ≥30%	• ≥3 major ASCVD risk factors • 2 major ASCVD risk factors with ≥1 moderate risk non-conventional risk factor • ≥1 other high-risk features	• Preexisting ASCVD • Diabetics with ≥2 other major ASCVD risk factors or evidence of target organ damage • Familial homozygous hypercholesterolemia	CAD with ≥1 feature of ***high risk group***	CAD with ≥1 feature of ***very high risk group*** or recurrent ACS (within one year) despite LDL-C <50 mg/dL or polyvascular disease

Clinical judgment to be used if patient has atherosclerotic peripheral arterial disease instead of coronary artery disease.
*A fasting blood sugar level from 100 to 125 mg/dL. It should be confirmed by repeat testing.
**Waist circumference is to be measured at the superior border of the iliac crest just after expiration. Increased waist circumference is defined as >90 cm in men and >80 cm in women. If increased waist circumference is the only risk factor, it should again be measured after 6 months after initiating heart healthy lifestyle measures.
***On two occasions at least 2 weeks apart. For reclassifying moderate risk group only.

Fig. 1: Risk stratification algorithm recommended by the LAI[10,11]

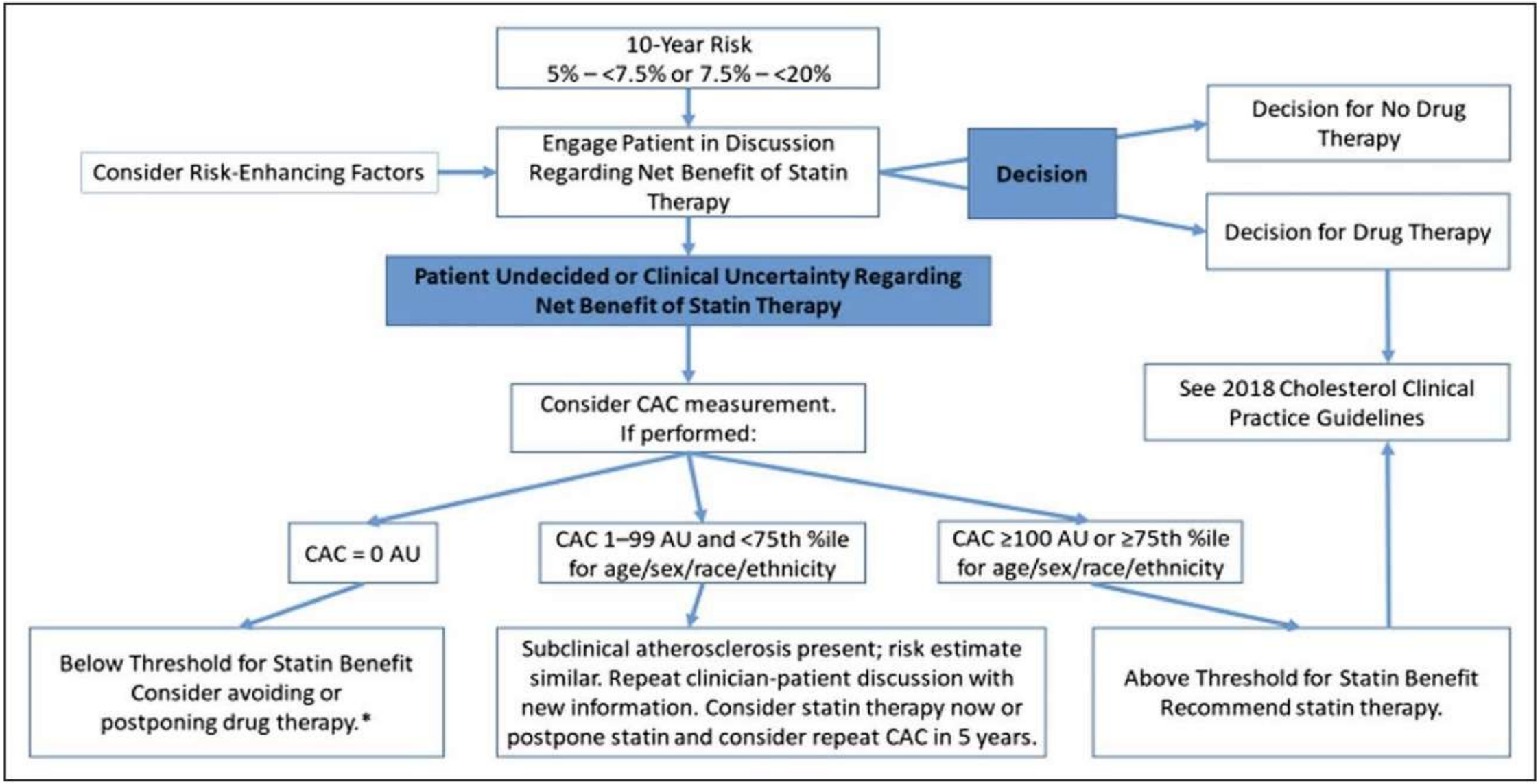
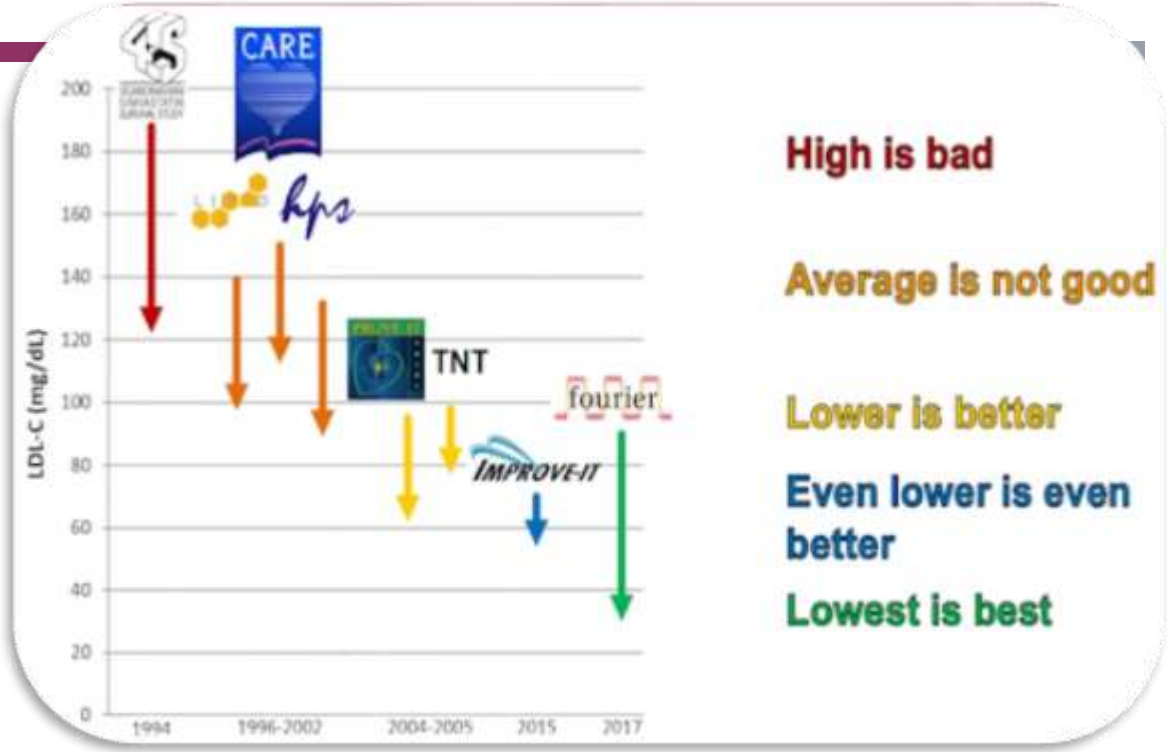


Figure 3. Algorithm of clinical approach to incorporate CAC measurement in risk assessment for borderline- and intermediate-risk patients.
*Clinicians and patients may not wish to postpone therapy in patients with a CAC score of 0 and diabetes mellitus, heavy current cigarette smoking, or strong family history of premature ASCVD. Blue shading indicates decision node. %ile indicates percentile; ASCVD, atherosclerotic cardiovascular disease; and CAC, coronary artery calcium.

EAS ESC European Society of Cardiology

- For secondary prevention in very-high-risk patients, an LDL-C reduction of >_50% from baseline and an **LDL-C goal of <55 mg/dL** are recommended.



LAI LIPID ASSOCIATION OF INDIA

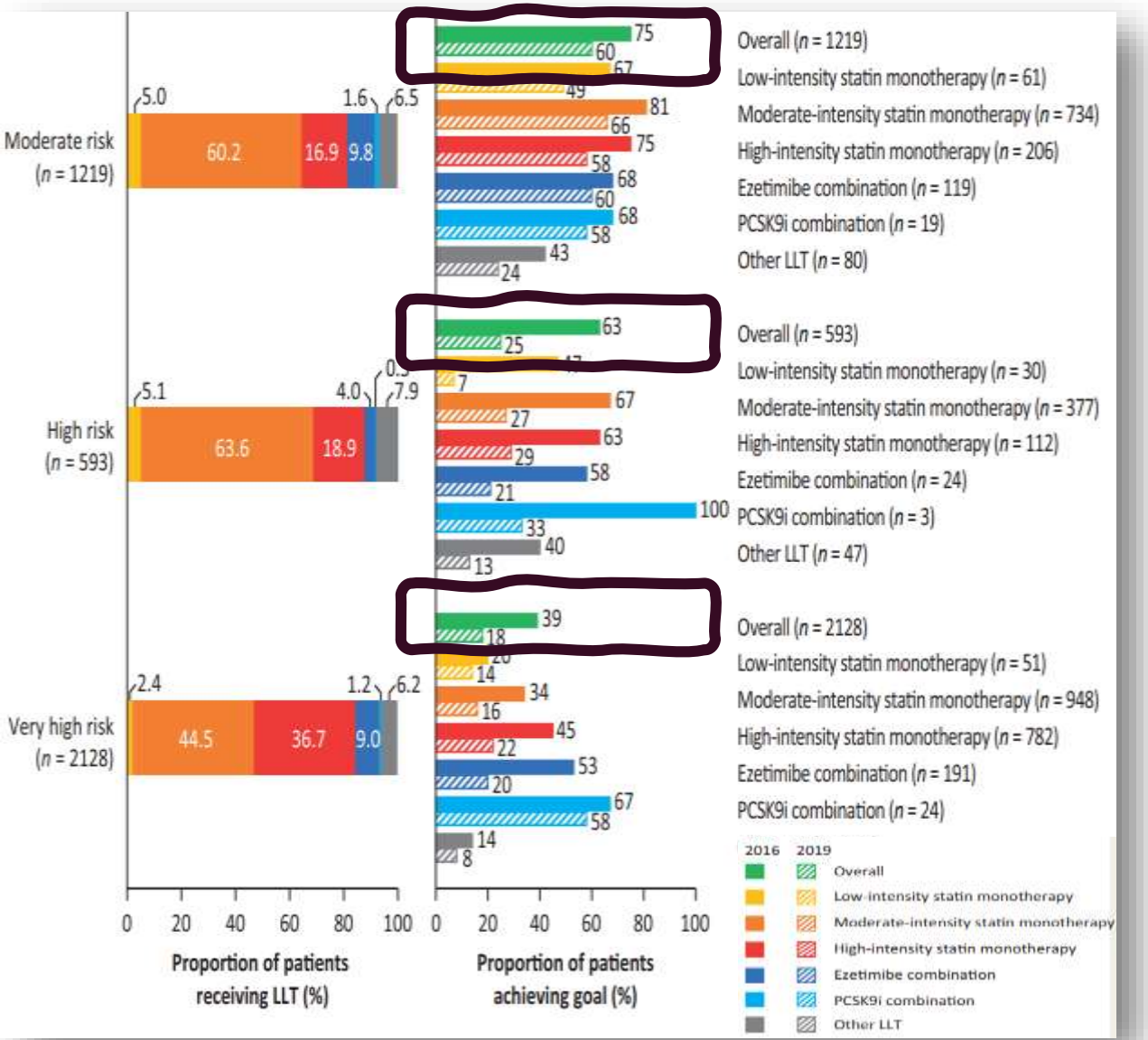
- For secondary prevention in very-high-risk patients, **LDL-C goal of <50 mg/dL** are recommended.

- Outcome of landmark Randomized Trials suggested LDL lower is better

From Trials to Guideline LDL Lower the better

Current Gaps in the Management of Dyslipidemia

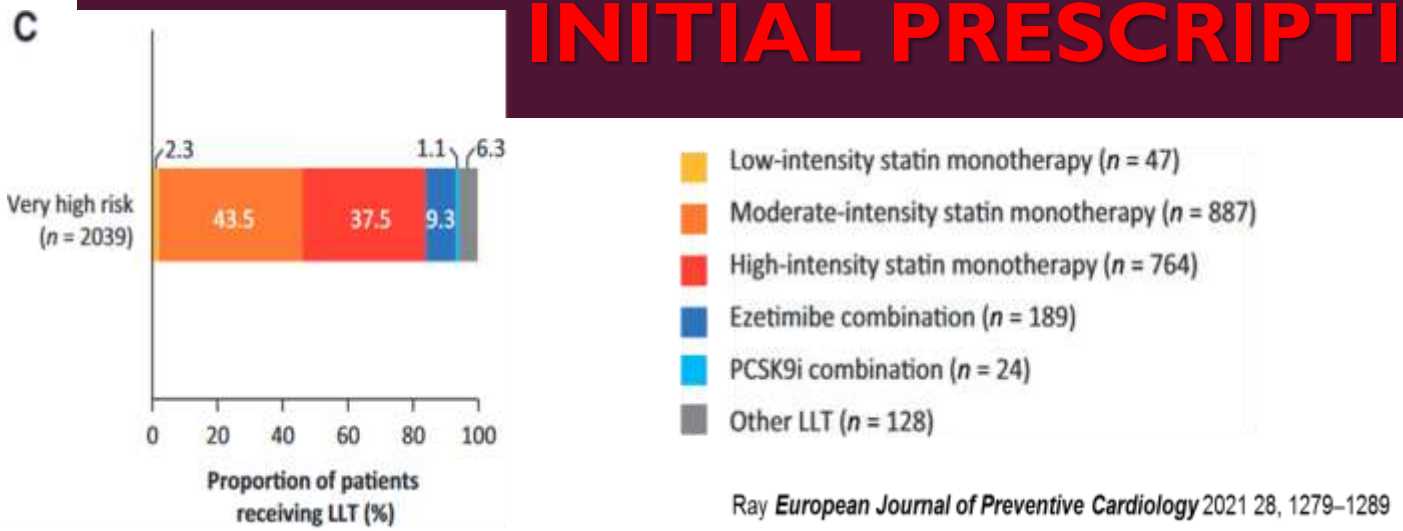
DA-VINCI Study



As per 2019 guidelines patients not reaching LDL-C Goal on statin treatment

- ***In moderate risk patients 40%*** patients not reaching LDL-C Goal
- ***In high risk patients 75%*** patients not reaching LDL-C Goal
- ***In very high risk patients 82%*** patients not reaching LDL-C Goal

REAL LIFE WITH THE CURRENT STRATEGY: INITIAL PRESCRIPTION IS UNDERPOWERED



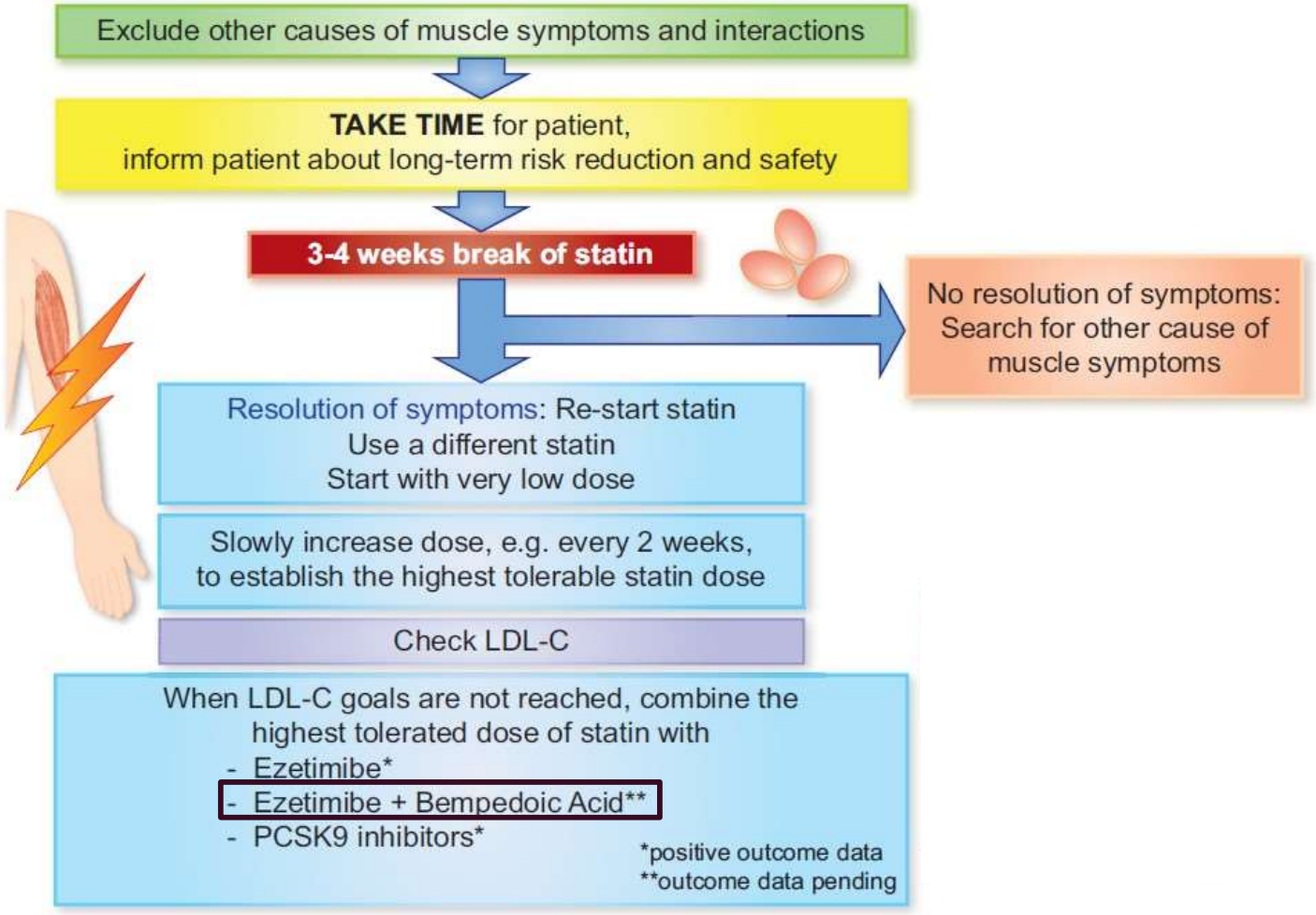
Ray *European Journal of Preventive Cardiology* 2021 28, 1279–1289

DA VINCI (***European Observational Study***): subset of patients at very high risk:

- 18% of the patients are at LDL-c target
- ***Statins: 37.5% at high intensity***
- Combination statin ezetimibe: 9.3%
- Combination statin PCSK9i: 1%

Current Gaps in the Management of Dyslipidemia

PATIENT OF SAMS[1]



STATIN INTOLERANCE

176 studies; 112 RCT; 64 cohort studies; n= 4 143 517 patients

Overall prevalence of SI: 9.1% (here: 372 922 patients)

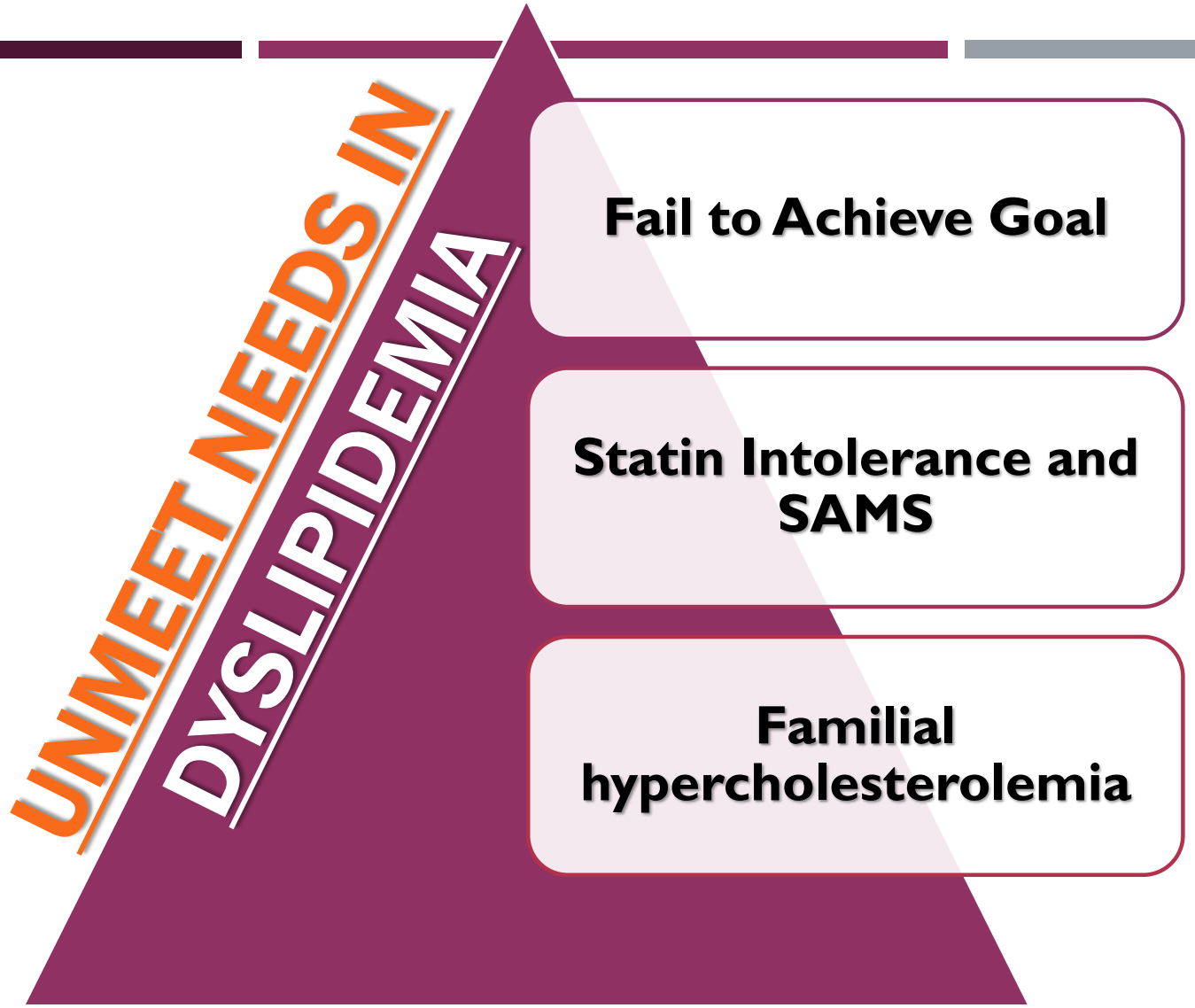
similar prevalence with NLA, ILEP, and EAS criteria prevalence of SI in RCT 4.9% vs. cohort studies 17% statin lipid solubility did not affect the prevalence of SI

Lipid and Blood Pressure Meta-Analysis Collaboration (LBPMC) Group and the International Lipid Expert Panel (ILEP)

Bytyçi et al., EHJ 2022; doi/10.1093/eurheartj/ehac015/6529098

1. Laufs & Isermann, EHJ 2020; 41(35):3343-5

2. Am J Cardiovasc Drugs. 2018; 18(3): 157–173


UNMEET NEEDS IN
DYSLIPIDEMIA
Fail to Achieve Goal
Statin Intolerance and SAMS
Familial hypercholesterolemia

BEST VALIDATED TARGET: LDL-C 'ERADICATION'
LOTS OF POTENT AND EMERGING THERAPIES

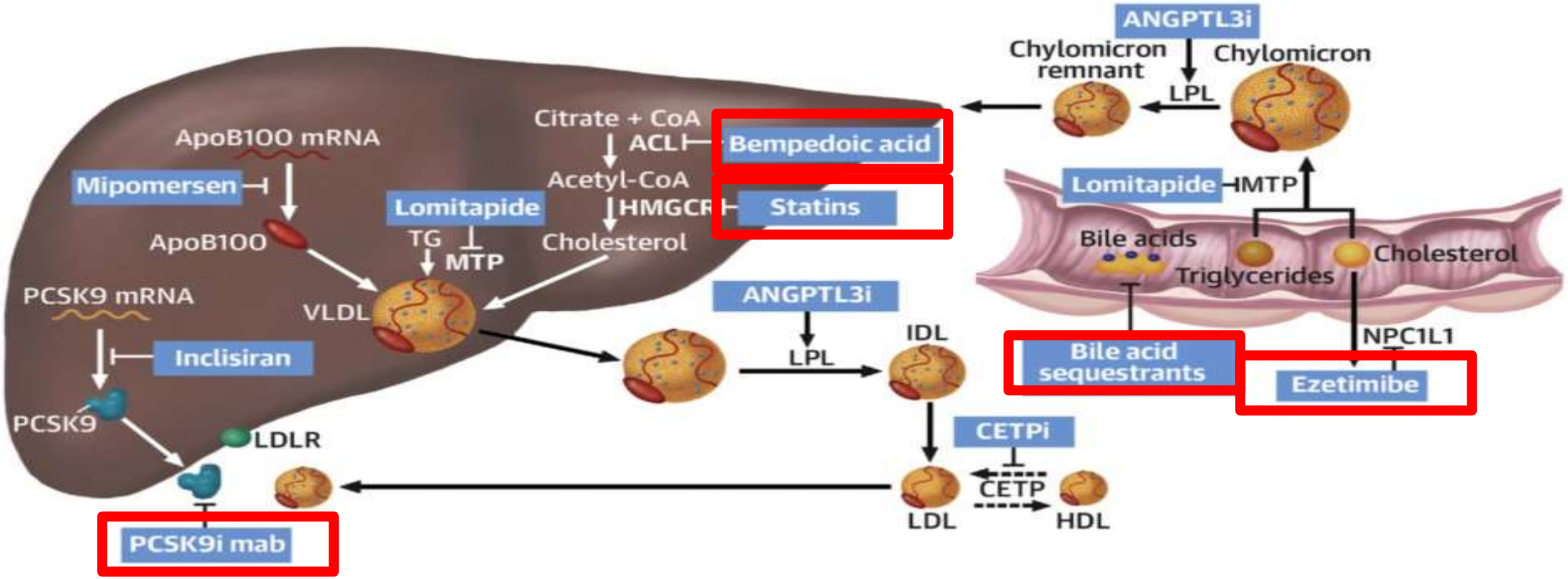


TABLE 1: Evolving targets and therapeutic agents.

New and evolving targets	Therapeutic agents
• Niemann–Pick C-1 like 1 (NPC1L1) receptor blocker • ACL blocker	• Ezetimibe • Bempedoic acid
PCSK9 inhibitor	Alirocumab and evolocumab
CETP inhibitor	Torcetrapib, dalcetrapib, anacetrapib, and evacetrapib
• Squalene synthase inhibitor • Inhibitor of apolipoprotein B100 expression	• Lapaquistat acetate • Mipomersen
MTP inhibitor	Lomitapide
• DGAT inhibitor • Thyromimetics or tiromes	• LCQ-908, AZD7687, and PF-04620110 • Eprotirome
• Apolipoprotein E mimetic peptides • Apolipoprotein A-I (ApoA1) synthesis inducer	• AEM-28 • RVX-208
• HDL-mimetic peptide • Liver X receptor agonists (LXRs)	• CER-001 • LXR-623
• PPAR-α and γ agonist • PPAR-α agonist	• Saroglitazar (Lipaglyn) • Fibrate (Gemfibrozil)
• PPAR-γ agonist • Phospholipase inhibitors	• Thiazolidinedione • Varespladib and darapladib
• Lipoprotein(a)-lowering agents • ASO against Lp(a)	• Niacin, PCSK9 antibodies and antisense oligonucleotides mipomersen • Pelacarsen
• Angiopoietin-like protein (ANGPTL) inhibitor • ANGPTL mRNA inhibitor	• Evinacumab • Vupanorsen
• Small interfering (si) RNA therapy • ApoC3 inhibitor • siRNA against Lp(a)	• Inclisiran • Volanesorsen • Olpasiran

(ACL: adenosine triphosphate-citrate lyase; ASO: antisense oligonucleotide; CETP: cholesteryl ester transfer protein; DGAT: diacylglycerol acyltransferase; HDL: high-density lipoprotein; MTP: microsomal triglyceride transfer protein; PCSK9: proprotein convertase subtilisin/kexin type 9; PPAR: peroxisome proliferator-activated receptor; siRNA: small interfering ribonucleic acid)

Traditional risk factors and risk-enhancing factors for ASCVD[6]

Traditional risk factors (used in the Pooled-cohort Equation)

Age
Cigarette smoking
Blood pressure
Presence or absence of diabetes mellitus
Serum TC
Serum HDL-C

Risk-enhancing factors

Family history of premature ASCVD (males, age <55 years; females, age <65 years)
Primary hypercholesterolemia (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])
Metabolic syndrome
CKD
Chronic inflammatory conditions such as such as psoriasis, RA, or HIV/AIDS
ABI <0.9
History of premature menopause (before age 40) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia
High-risk race/ethnicities (e.g., South Asian ancestry)
Lipid/biomarkers: Associated with increased ASCVD
- Persistently elevated, primary hypertriglyceridemia (≥175 mg/dL);
- If measured:
  - Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)
  - Elevated Lp(a) (≥50 mg/dL or ≥125 nmol/L)
  - Elevated apoB (≥130 mg/dL)

ABI Ankle

- 4 groups :

< 5% - Lifestyle modification

5-7.5% - Moderate intensity statins

>7.5% to <20% - Moderate intensity statins with AIM to decrease LDL by 30-50%

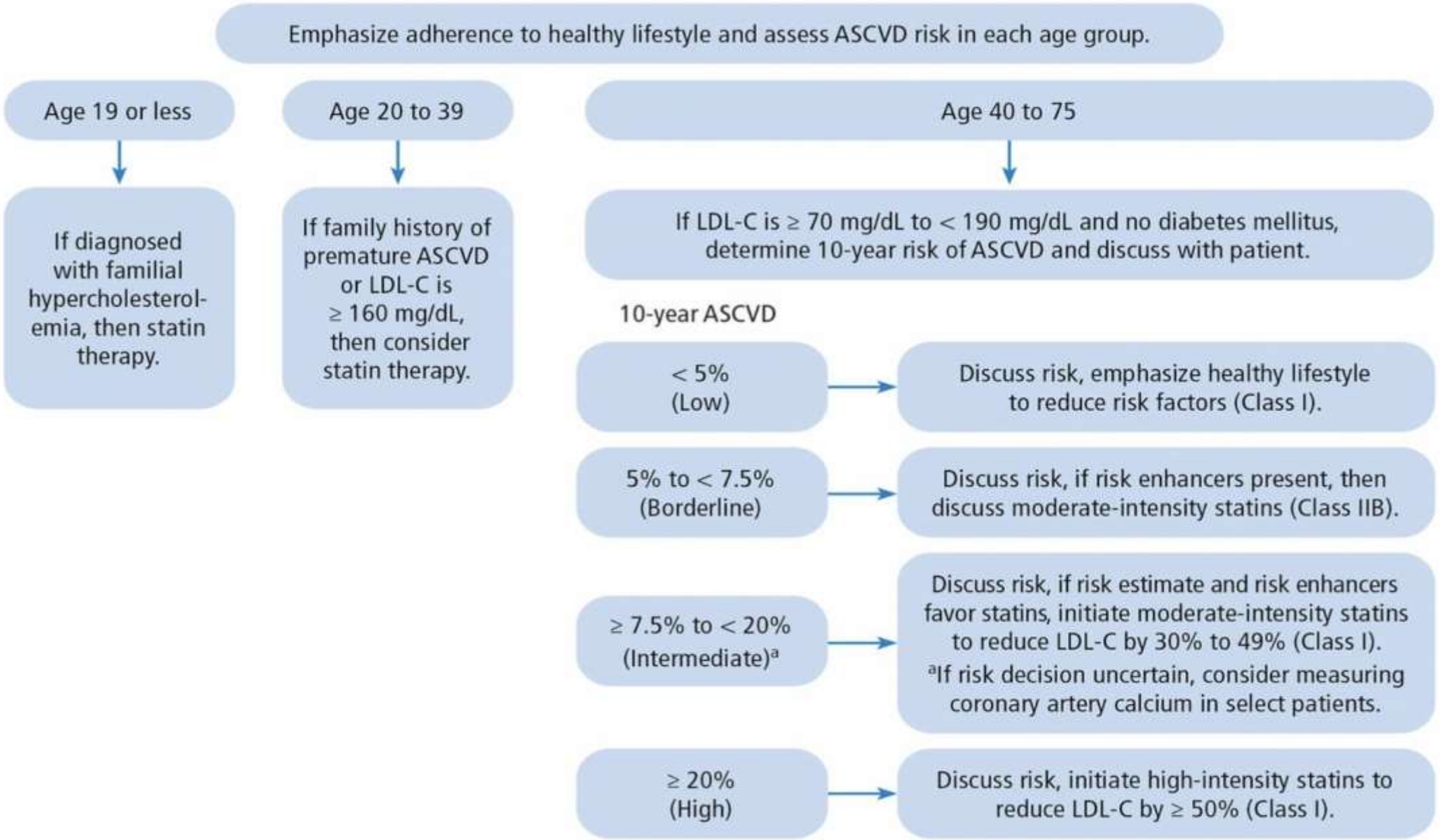
>20% - High risk ; To use high intensity statins with AIM to decrease LDL >50%

Always start Moderate intensity statins –

LDL >190 mg/dL

DM 40-75 years

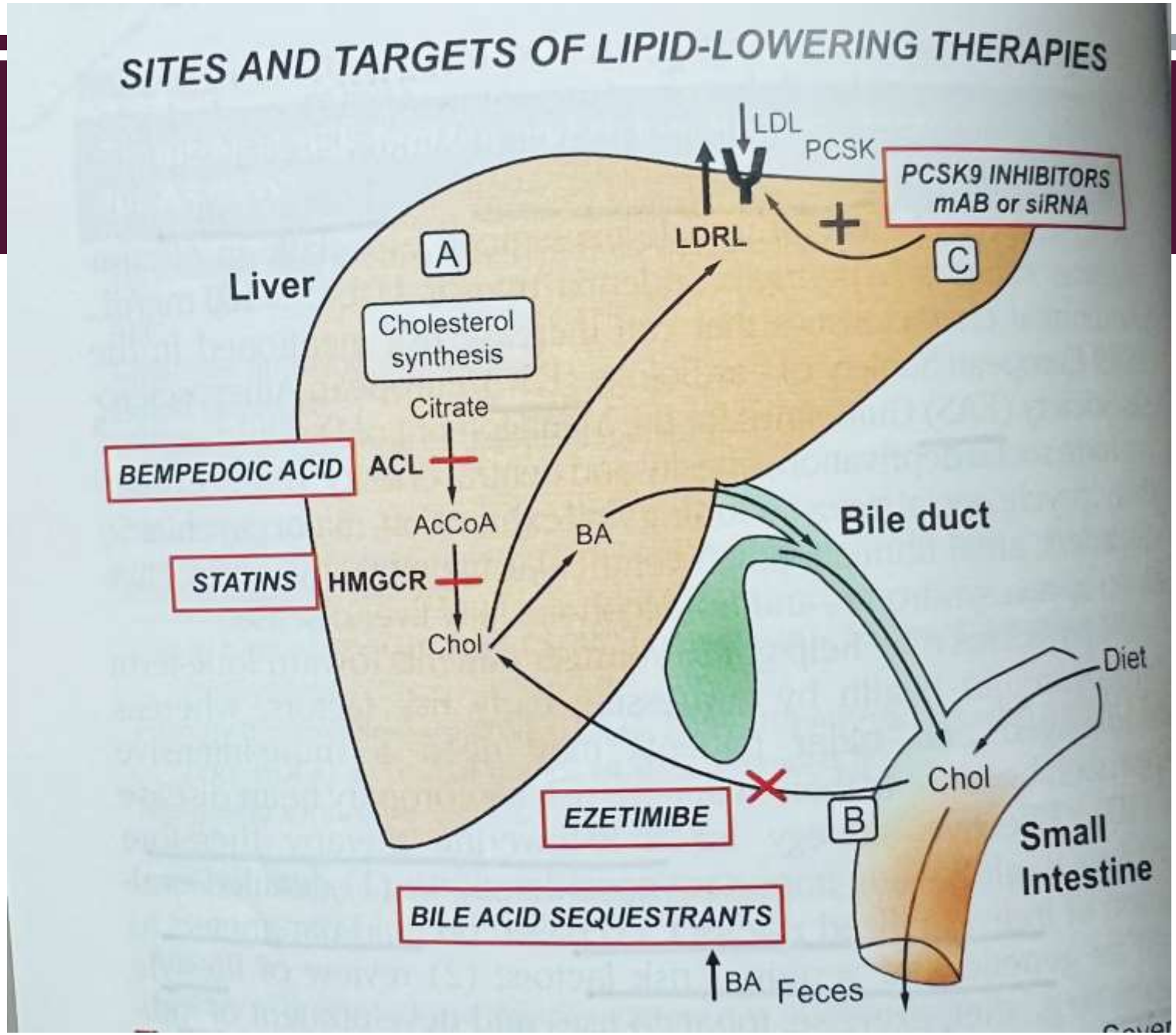
> 75 years


Emphasize adherence to healthy lifestyle and assess ASCVD risk in each age group.
Age 19 or less
If diagnosed with familial hypercholesterol-emia, then statin therapy.
Age 20 to 39
If family history of premature ASCVD or LDL-C is ≥ 160 mg/dL, then consider statin therapy.
Age 40 to 75
If LDL-C is ≥ 70 mg/dL to < 190 mg/dL and no diabetes mellitus, determine 10-year risk of ASCVD and discuss with patient.
10-year ASCVD
< 5% (Low)
Discuss risk, emphasize healthy lifestyle to reduce risk factors (Class I).
5% to < 7.5% (Borderline)
Discuss risk, if risk enhancers present, then discuss moderate-intensity statins (Class IIB).
≥ 7.5% to < 20% (Intermediate)[a]
Discuss risk, if risk estimate and risk enhancers favor statins, initiate moderate-intensity statins to reduce LDL-C by 30% to 49% (Class I).
[a]If risk decision uncertain, consider measuring coronary artery calcium in select patients.
≥ 20% (High)
Discuss risk, initiate high-intensity statins to reduce LDL-C by ≥ 50% (Class I).

SCORE : ESC GUIDELINES

- VERY HIGH RISK (SCORE >10%) – Statin therapy to be given with target of >50% reduction in LDL or LDL <55 mg/dL (Includes documented ASCVD , previous ACS or DM for 20 years or with target end organ damage)
- HIGH RISK (SCORE 5-10%) – 50% reduction in LDL or LDL <70 mg/dL (Includes DM/CKD/ LDL >190/ TG>310/bp>180/110)
- MODERATE RISK (SCORE 1-5%) – Aim for LDL <100 mg/dL
- LOW RISK (SCORE <1%) – Aim for LDL < 116 mg/dL

Very high Risk:	Subjects with any of the following: ▪ CVD ▪ Type 2 diabetes, or type 1 diabetes & target organ damage ▪ Patients with moderate to severe CKD (GFR <60mL/min/1.73m^2) ▪ SCORE ≥ 10%
High Risk:	Subjects with: ▪ Markedly elevated single risk factors such as: - Familial dyslipidaemias - Severe hypertension ▪ SCORE ≥ 5% and <10%
Moderate Risk:	SCORE ≥ 1% and <5% at 10 years, further modulated by: ▪ family history of premature CAD ▪ abdominal obesity ▪ physical activity pattern ▪ HDL-C ▪ TG ▪ hsCRP ▪ social class
Low Risk:	SCORE less than 1% and free of qualifiers

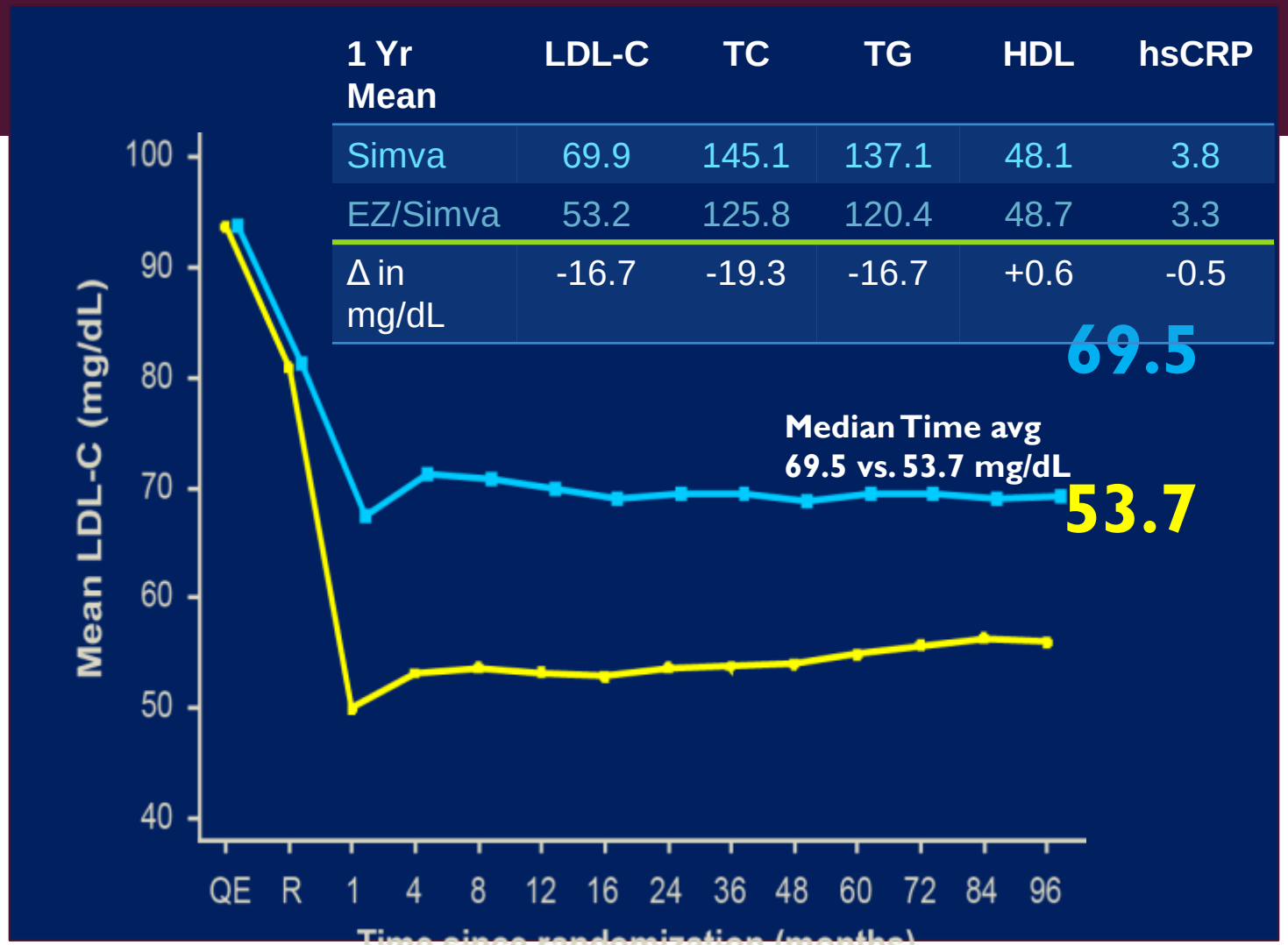

SITES AND TARGETS OF LIPID-LOWERING THERAPIES
LDL
PCSK
PCSK9 INHIBITORS
mAB or siRNA
LDRL
+
A
C
Liver
Cholesterol
synthesis
Citrate
BEMPEDOIC ACID
ACL
AcCoA
BA
Bile duct
STATINS
HMGCR
Chol
Diet
Chol
EZETIMIBE
B
Small
Intestine
BILE ACID SEQUESTRANTS
BA
Feces

EZETIMIBE

- Cholesterol absorption inhibitor
- Binds to NPC1L1 on brush border epithelium of small intestine and interrupts intestinal absorption of cholesterol and phytosterols
- Decrease LDL by 8.5% in monotherapy
- Decrease LDL by 12-19% with statins
- Many studies on CIMT
- PRECISE-IVUS trial : Increased coronary plaque regression on serial IVUS
- CKD – FDA approved Ezetimibe and Statin combination (**SHARP**)
- IMPROVE IT trial – Decrease MACE, LDL (more in DM within 1st year of trial)

IMPROVE-IT: LDL-C AND LIPID CHANGES

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5

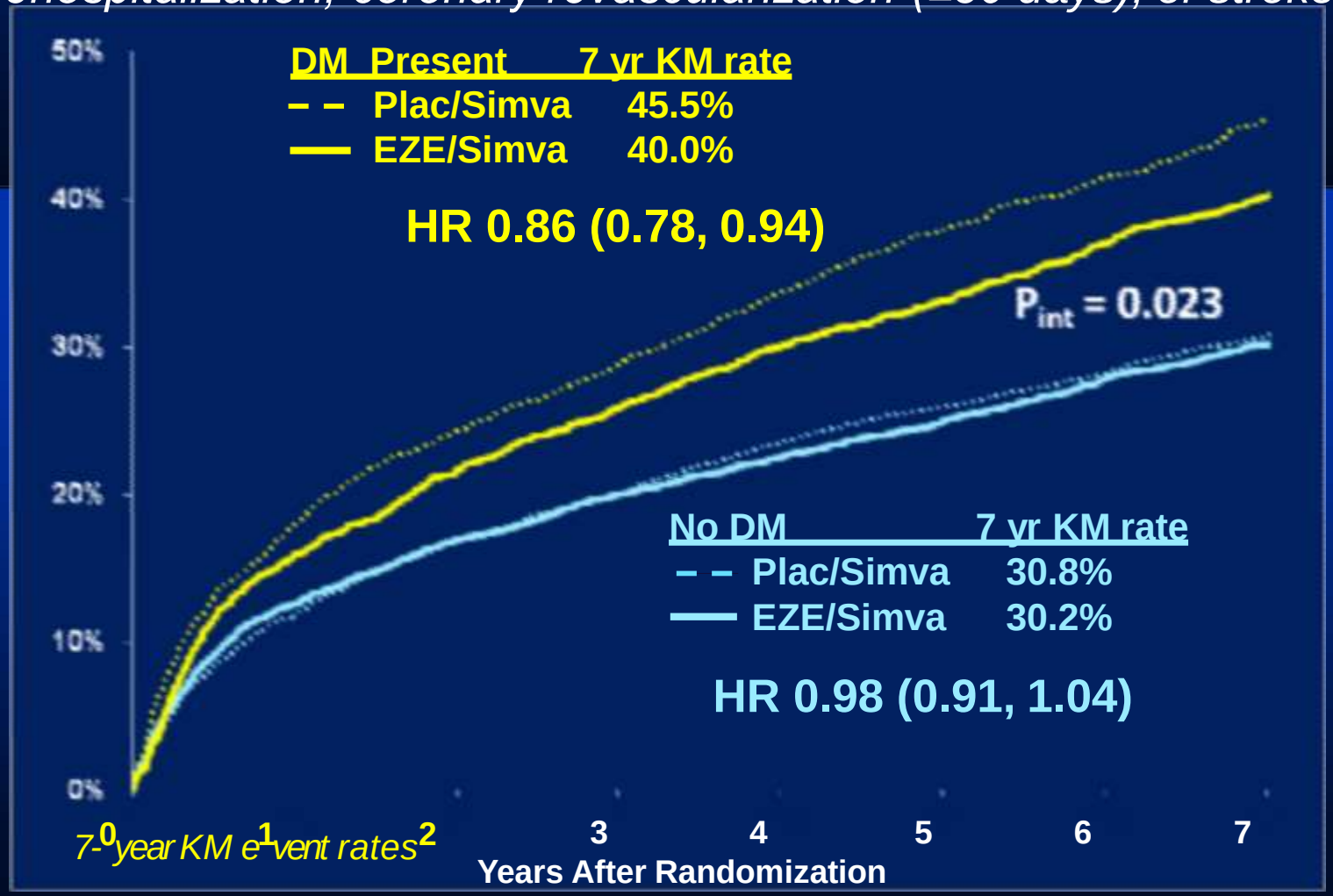


Cannon CP, N Engl J Med. 2015;372:2387

PRIMARY ENDPOINT — ITT DIABETIC VS. NON DIABETIC

IMPROVE-IT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



INDICATIONS

- Patients unable to tolerate statins
- Achieve target LDL levels despite maximally tolerated doses of high intensity statins
- Primary hypercholesterolemia (as mono or combination therapy) to reduce LDL, ApoB, TC
- Sitosterolemia
- Add on therapy to statins for primary prevention

- DOSE : 10 mg once a day , with or without food
- No dose adjustment in hepatic/renal failure
- Avoid with bile acid binding resins (either 2 hrs before or 4 hrs after resin)
- Drug interactions : HIV protease inhibitors, Gemfibrozil, Cyclosporine

PCSK-9 INHIBITORS

- Evolocumab (Repatha), Alirocumab (Praluent)
- Mechanism of action –
- PCSK9 is a hepatic protease that attaches to and internalizes LDL- receptor into lysosomes and promotes degradation of LDL- receptors
- PCSK9 inhibitor inactivates PCSK9 and prevents interaction with LDL receptor thus increasing LDL receptors on Liver surface to clear LDL
- Decrease TC, ApoB, TG, Lp(a)

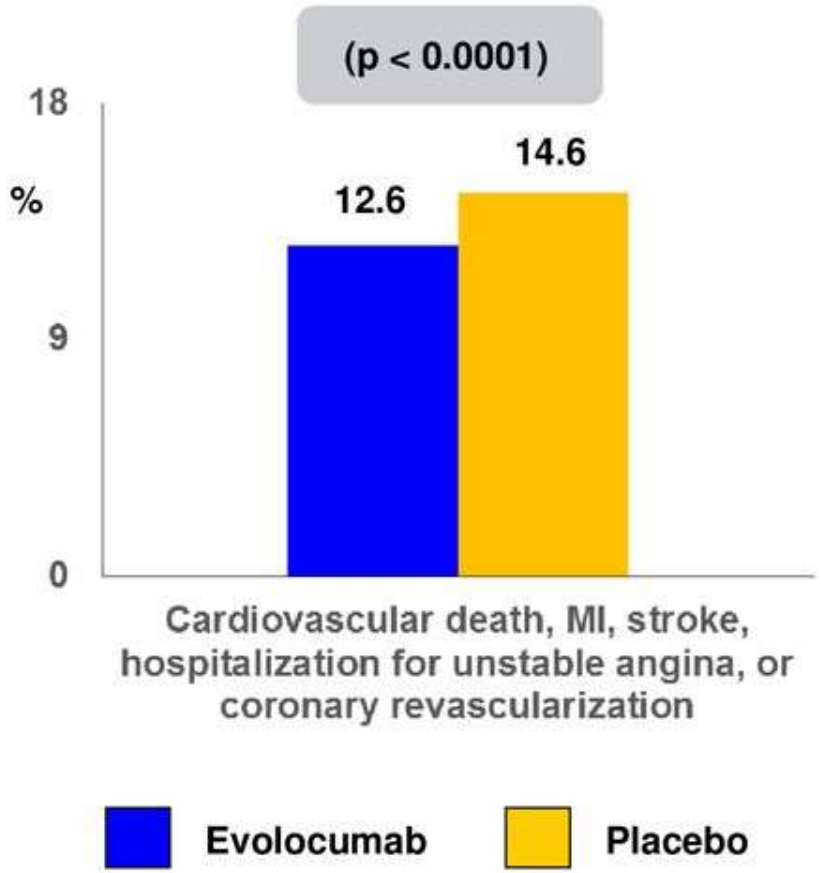
ALIROCUMAB: POST HOC DATA FROM THE ODYSSEY LONG TERM

Event	Alirocumab (N=1550)	Placebo (N=788)	P Value†
Summary of adverse events — no. of patients (%)			
Any adverse event	1255 (81.0)	650 (82.5)	0.40
Serious adverse event	290 (18.7)	154 (19.5)	0.66
Adverse event leading to study-drug discontinuation	111 (7.2)	46 (5.8)	0.26
Adverse event leading to death	8 (0.5)	10 (1.3)	0.08
Cardiovascular adverse events of interest — no. of patients (%)			
Death from coronary heart disease, including death from unknown cause	4 (0.3)	7 (0.9)	0.26
Nonfatal myocardial infarction	14 (0.9)	18 (2.3)	0.01
Fatal or nonfatal ischemic stroke	9 (0.6)	2 (0.3)	0.35
Unstable angina requiring hospitalization	0	1 (0.1)	0.34
Congestive heart failure requiring hospitalization	9 (0.6)	3 (0.4)	0.76
Ischemia-driven coronary revascularization procedure	48 (3.1)	24 (3.0)	1
Positively adjudicated cardiovascular events, including all cardiovascular adverse events listed above	72 (4.6)	40 (5.1)	0.68
Adjudicated major adverse cardiovascular events in post hoc analysis‡	27 (1.7)	26 (3.3)	0.02

CV outcomes was lower with Alirocumab than with placebo (1.7% vs. 3.3%; hazard ratio, 0.52; P = 0.02).

FOURIER

Trial design: Patients with established cardiovascular disease on statin therapy were randomized to evolocumab 140 mg subcutaneous every 2 weeks or 420 mg monthly (n = 13,784) versus placebo every 2 weeks (n = 13,780).



Results

- Cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization: 12.6% of the evolocumab group versus 14.6% of the placebo group (p < 0.0001)
- Any serious adverse event: 24.8% with evolocumab versus 24.7% with placebo

Conclusions

- Among patients with elevated cardiovascular risk on statin therapy, evolocumab versus placebo was effective at reducing adverse cardiovascular events
- Serious adverse events were similar between treatment groups

Sabatine MS, et al. N Engl J Med 2017;Mar 17:[Epub]

Table 1: Summary of FOURIER and ODYSSEY OUTCOMES trials

	FOURIER	ODYSSEY OUTCOMES
Study drug	Evolocumab	Alirocumab
Date of publication	May 4, 2017	November 29, 2018
Study design	Randomized, double-blinded, placebo-controlled	Randomized, double-blinded, placebo-controlled
Sample size	27,564	18,924
Patient characteristics	ASCVD; LDL-C ≥1.81 mmol/l (≥70 mg/dl) on statin therapy	ACS in previous 1–12 months; LDL-C ≥1.81 mmol/l (≥70 mg/dl); non-HDL-C ≥2.59 mmol/l (≥100 mg/dl); ApoB ≥2.07 mmol/l (≥80 mg/dl); high-intensity or max tolerated statin dose
Treatment dose	Subcutaneous 140 mg every 2 weeks or 420 mg monthly	Subcutaneous 75 mg every 2 weeks
Primary endpoint	MACE: composite of cardiovascular death, MI, stroke, hospitalization for UA or coronary revascularization	MACE: composite death from CAD, nonfatal MI, fatal/nonfatal ischemic stroke or UA requiring hospitalization
Follow-up duration	48 weeks	Average of 2.8 years
Primary endpoint HR	0.85; 95% CI [0.79–0.92]; p<0.001	0.85; 95% CI [0.78–0.93]; p<0.001
Mean percentage of LDL-C reduction	59% at 48 weeks	62.7% at 4 months; 61.0% at 12 months; 54.7% at 48 months
Injection-site reaction adverse events	2.1% in treatment versus 1.6% in placebo	3.8% in treatment versus 2.1% in placebo

ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; HDL-C = HDL cholesterol; LDL-C = LDL cholesterol; MACE = major adverse cardiac events; UA = unstable angina.

INDICATIONS

- Heterozygyous familial hypercholesterolemia for primary prevention with maximally tolerated statins and ezetimibe
- Maximally tolerated statins and Ezetimibe unable to achieve target LDL goals
- Homozygous familial hypercholesterolemia
- Peripheral arterial disease : Decreased MALE (Acute limb ischemia, major amputation, urgent peripheral revascularization), regardless of stage of peripheral arterial disease at baseline

BEMPEDOIC ACID

- Prodrug that is converted to active metabolite in liver by ACSVL1 (present in hepatocyte)
- Inhibit Adenosine triphosphate citrate lyase enzyme (ACL)
- LDL receptor upregulation
- Increased clearance of LDL
- INDICATIONS :

Heterozygous Familial Hypercholesterolemia

ASCVD with maximally tolerated doses of statins

Unable to tolerate statins

BEMPEDOIC ACID

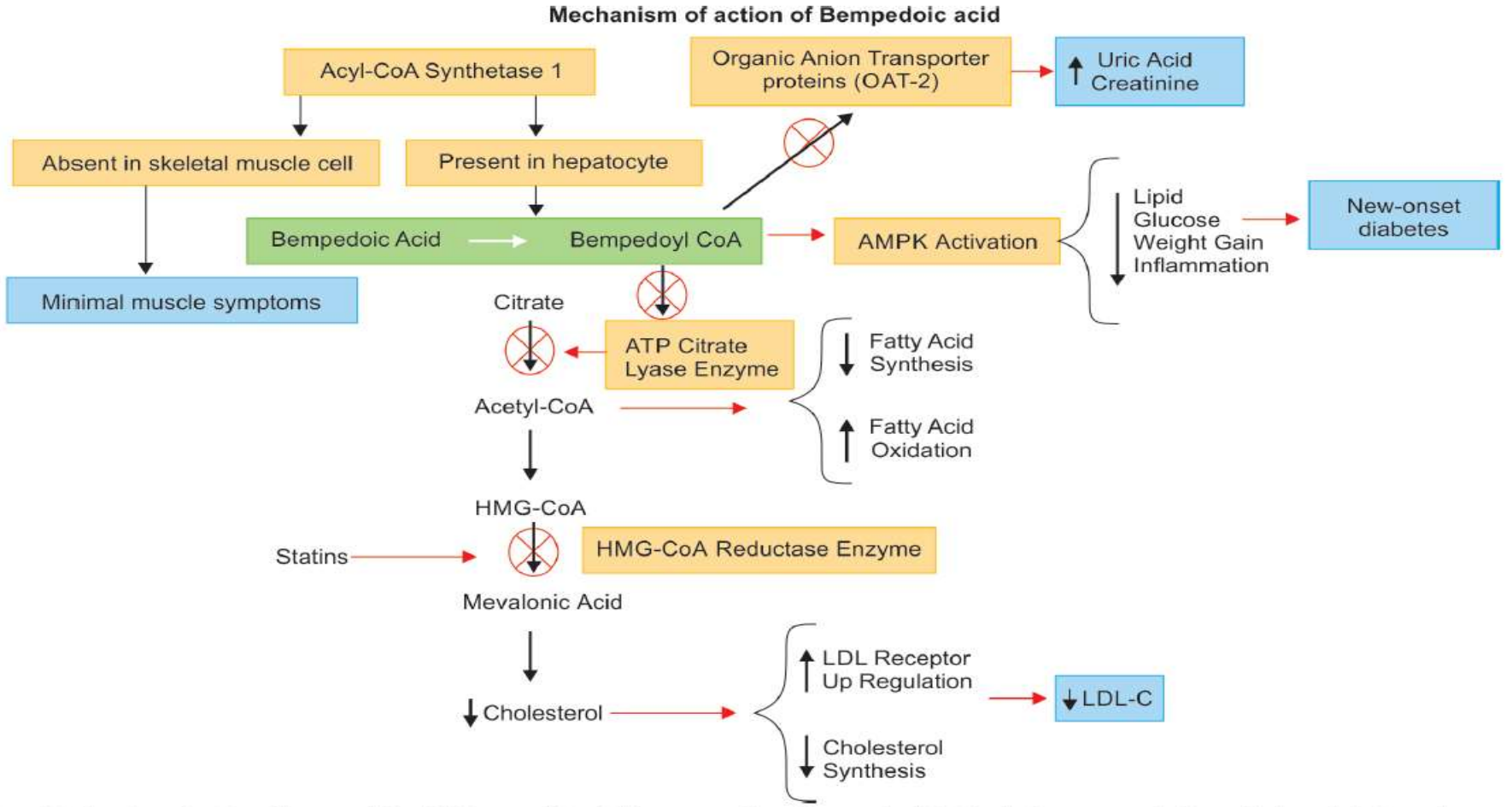
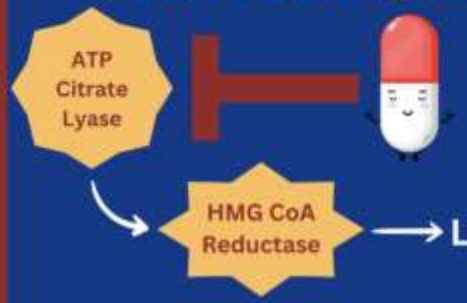


Fig. 2: Mechanism of action of bempedoic acid. Bempedoic acid is converted into bempedoyl CoA in the hepatocyte by long-chain acyl-CoA synthetase 1, which reduces intrahepatic cholesterol by inhibiting ACL, one step upstream of HMG-CoA reductase enzyme, which is inhibited by statins. LDL-C receptors are therefore upregulated, resulting in a decrease in serum LDL-C levels

CLEAR Outcomes Trial

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients
Nissen et al. March 2023. NEJM.

BEMPEDOIC ACID



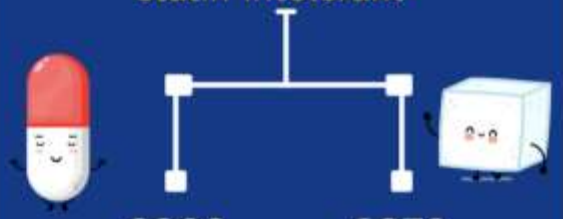
ATP Citrate Lyase inhibitor that targets cholesterol synthesis upstream of statins

QUESTION

Does bempedoic acid decrease adverse CV events in patients who require 1* or 2* prevention of CV disease but are statin-intolerant?

METHODS

Randomized, double-blinded study
Patients were 18-85 years old, with or at high risk for CVD who were statin-intolerant*



6992 **6978**

1:1 ratio of bempedoic acid 180mg or placebo
Median follow-up for 40.6 months
(> 90% white in both arms)

*Statin intolerance defined as inability to tolerate ≥2 statins, one at a low dose

PRIMARY ENDPOINT

Composite MACE†

11.7% **13.3%**

HR 0.87, 95% CI 0.79-0.96 (p = 0.004)

†MACE: death from CV cause, nontal MI, nonfatal stroke, coronary revascularization

SECONDARY ENDPOINTS

Death from CV cause, nonfatal stroke, or nonfatal MI	**8.2%**	**9.5%**
Fatal or nonfatal MI	**3.7%**	**4.8%**
Coronary revascularization	**6.2%**	**7.6%**
	All significant	
Fatal or nonfatal stroke, death from CV cause, death from any cause	**Non-significant**	

Adverse events: ↑ gout & cholelithiasis in bempedoic acid group

CONCLUSION

Use of bempedoic acid compared to placebo in patients with or at high risk for CVD resulted in a 13% relative risk reduction in composite MACE at 40 months.

Created by: @CaliRClark. Reviewed by @EuniceDuganMD, @DrAlaaDiab, @TySweeney6, @DeveshRaiMD

INCLISIRAN

- Monoclonal antibody against PCSK9
- siRNA that inhibits intracellular PCSK9 synthesis in hepatocytes by binding intracellularly to RNA and RNA induced silencing complex
- Long acting
- Used in patients where LDL goals are not achieved
- DOSE : 300 mg (2 doses) s.c on Day 1, 90,270, 450
- Decrease LDL by 56%

OMEGA 3 FATTY ACIDS

- PUFA – Reduce TG and VLDL
- No effect on LDL
- Eicosapentaenoic acid and Docosahexaenoic acid
- Also reduce inflammation, pro-inflammatory compounds, improve endothelial function, oxidative stress, plaque formation, rupture, platelet aggregation, thrombus formation
- TRIALS : REDUCE IT, STRENGTH
- INDICATION : Raised TG (>500 mg/dL)
- Dose : 4g/dL
- Contraindications : Fish or shell fish allergy, prolonged bleeding time, arthalgia, peripheral edema, constipation, Atrial fibrillation, flutter

REDUCING RESIDUAL CARDIOVASCULAR RISK: WHAT AFTER STATINS?

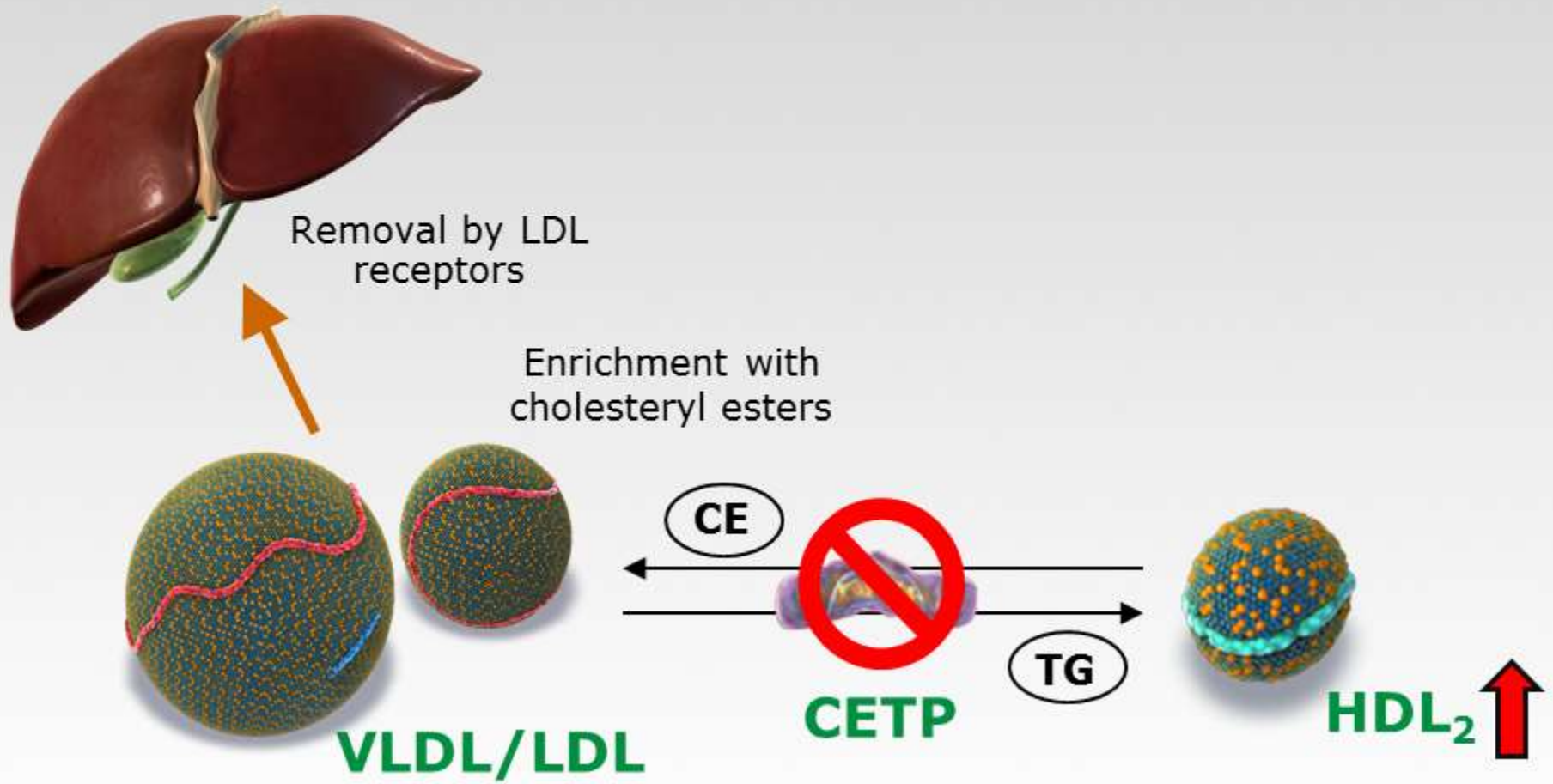
- **Currently available option (commonly used)**
  - **Fenofibrate**
    - **FIELD**- 11% risk reduction (p=0·16)
    - **ACCORD**- 8% risk reduction (P = 0.32)
  - **Ezetimibe**
    - **SHARP**- 17% risk reduction (P = 0.29)
    - **IMPROVE-IT**- 6% risk reduction (p=0.016)
  - **Niacin**
    - **AIM-HIGH**- ↑es 2% risk (P=0.79)
    - **HPS-THRIVE-2**- 4% risk reduction (P = 0.29)

All commonly used add on lipid lowering therapy have minimal and mostly non significant CV Risk reduction hence, there is a requirement of new targets and new drugs.

FIBRATES

- Decrease TG
- Reduction is LDL is low when compared to statins/PCSK9 inhibitors
- Use when TG>200 mg/dL and LDL<40 mg/dL
- First line treatment in decreasing risk of pancreatitis in hypertriglyceridemia
- Mechanism of action – PPAR alpha agonist and activates synthesis of enzymes of fatty acid oxidation thus decreasing VLDL

CETP Inhibition and the Effect on Lipoprotein Levels



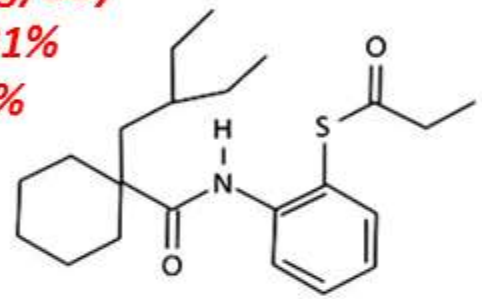
Comparison of CETP Inhibitors

Dalcetrapib

Dose: 600 mg/day

HDL-C: ↑ ~31%

LDL-C: ↓ ~2%

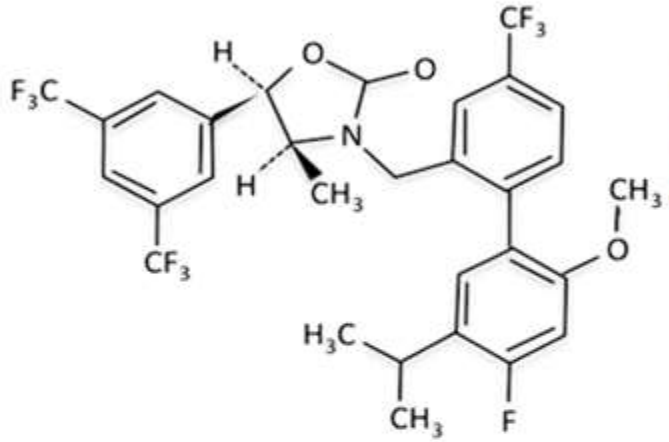


Anacetrapib

Dose: 100 mg/day

HDL-C: ↑ ~138%

LDL-C: ↓ ~40%

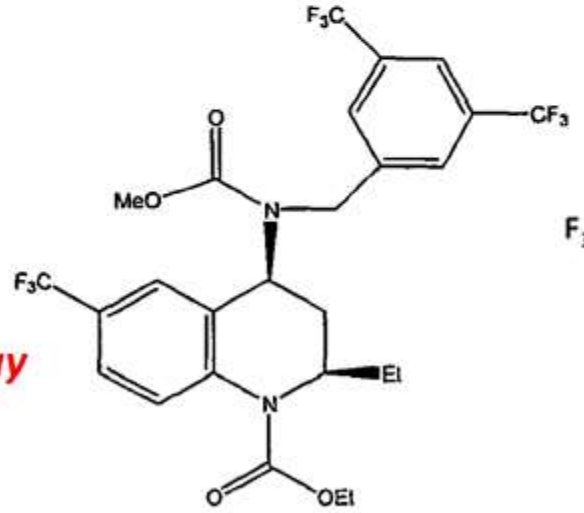


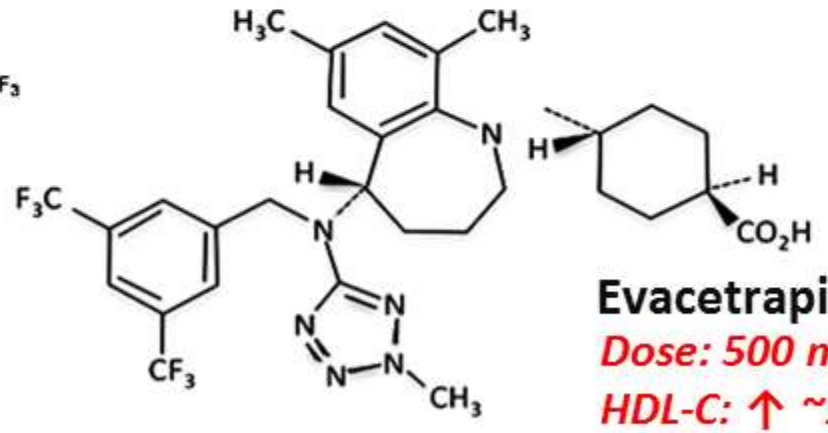
Torcetrapib

Dose: 60 mg/day

HDL-C: ↑ ~61%

LDL-C: ↓ ~24%





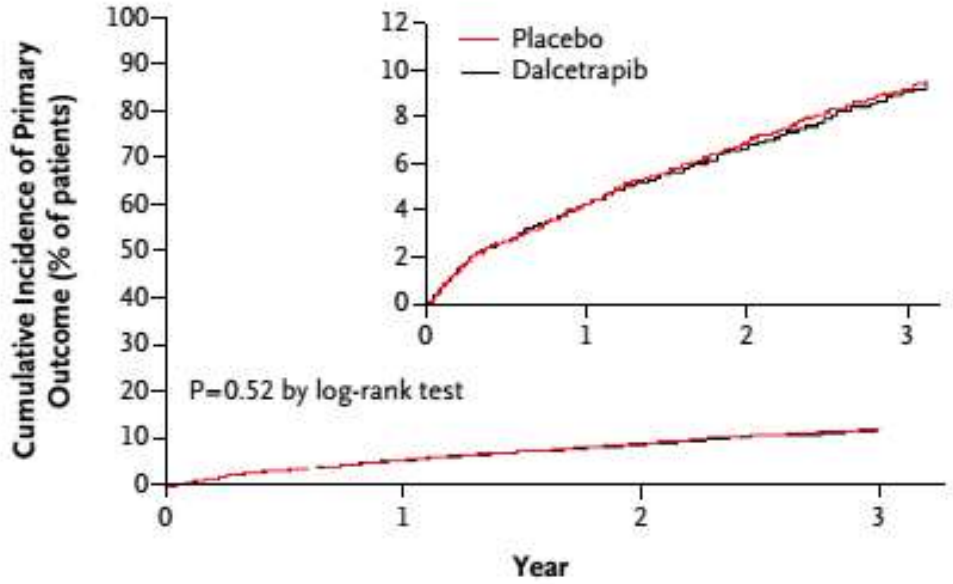
Evacetrapib

Dose: 500 mg/day

HDL-C: ↑ ~129%

LDL-C: ↓ ~36%

FAILURE OF DALCETRAPIB: DAL-OUTCOMES



No. at Risk				
Placebo	7933	7386	6551	1743
Dalcetrapib	7938	7372	6495	1736

Cumulative incidence in the two study groups of the composite primary end point of death from coronary heart disease, a major nonfatal coronary event (myocardial infarction, hospitalization for unstable angina with objective evidence of acute myocardial ischemia, or resuscitation after cardiac arrest), or stroke of presumed

HR: 1.04
P= 0.52

Different HDLs in in healthy persons and in established CVD

Functional HDL not increased

Increased CRP

Increased BP

Dalcetrapib increased HDL cholesterol levels but did not reduce the risk of recurrent cardiovascular events.

N Engl J Med 2012;367:2089-99.

Apo B synthesis inhibitor: Mipomersen

- It is an antisense therapeutic that targets the messenger RNA for Apo-lipoprotein B.
- It is administered as a Subcutaneous weekly injection.
- **Approved for Homozygous Familial Hypercholesterolemia**

MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN (MTTP) INHIBITOR

Lomitapide

- Lomitapide inhibits the microsomal triglyceride transfer protein (MTP or MTTP) which is **necessary for very low-density lipoprotein (VLDL)** assembly and secretion in the liver.

- Phase -3 results at 26 weeks showed an average 40% reduction in LDL with lomitapide.

- **Approved for Homozygous Familial Hypercholesterolemia**

NEWER ANTIBODIES

1. GENE THERAPY

VOLANESOREN ,VUPANORSEN,PELACARSEN

AKCEA-APO C III : 2nd generation anti sense oligonucleotide to apo C III and TG

2. EVINACUMAB

Reduces TG

Antibody to ANGPTL-3

FDA approved for homozygous FH

THANK YOU