Advanced Therapies for Cholesterol Management

February 13, 2024

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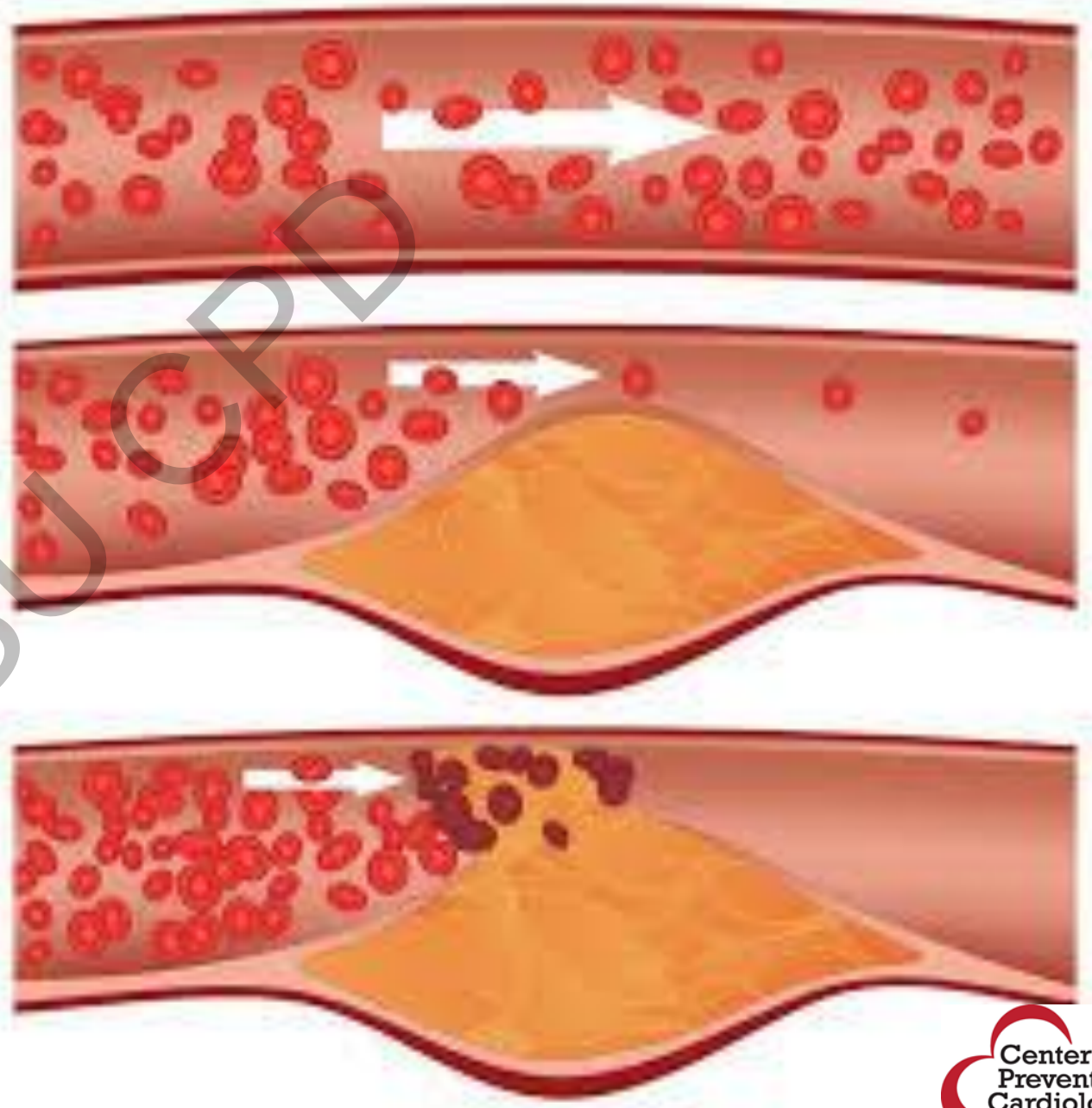
Objectives

1. Evaluate strategies to interpret test results accurately
2. Refine risk assessment, and identify treatment goals for primary and secondary prevention of atherosclerotic cardiovascular disease.
3. Discuss the available statin and non-statin therapies for management of hyperlipidemia.

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Why Lower Cholesterol?

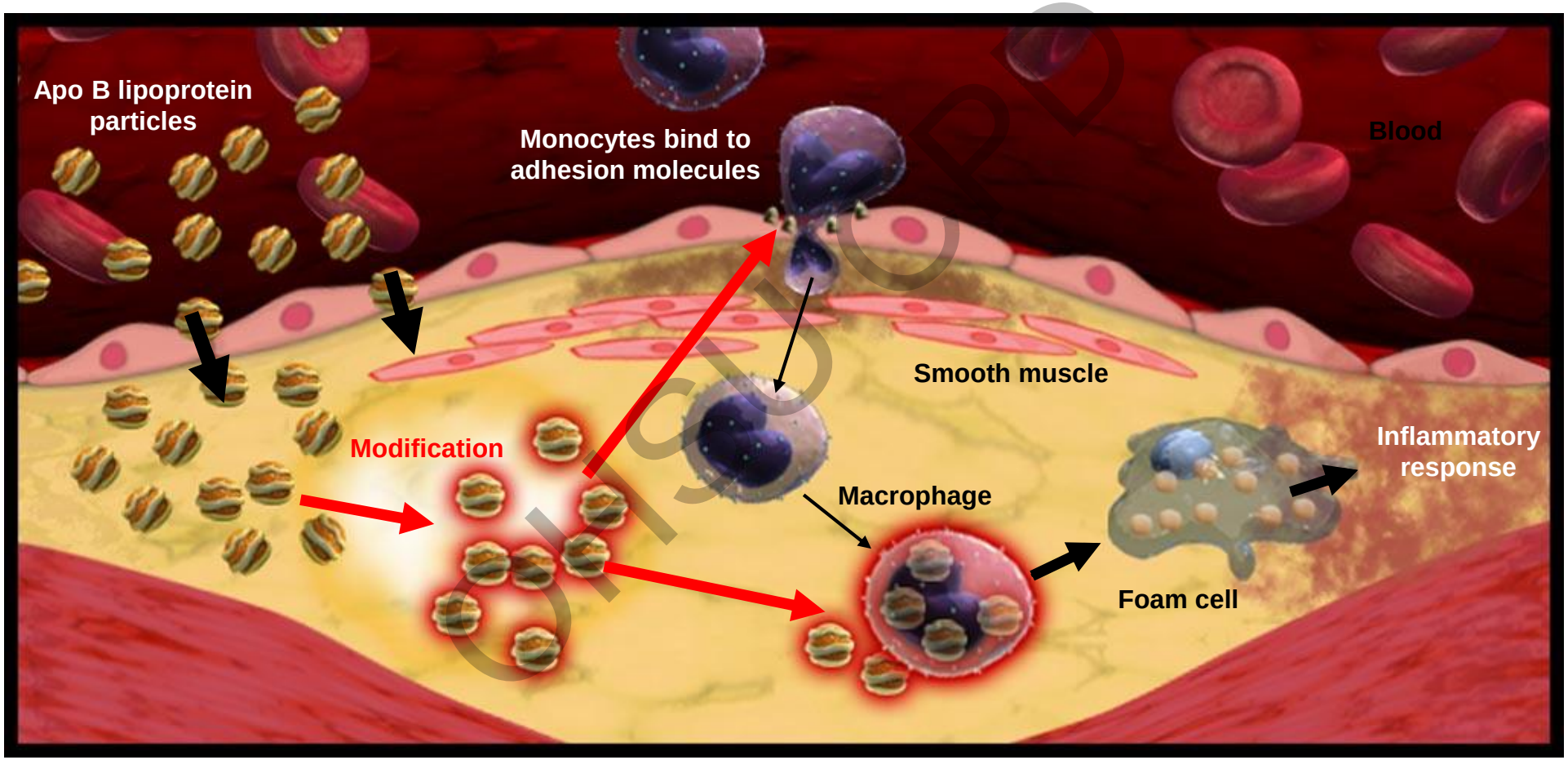
- More than half of U.S. adults don’t know heart disease is leading cause of death, despite 100-year reign
- Nearly half of all people in the U.S. (48.6% have some type of cardiovascular disease (CVD).
- 3.72 million deaths globally were attributed to high LDL-C



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Circulation. 2024;149:e00–e00.

Plasma Lipids and the Artery wall

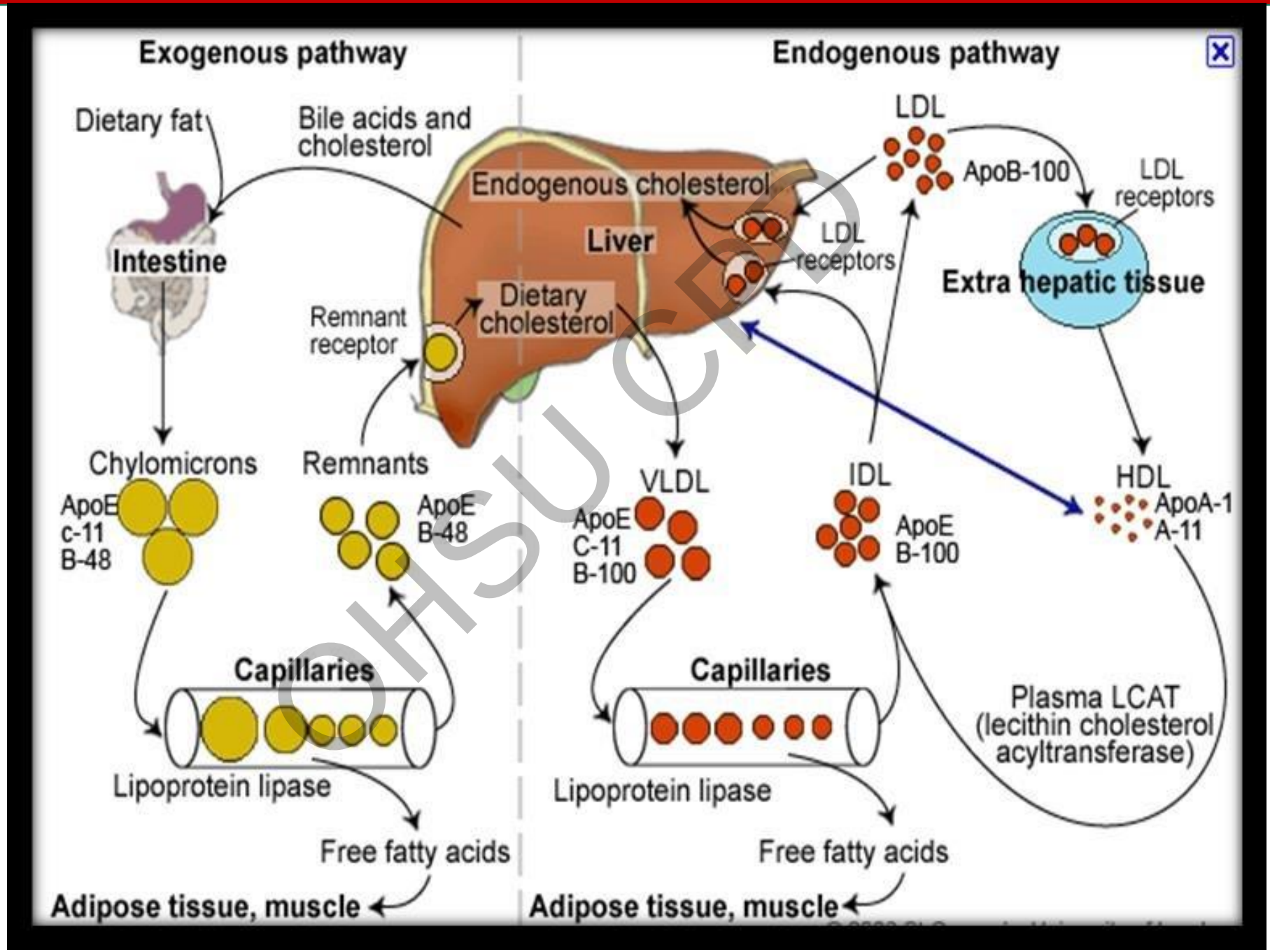


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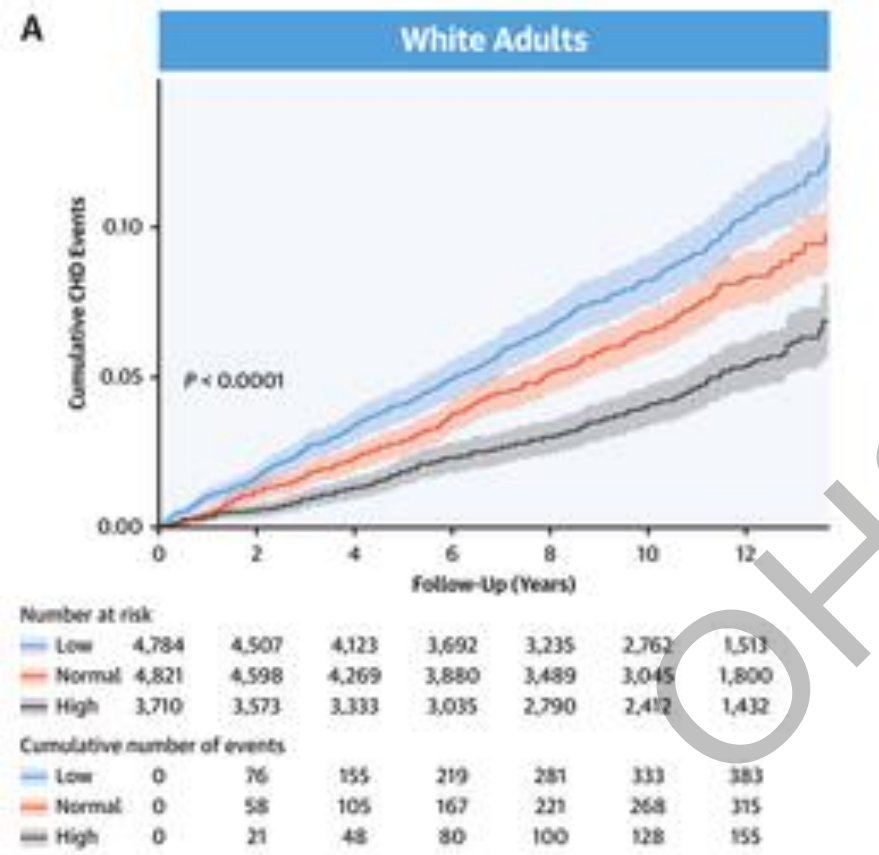
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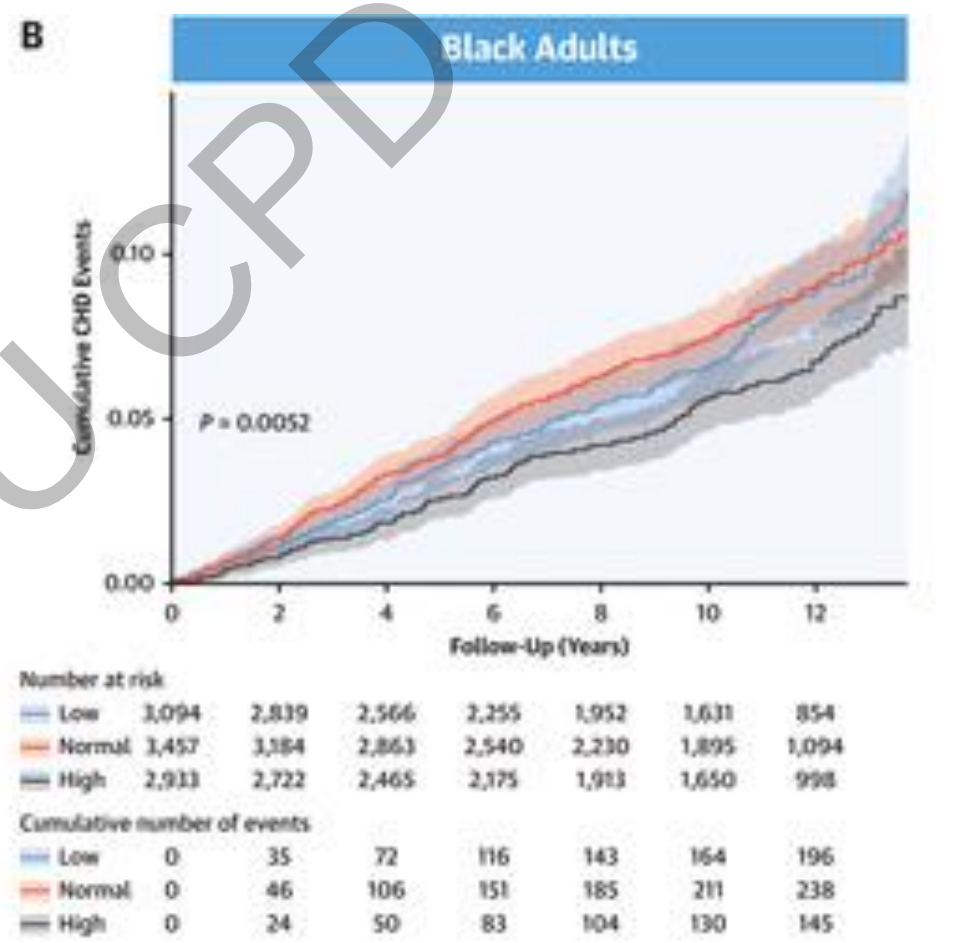


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Race-Dependent Association of HDL with Incident CAD





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JACC 2022 Nov, 80 (22) 2104-2115

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Measurement	Desirable Values	High Alert Values (refer to Lipid Specialist)
Total Cholesterol	< 200 mg/dL	
Triglycerides	< 150 mg/dL fasting < 175 mg/dL non-fasting	500-999 mg/dL severe > 1000 mg/dL critical
HDL-C	> 40 mg/dL men > 50 mg/dL women	< 20 mg/dL
LDL-C	< 100 mg/dL < 70 mg/dL ASCVD/high risk **< 55 mg/dL very high risk**	< 50 mg/dL untreated > 190 mg/dL
Non-HDL-C	< 130 mg/dL < 100 mg/dL ASCVD/high risk **< 85 mg/dL very high risk**	> 220 mg/dL Consider inherited hyperlipidemia

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Journal of Clinical Lipidology (2021)15, 629-648
JACC, Vol 80, No 14 (2022) 1366-1418

Case

60 year old man with CAD hx PCI of LAD in 2019, HLD, HTN, DM2, OSA, and obesity

Started rosuvastatin 10 mg daily, tolerates well

Total cholesterol	163 mg/dL
Triglycerides	315 mg/dL
HDL-C	40 mg/dL
LDL-C	60 mg/dL
Non-HDL	123 mg/dL

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Methods of measuring LDL cholesterol

Method			Pros	Cons
Beta quantification (ultracentrifugation)	Direct		Gold Standard	Time consuming Expensive
Friedewald's equation	Indirect	LDL-c = TC – (HDL-c+VLDL-c) VLDL-c = TG/5 (fixed ratio)	Time & cost effective	Inaccurate in low LDL-c or high TG
Martin/Hopkin's equation	Indirect	LDL-c = TC – (HDL-c+VLDL-c) VLDL-c = TG/novel factor (adjustable ratio)	-Time & cost effective -More accurate than Friedewald's -Preferred for LDL-c < 70 mg/dL	-Need to use smart phone app if not lab's standardized method
Sampson's equation	Indirect	$\text{LDL-c} = \frac{\text{TC}}{0.948} - \frac{\text{HDL-c}}{0.971} - \left(\frac{\text{TG}}{8.56} + \frac{\text{TG x nonHDL}}{2140} - \frac{\text{TG}^2}{16100}\right) - 9.44$	-Time & cost effective -More accurate than Friedewald's -Preferred for TG 400-800 mg/dL	-Lacks extensive independent validation -Lacks validation if LDL-c < 40 mg/dL
Homogenous assays	Direct	163, 315, 40, 123	Time & cost effective compared to ultracentrifugation	Not extensively validated

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Eur Heart J, Volume 42(22);7 June 2021:2154–2169

Case

60 year old man with CAD hx PCI of LAD in 2019, HLD, HTN, DM2, OSA, and obesity

Started rosuvastatin 10 mg daily, tolerates well

LDL < 70	Non-HDL < 100
LDL < 55	Non-HDL < 85

Total cholesterol	163 mg/dL
Triglycerides	315 mg/dL
HDL-C	40 mg/dL
LDL-C	60 mg/dL
Non-HDL	**123 mg/dL**

LDL 85 mg/dL with Hopkins/Martin equation instead of Friedewald equation

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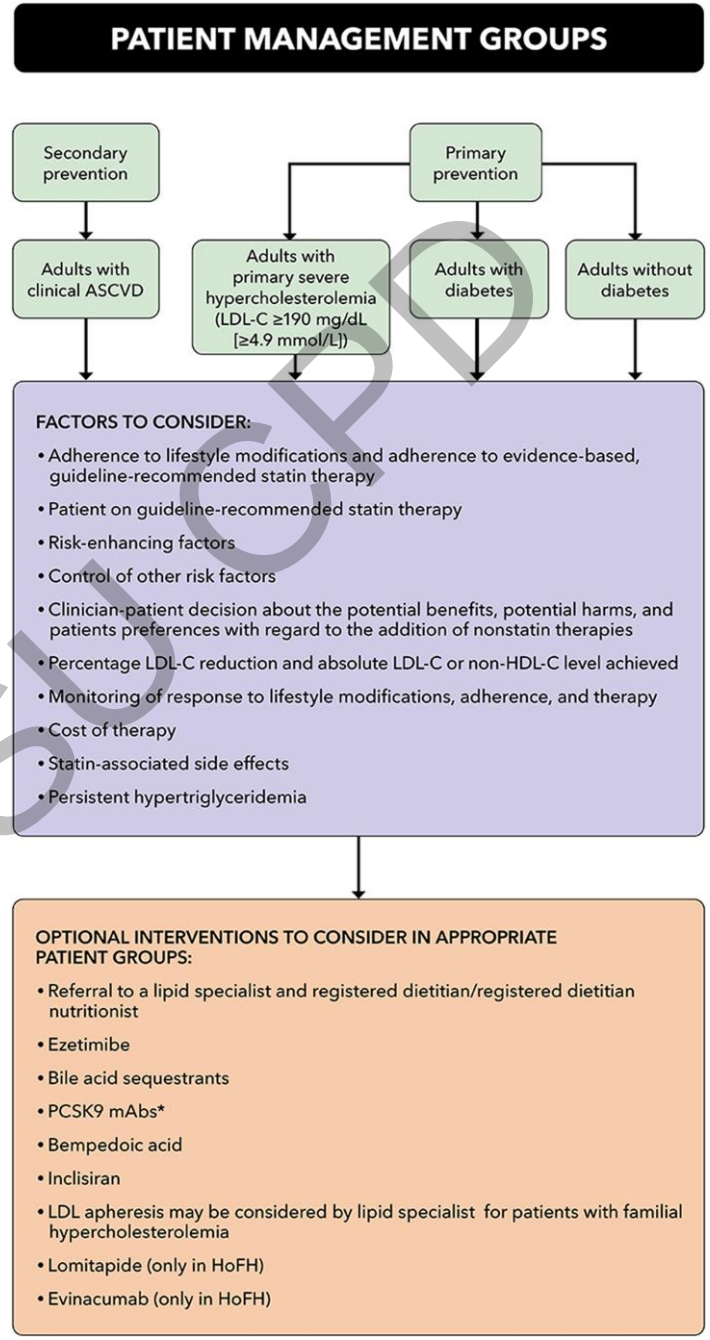
History of National Lipid Guidelines in the US

- **1988 ATP I** – LDL ≤ 130 mg/dL if 2 or more risk factors
- **1993 ATP II** – LDL ≤ 100 mg/dL if known CHD
- **2001 ATP III** – introduced 10-year risk using Framingham
- **2004 ATP III update** – LDL ≤ 70 mg/dL if secondary prevention or high risk
- **2013 ACC/AHA** – high dose potent statin vs not, no LDL goals or targets
- **2016 ACC Expert Consensus** – CVOT ezetimibe
- **2017 ACC Focused Update to 2016** – CVOT evolocumab, LDL goal ≤ 70 resumed
- **2019 ACC/AHA Multi-society** – CVOT alirocumab, PCSK9 mAbs FDA'd for ASCVD
- **2022 ACC Expert Consensus** – LDL ≤ 55 mg/dL if very high risk, bempedoic acid, evinacumab, and inclisiran approved

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NCEP-ATP – National Cholesterol Education Program – Adult Treatment Panel
AHA/ACC Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-C Lowering in the Management of ASCVD Risk: A Report of the ACC Solution Set Oversight Committee



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Case

- 60 year old gentleman
- Hypercholesterolemia
- Hypertension on lisinopril and carvedilol BP 129/72
- Diabetes with A1C 6.7% on metformin
- OSA on CPAP
- Obesity
- CAD hx PCI of LAD in 2019

Total cholesterol	253 mg/dL
Triglycerides	465 mg/dL
HDL-C	39 mg/dL
LDL-C	121 mg/dL
Non-HDL	214 mg/dL
Lp(a)	< 6 mg/dL

He did not tolerate simvastatin 80 mg in the distant past or atorvastatin 40 mg after his MI due to severe myalgias

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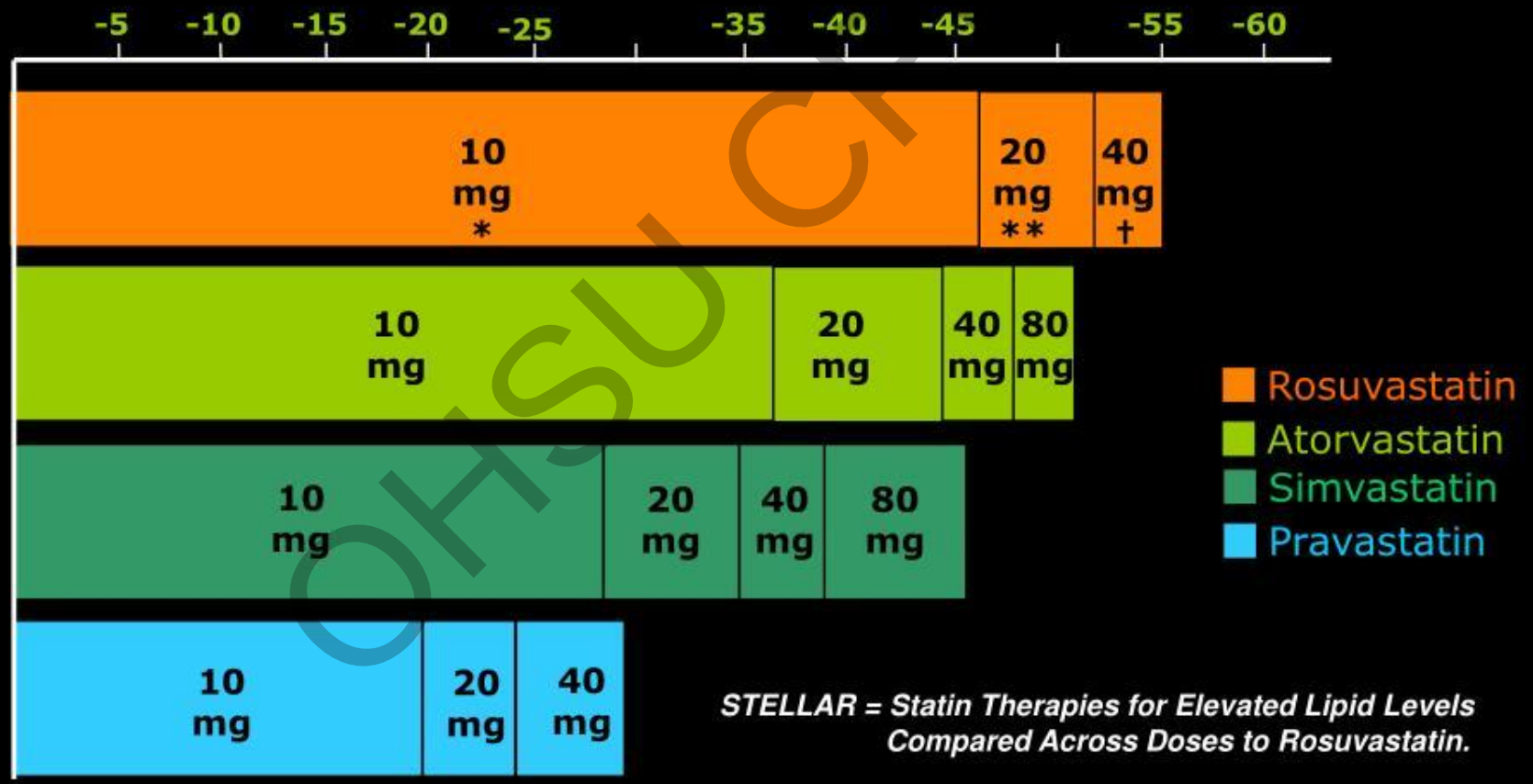
	Low-Intensity Lowers LDL < 30%		Moderate-Intensity Lowers LDL 30-49%		High-Intensity Lowers LDL ≥ 50%	
Statin	18-21%	23-30	32-40	40-45%	50-56%	58-63%
Rosuvastatin			5 mg	10 mg	**20 mg**	**40 mg**
Atorvastatin			10 mg	20 mg	**40 mg**	**80 mg**
Simvastatin	5 mg	10 mg	20 mg	40 mg		
Pravastatin	10 mg	20 mg	40 mg	80 mg		
Lovastatin	10 mg	20 mg	40 mg	80 mg		
Fluvastatin	20 mg	40 mg	80 mg			

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- Muscle side effects worse with higher mg doses
- Long ½ life – rosuvastatin and atorvastatin, consider less than daily dosing to create lower doses
- Cytochrome P450 3A4 – lovastatin, simvastatin, atorvastatin
- Severe CKD – atorvastatin
- 6-7% further LDL reduction with each doubling of a statin

Double dose of statins results in ~6% reduction of LDL

The STELLAR Trial



STELLAR = Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin.

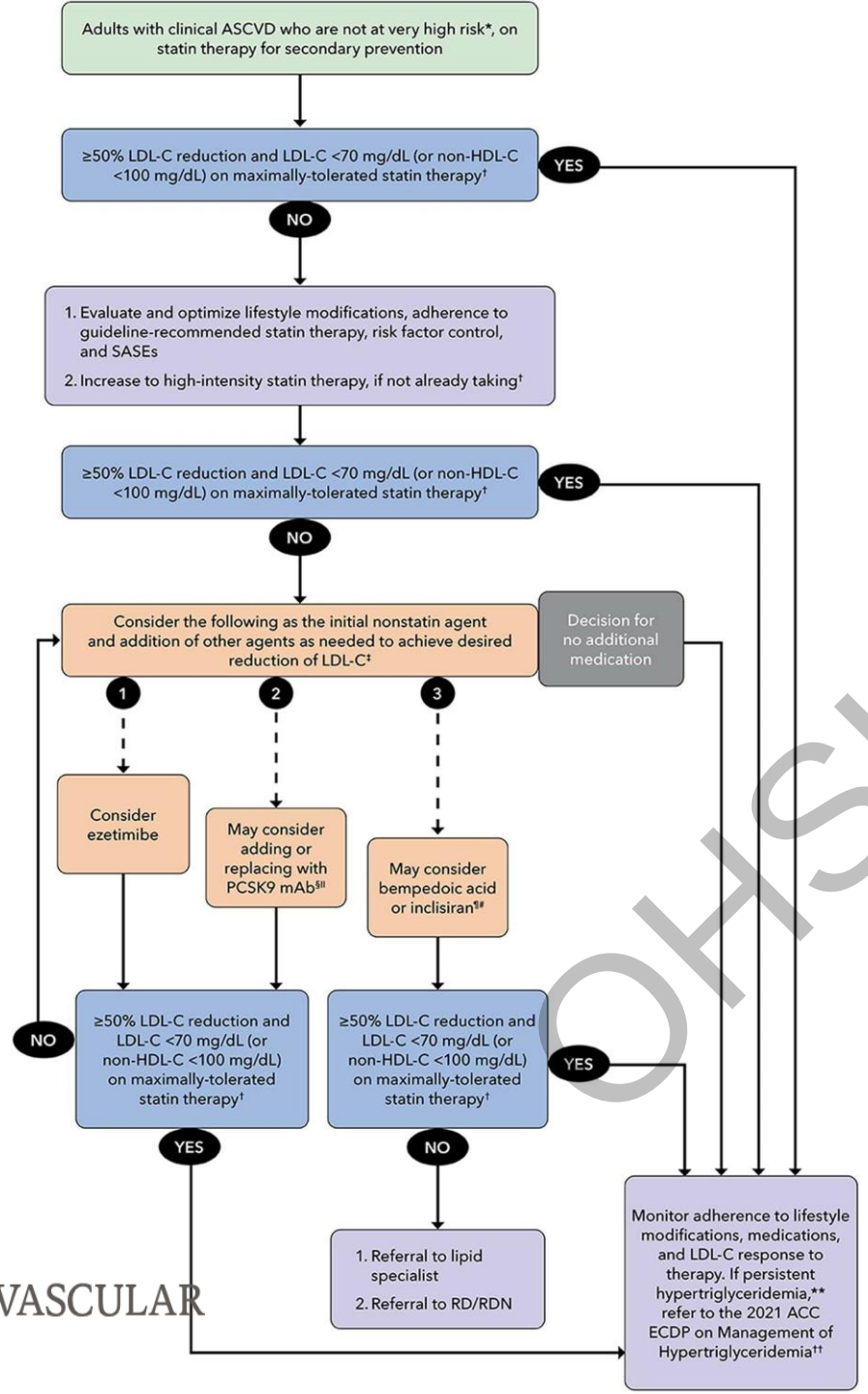
*P<.002 vs atorvastatin 10 mg; simvastatin 10, 20, 40 mg; pravastatin 10, 20, 40 mg.
**P<.002 vs atorvastatin 20, 40 mg; simvastatin 20, 40, 80 mg; pravastatin 20, 40 mg.
†P<.002 vs atorvastatin 40 mg; simvastatin 40, 80 mg; pravastatin 40 mg.
Adapted from Jones et al. *Am J Cardiol* 2003;92:152–160.

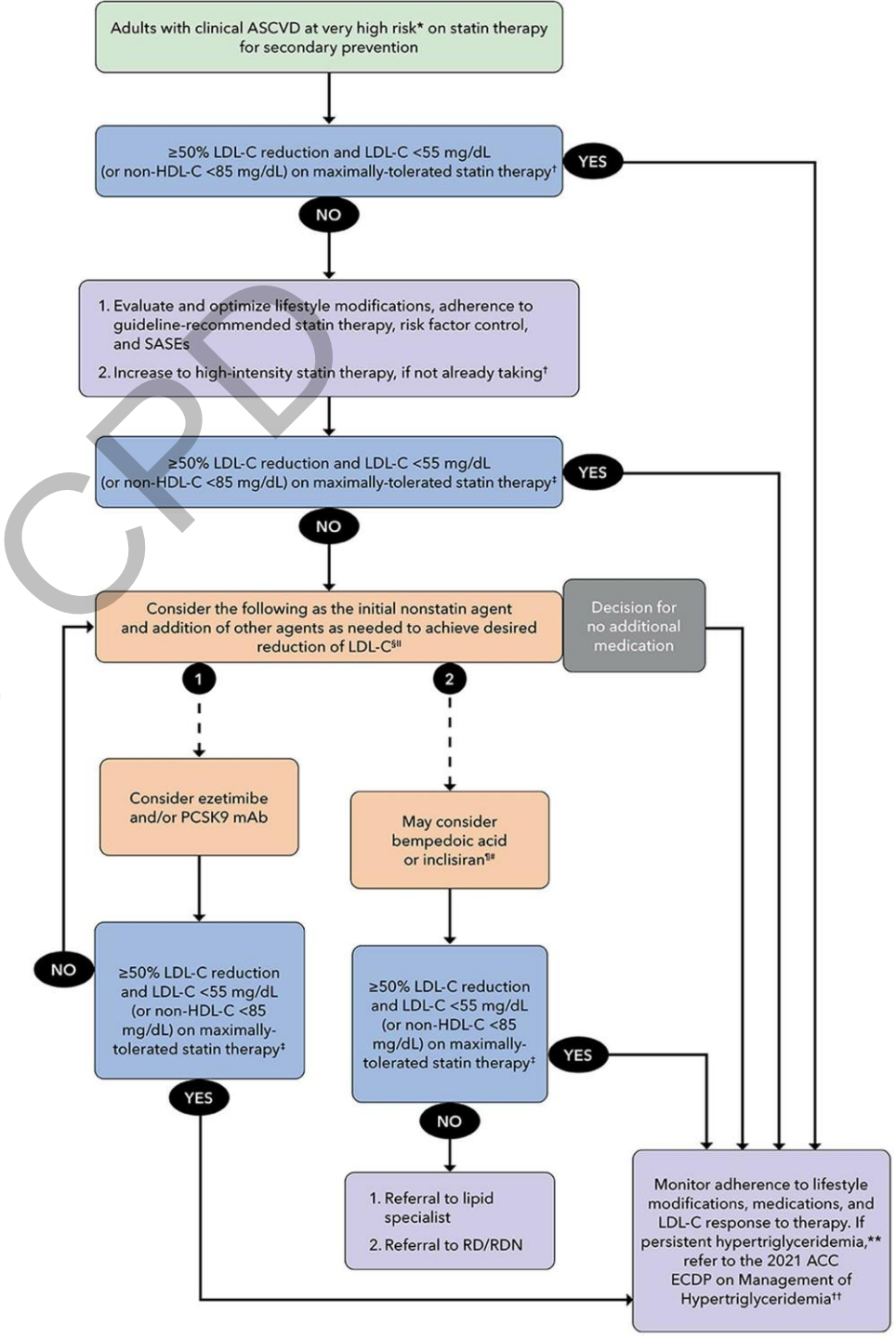
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	Low-Intensity Lowers LDL < 30%		Moderate-Intensity Lowers LDL 30-49%			High-Intensity Lowers LDL ≥ 50%	
Statin	18-22%	22-32	32-40	40-45%	45-53%	54-58%	58-63%
Rosuvastatin	½ 2x/wk	½ QOD	QOD	5 mg	10 mg	**20 mg**	**40 mg**
Atorvastatin			10 mg	20 mg	**40 mg**	**80 mg**	
Simvastatin	5 mg	10 mg	20 mg	40 mg			
Pravastatin	10 mg	20 mg	40 mg	80 mg			
Lovastatin	10 mg	20 mg	40 mg	80 mg			
Fluvastatin	20 mg	40	80 mg				
Pitavastatin (Livalo or Zypitamag)		1 mg	2 mg	4 mg			
Ezetimibe	10 mg						

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UMHS Lipid Therapy Guideline, July, 2020
AACE Lipid Management Algorithm, Endocr Pract. 2020;26(No. 10) 1197





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Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

Major ASCVD Events

- Recent ACS (past 12 months)
- History of MI
- History of ischemic stroke
- Symptomatic PAD (history of claudication with ABI < 0.85 or previous revascularization, or amputation)

High-Risk Conditions

- Age ≥ 65 years
- HeFH
- History of CABG or PCI
- Diabetes
- HTN
- CKD
- Current smoking
- Persistently elevated LDL > 100 mg/dL despite maximally tolerated statin and ezetimibe
- History of congestive CHF

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Risk Enhancers and Biomarkers:

- Family history of premature ASCVD
- Metabolic syndrome
- Chronic kidney disease
- History of preeclampsia or premature menopause
- Chronic inflammatory disorders
- High-risk ethnic groups (e.g., South Asian)
- Persistently elevated LDL-C levels ≥ 160 mg/dL
- Persistent elevations of triglycerides ≥ 175 mg/dL
- Apolipoprotein B ≥ 130 mg/dL
- Lipoprotein(a) ≥ 50 mg/dL or 125 nmol/L
- High-sensitivity C-reactive protein ≥ 2.0 mg/L

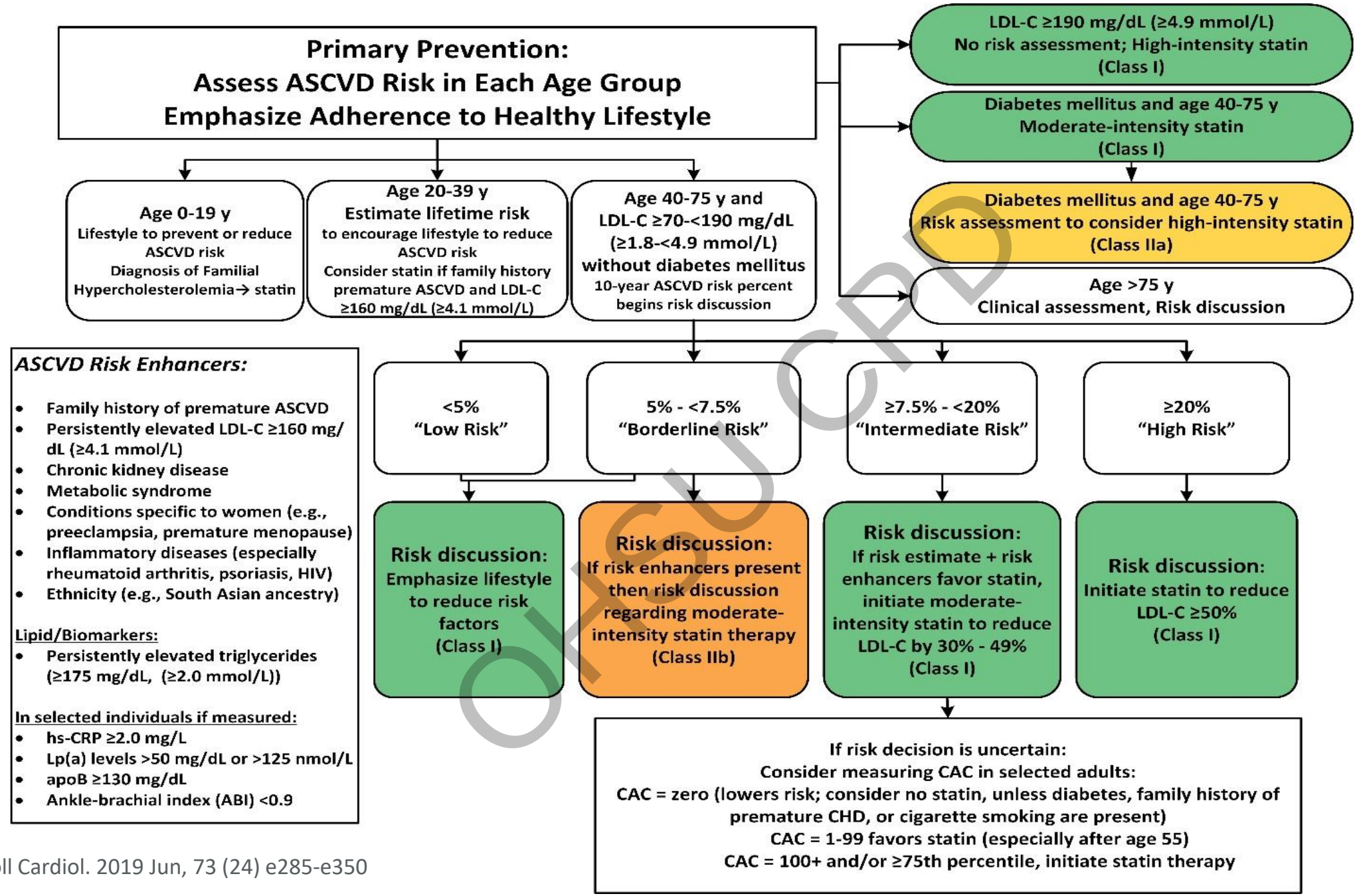
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Recommendations for pharmacological low-density lipoprotein cholesterol lowering up to 70 years of age (recommendations for persons aged >70 years, see respective recommendations tables) (2)

Recommendations	Class	Level
In patients with established ASCVD, lipid-lowering treatment with an ultimate LDL-C goal of ≥50% reduction vs baseline and an LDL-C of <1.4 mmol/L (<55 mg/dL) is recommended.	I	A
If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.	I	B
For primary prevention patients at very high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered.	IIb	C

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J Am Coll Cardiol. 2019 Jun, 73 (24) e285-e350

Recommendations for the treatment of dyslipidaemias in older people (>70 years)

Recommendations	Class	Level
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.	I	A
Initiation of statin treatment for primary prevention in older people aged ≥70 may be considered, if at high risk or above.	IIb	B
It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions.	I	C

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2021 ESC Guidelines on cardiovascular disease prevention in clinical practice
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)

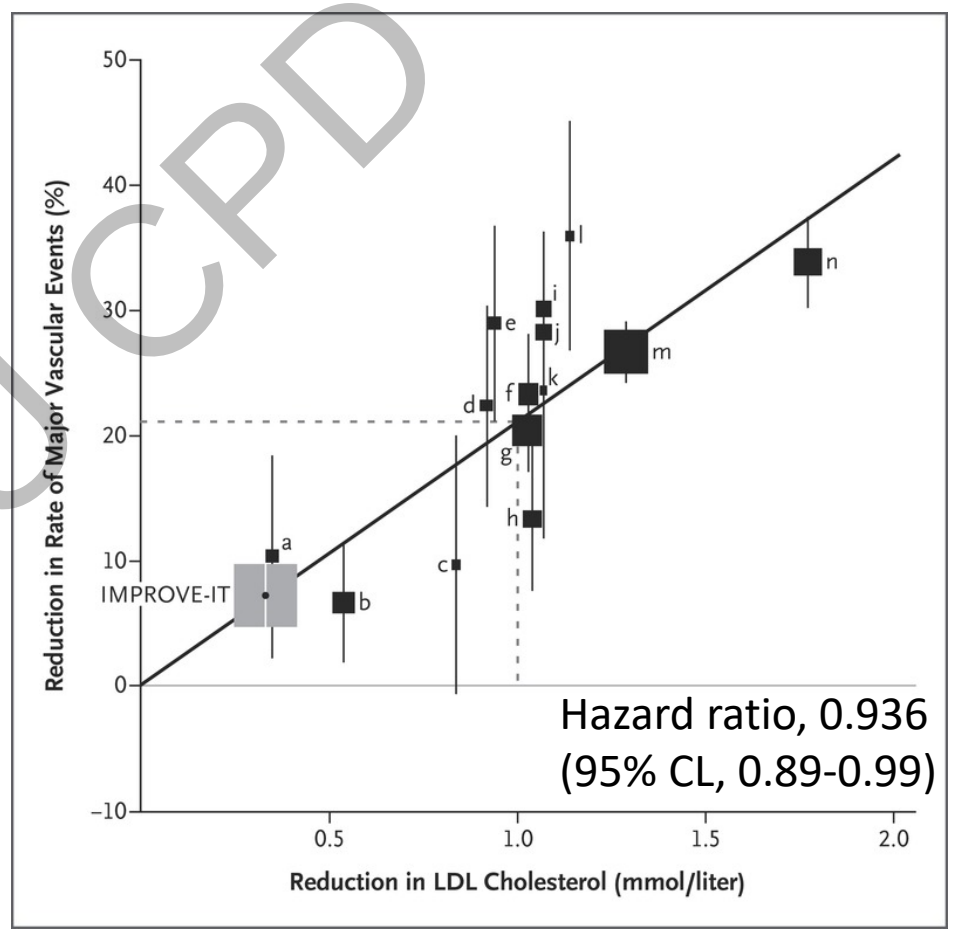
Ezetimibe

- Absorption inhibitor
- 10 mg daily, oral
- 15-20% LDL reduction
- Cheap with few side effects

IMPROVE-IT Trial

- 18,000 patients
- Ezetimibe added to simvastatin 40-80 mg showed a significant 6.4% decrease in major CV events
- Results: LDL 70 mg/dL on statin vs 54% on statin + ezetimibe

IMPROVE-IT Trial Data and Statin Trials (CTT Collaboration) for Change in LDL versus Clinical Benefit

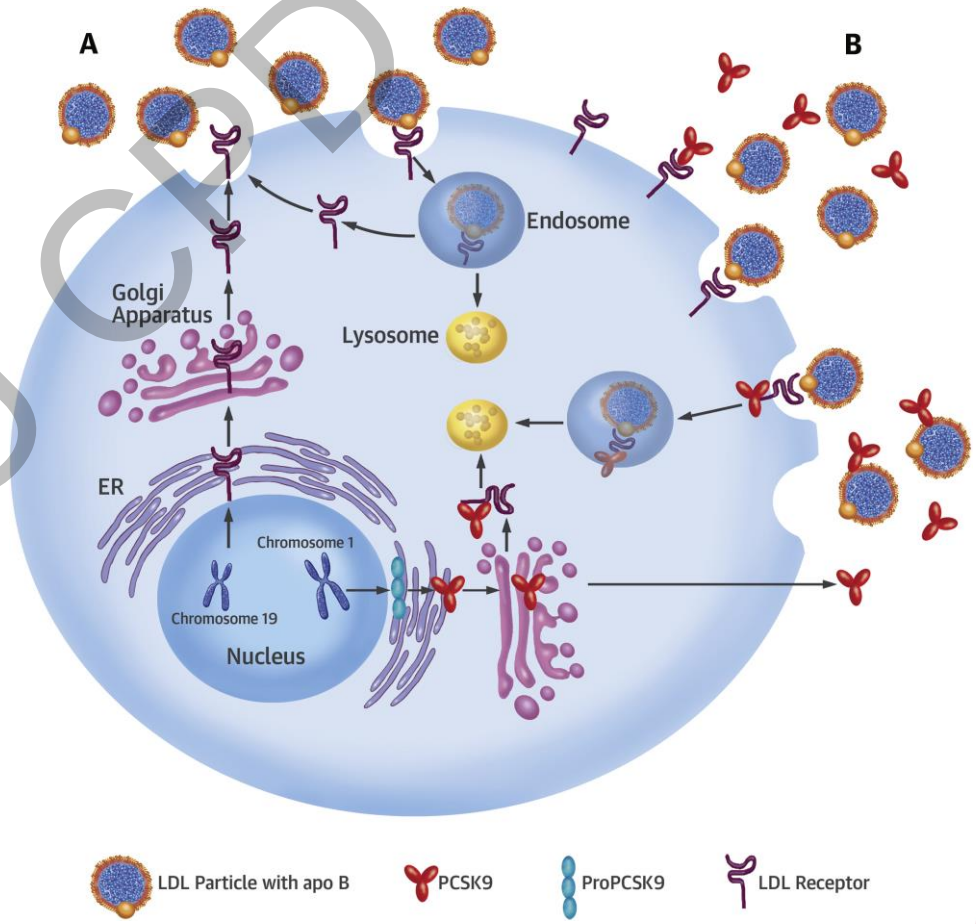


Lancet 2005; 366:1267-78
Lancet 2010; 376:1670-81
N Engl J Med 2015; 372:2387-2397

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PCSK9 Inhibitors Monoclonal Antibodies

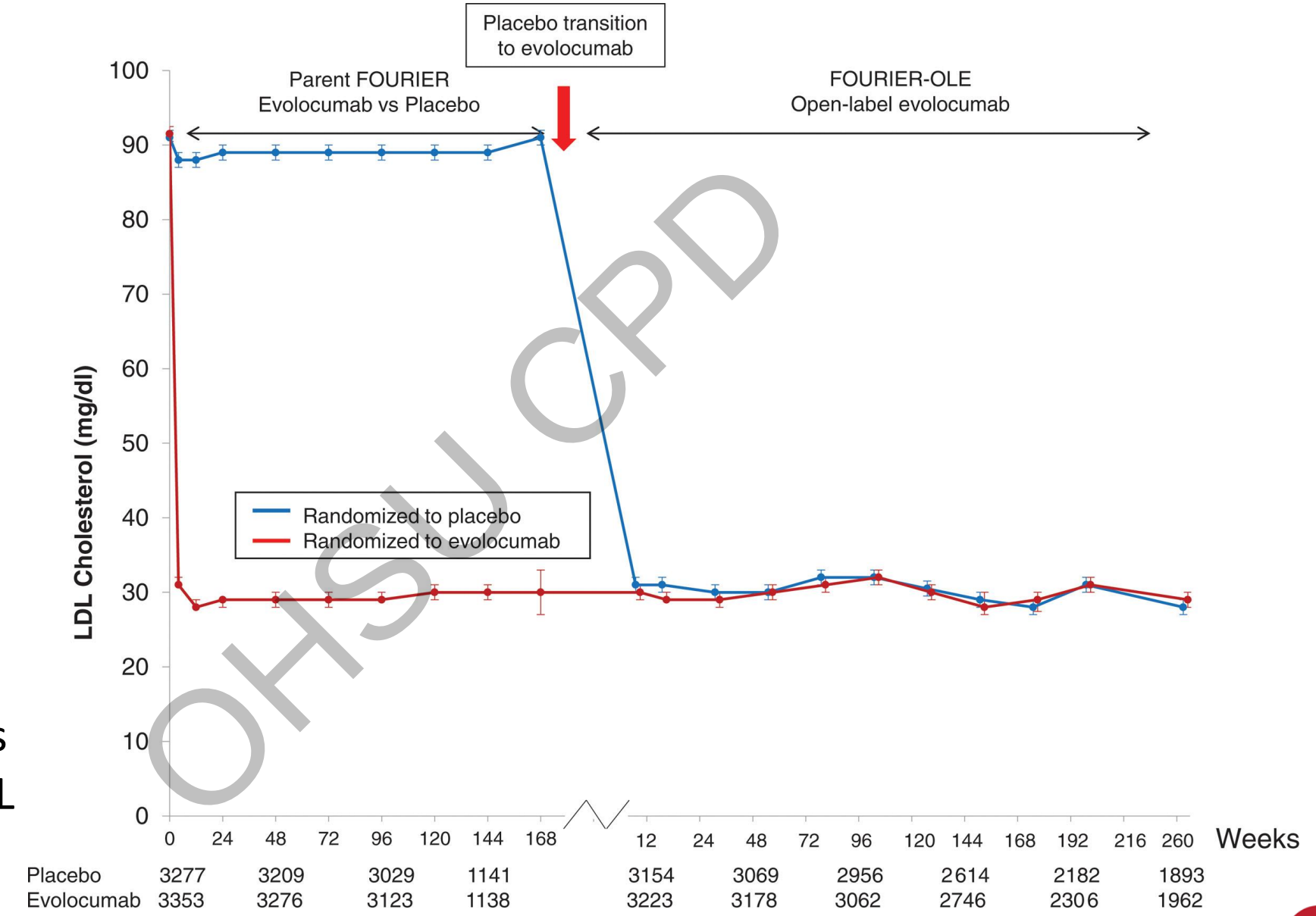
- Inhibiting PCSK9 protein prolongs the life of LDL receptors
- Reduces LDL-C by 50-60%
- May decrease Lp(a) 20-30%
- Well tolerated
- SQ injection every 2 weeks (monthly dosing option)
- Evolocumab and Alirocumab



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FOURIER and FOURIER-OLE Trials

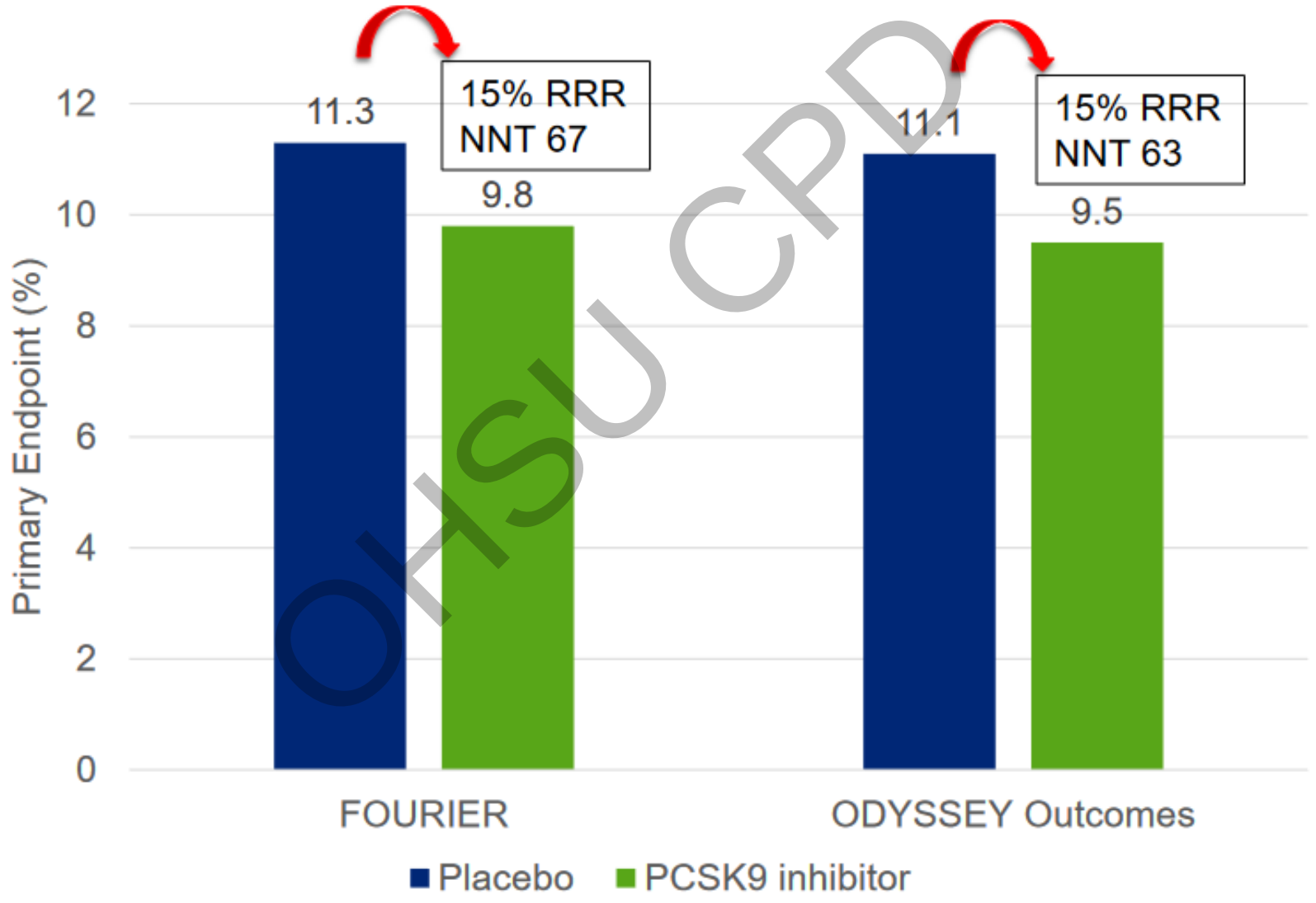
- 27,564 patients
- Established CVD
- Evolocumab added to statin vs placebo
- 5-point MACE reduction without excess safety events with LDL < 20 mg/dL



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Circulation 2022;146(15):1109-1119

Improving CV Outcomes



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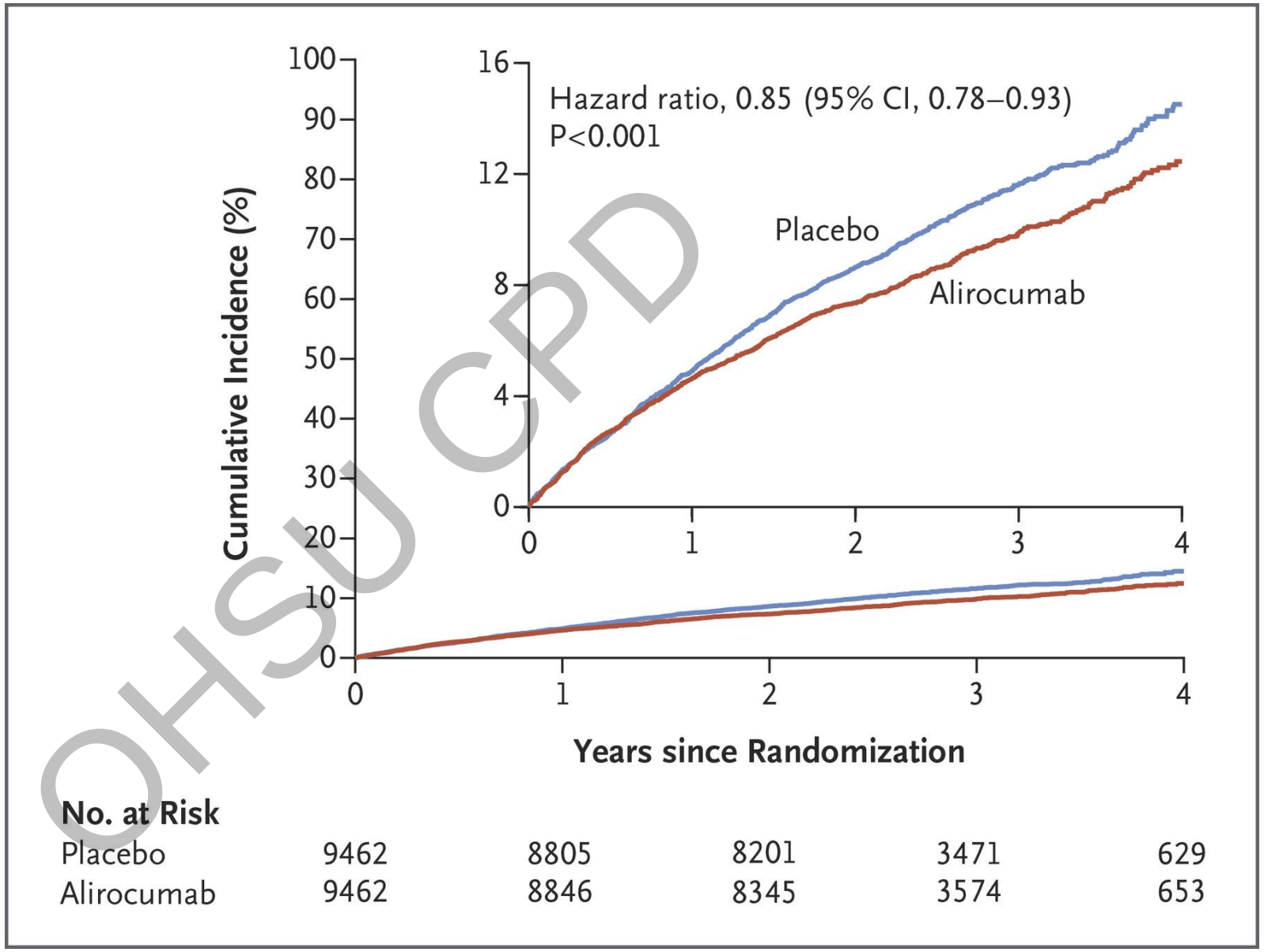
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N Engl J Med. 2017;376:1713-1722; *N Engl J Med.* 2018;379:2097-2107.

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ODYSSEY OUTCOME Trial

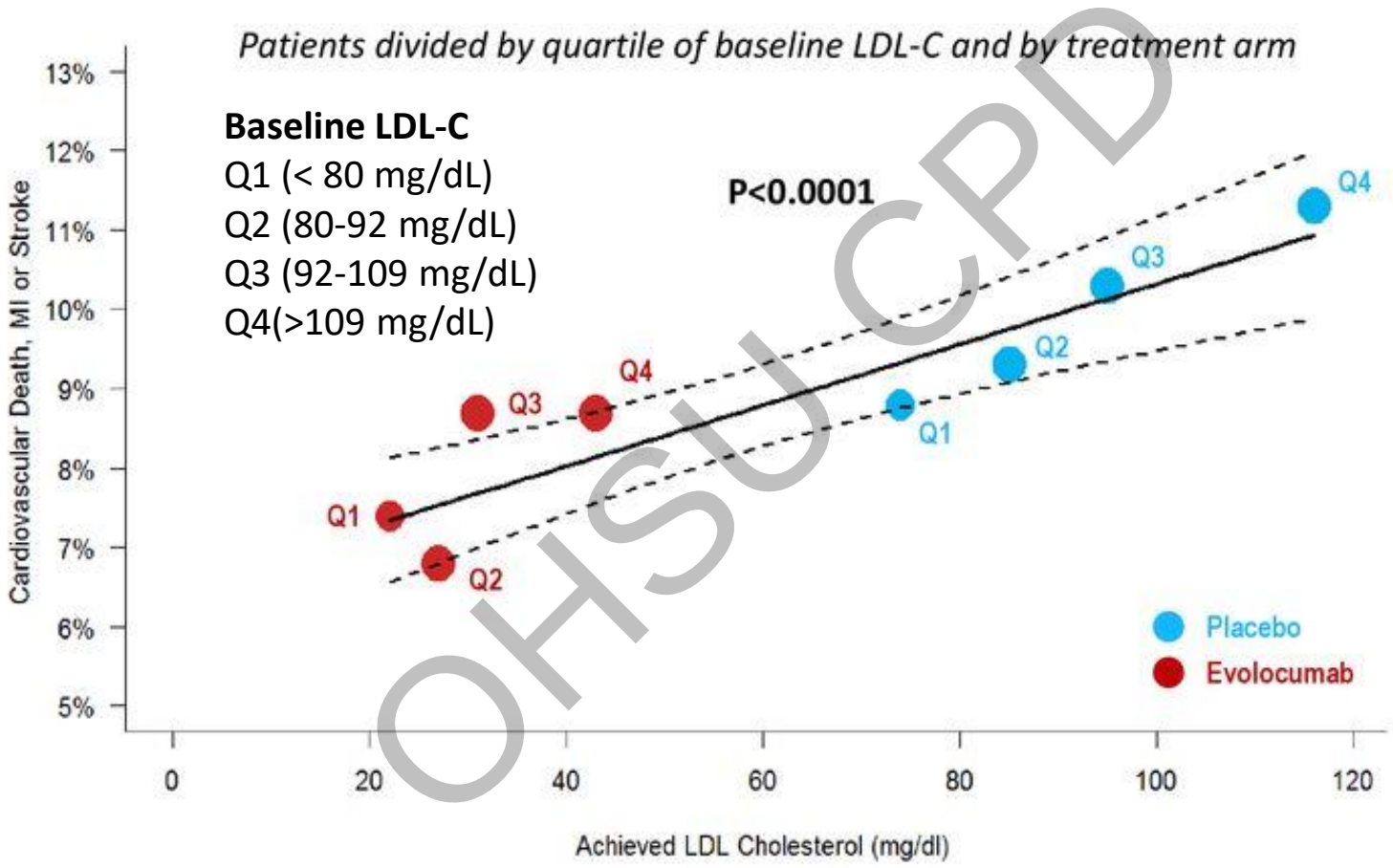
- 18,924 patients
- Recent ACS
- LDL > 70 mg/dL
- Alirocumab added to statin therapy
- Target LDL 25-50 mg/dL
- Median follow-up 2.8 years



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N Engl J Med 2018; 379:2097-2107

Lower LDL-C Is Better



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N Engl J Med 2017;Mar 17

Case

60 year old man with CAD hx PCI of LAD in 2019, HLD, HTN, DM2, OSA, and obesity

Medications: **rosuvastatin**, **ezetimibe**, lisinopril, carvedilol, aspirin, metformin

Met with dietician, working on dietary improvements

Weight down 8 lbs

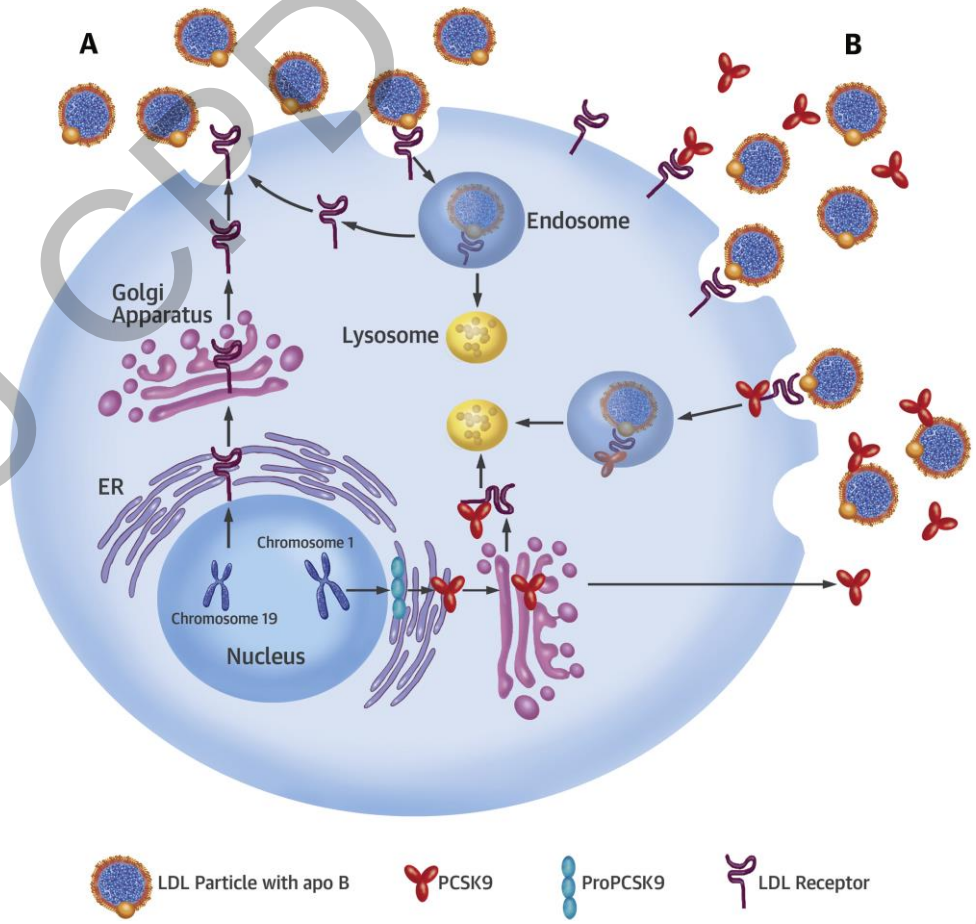
Total cholesterol	151 mg/dL
Triglycerides	195 mg/dL
HDL-C	38 mg/dL
LDL-C	74 mg/dL
Non-HDL	113 mg/dL

"I'm tired of taking all of these pills, can I switch to the cholesterol medication that you take every 6 months?"

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Inclisiran

- siRNA that inhibits PCSK9 production
- 284 mg SQ on day 1, day 90, and then every 6 months
- LDL lowering similar to mAbs
- Well tolerated
- Unlike PCSK9 mAbs medication is designed to give in clinic rather than dispense through pharmacy benefits
- Insurance may require PCSK9 mAbs be tried first

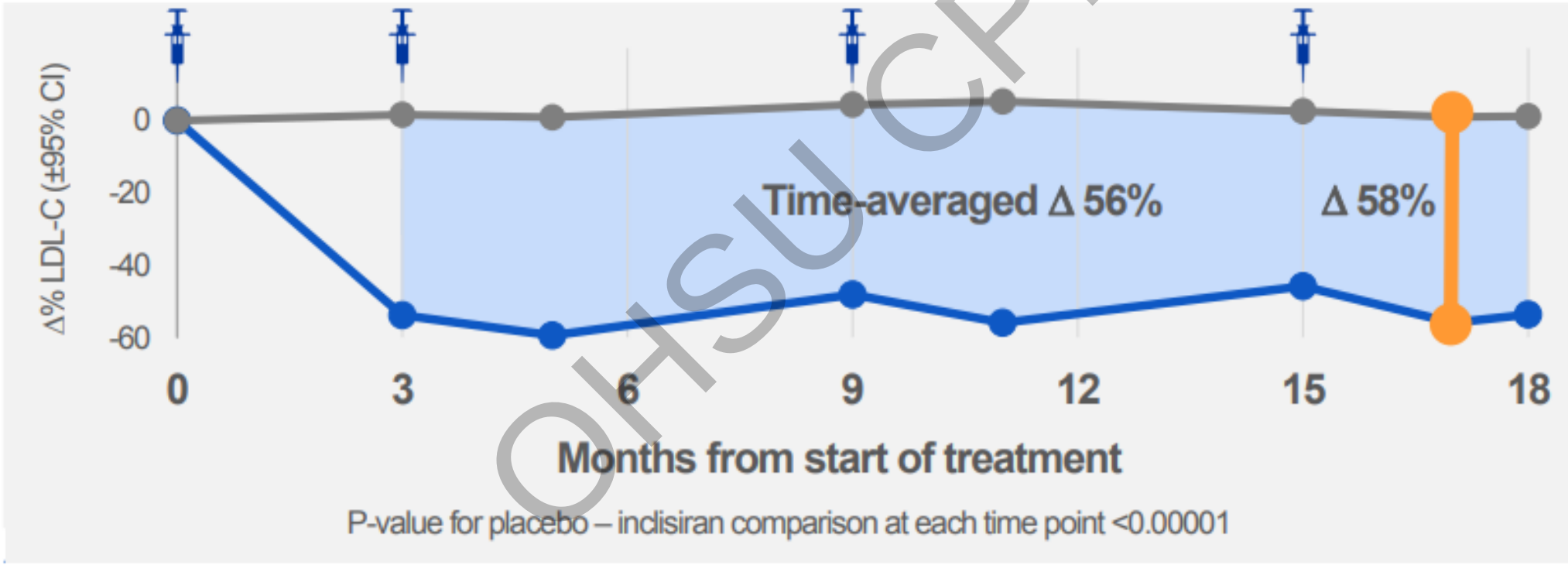


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ORION-10: Efficacy

Durable and potent with consistent effect over 18 months

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



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

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Cholesterol Lowering and Cardiovascular Outcomes

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CVOT shows benefit:

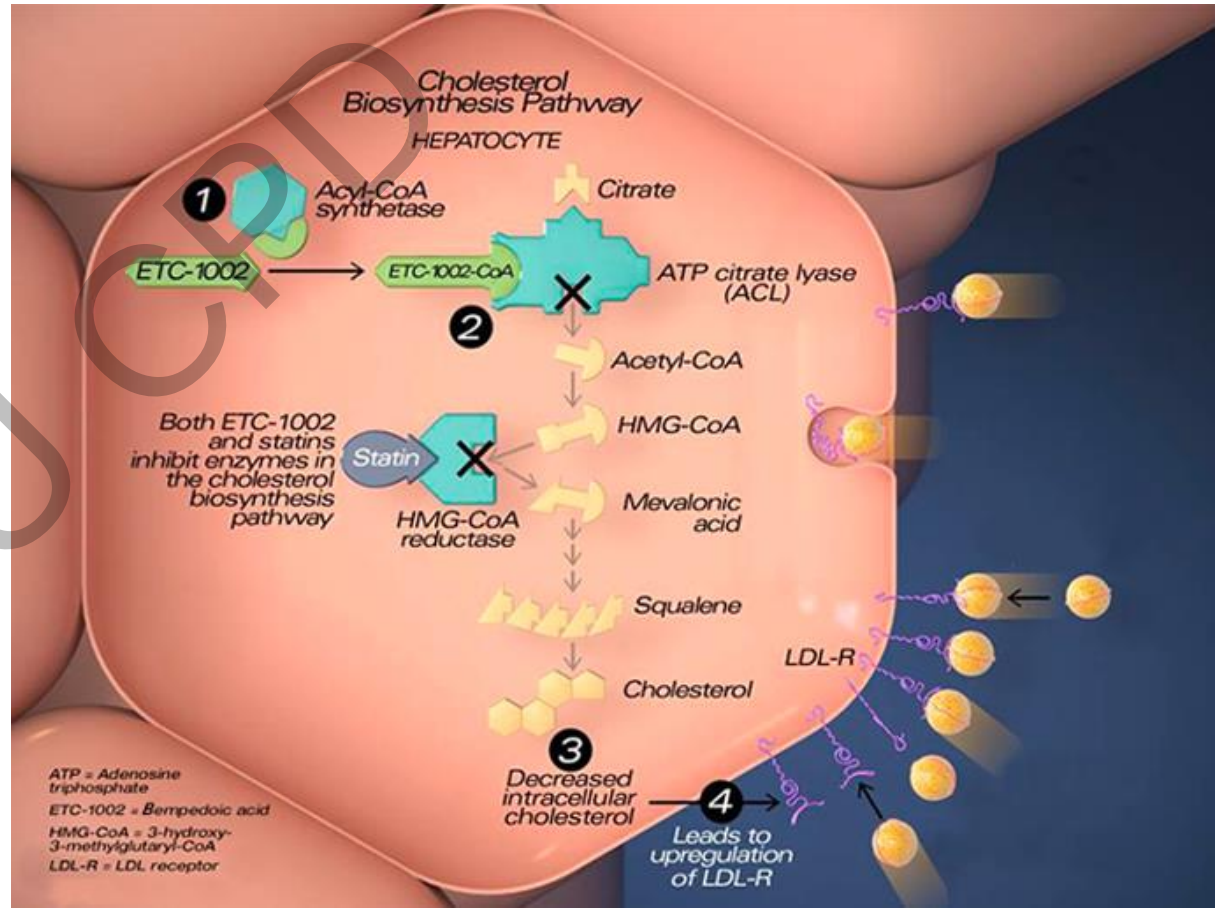
- Statins
- Ezetimibe
- Alirocumab
- Evolocumab

CVOT expected completion:

- Bempedoic acid – 2023
- Inclisiran – 2026 and 2027
- Bile acid sequestrants – 1984
- Evinacumab – HoFH
- Lomitapide – HoFH
- LDL apheresis – benefit assumed

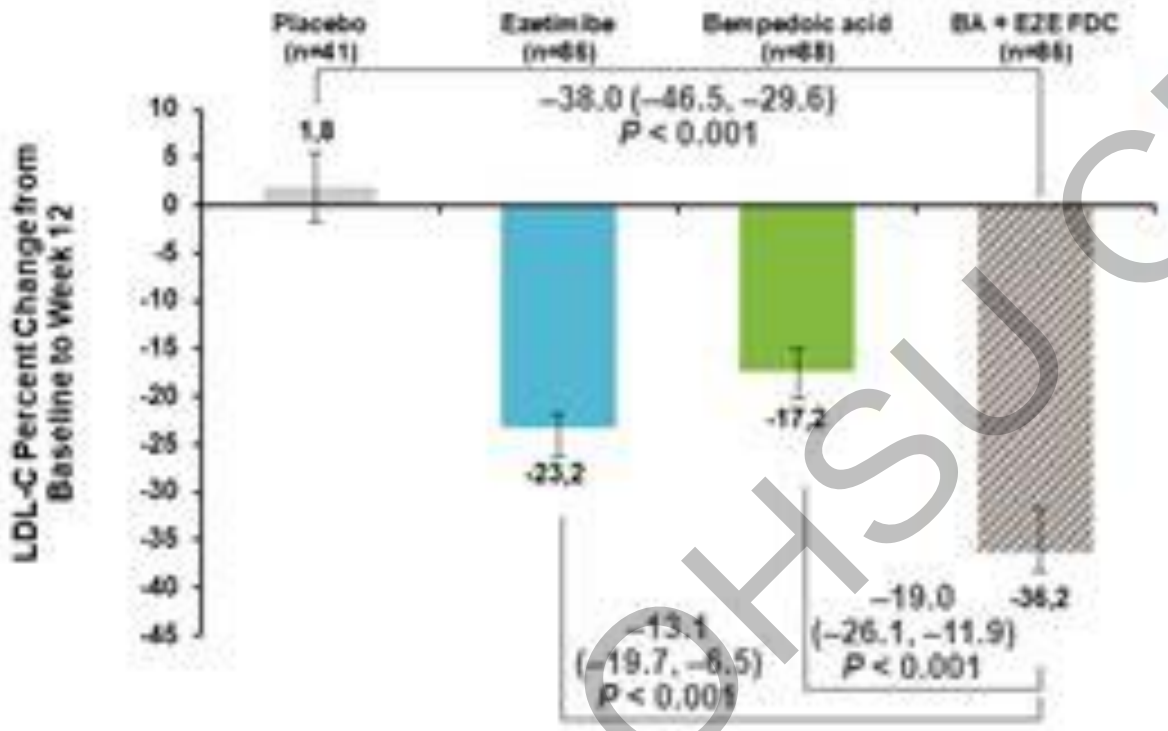
Bempedoic Acid

- ACL inhibitor blocks cholesterol synthesis in the liver
- 180 mg daily
- LDL reduction of 15-25% (greater when not taking a statin)
- Side effects: increased uric acid and gout, tendon rupture
- Combination product with ezetimibe



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Phase 3 Trial of Bempedoic Acid or Ezetimibe Alone or in Fixed-dose Combination vs Placebo



BA, bempedoic acid; EZE, ezetimibe; LS, least square.

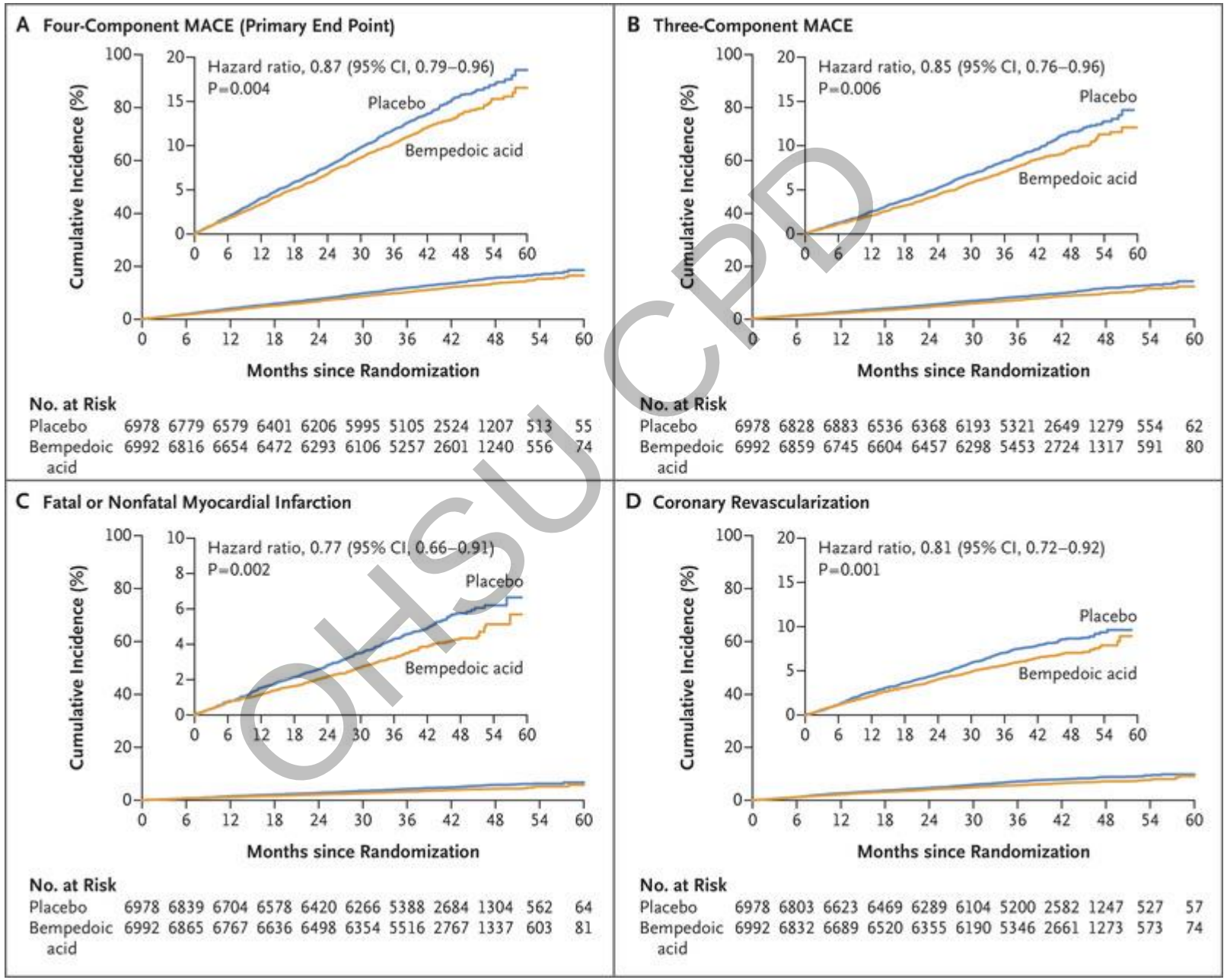
Ballantyne CM et al. *Eur J Prev Cardiol*. 2020;27:593-603.

- Patients at high risk due to ASCVD or HeFH with LDL-C ≥100 mg/dL, or multiple CVD risk factors with LDL-C ≥130 mg/dL
- All treatments added to stable background maximally tolerated statin therapy
- No safety concerns

	Non-HDL-C	Apo B
	LS Mean %Δ at 12 weeks	
Placebo	1.8	5.5
EZE	-19.9	-15.3
BA	-14.1	-11.8
BA + EZE	-31.9	-24.6

All *P*<0.05 for BA + EZE vs placebo, EZE and BA

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A Four-Component MACE (Primary End Point)
Hazard ratio, 0.87 (95% CI, 0.79–0.96)
P=0.004
Placebo
Bempedoic acid
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 6978 6779 6579 6401 6206 5995 5105 2524 1207 513 55
Bempedoic acid 6992 6816 6654 6472 6293 6106 5257 2601 1240 556 74
B Three-Component MACE
Hazard ratio, 0.85 (95% CI, 0.76–0.96)
P=0.006
Placebo
Bempedoic acid
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 6978 6828 6883 6536 6368 6193 5321 2649 1279 554 62
Bempedoic acid 6992 6859 6745 6604 6457 6298 5453 2724 1317 591 80
C Fatal or Nonfatal Myocardial Infarction
Hazard ratio, 0.77 (95% CI, 0.66–0.91)
P=0.002
Placebo
Bempedoic acid
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 6978 6839 6704 6578 6420 6266 5388 2684 1304 562 64
Bempedoic acid 6992 6865 6767 6636 6498 6354 5516 2767 1337 603 81
D Coronary Revascularization
Hazard ratio, 0.81 (95% CI, 0.72–0.92)
P=0.001
Placebo
Bempedoic acid
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 6978 6803 6623 6469 6289 6104 5200 2582 1247 527 57
Bempedoic acid 6992 6832 6689 6520 6355 6190 5346 2661 1273 573 74

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FDA-approved indications for cholesterol lowering medications

- ❑ High cholesterol
  - Statins
  - Ezetimibe
  - Bile acid sequestrants
- ❑ ASCVD and LDL above goal
- ❑ Familial Hypercholesterolemia
  - PCSK9 mAbs
  - Inclisiran
  - Bempedoic acid
- ❑ Homozygous Familial Hypercholesterolemia (HoFH)
  - Lomitapide
  - Evinacumab

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Challenges of PCSK9i Prior Authorizations

- Most insurance plans require patient to try and fail at least 2 statins
- Many require taking ezetimibe prior to PCSK9i approval
- Some insurance requires that PCSK9i be prescribed by:
  - Cardiologist
  - Endocrinologist
  - Lipidologist – National Lipid Association, American Society of Preventive Cardiology
- Usually require a lipid panel within the past 3 months
- May require more advanced ASCVD than what the patient has
- Often denied for inaccurate reasons clearly stated in chart notes

– suggest creating a robust appeal system

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Case

60 year old man with CAD s/p PCI of LAD in 2019, HLD, HTN, DM2, OSA, and obesity

Lipid lowering medications:

Rosuvastatin 10 mg daily

Ezetimibe 10 mg daily

Evolocumab 140 mg every 2 weeks

Total cholesterol	86 mg/dL
Triglycerides	125 mg/dL
HDL-C	42 mg/dL
LDL-C	19 mg/dL
Non-HDL	44 mg/dL

“Is my cholesterol too low?”

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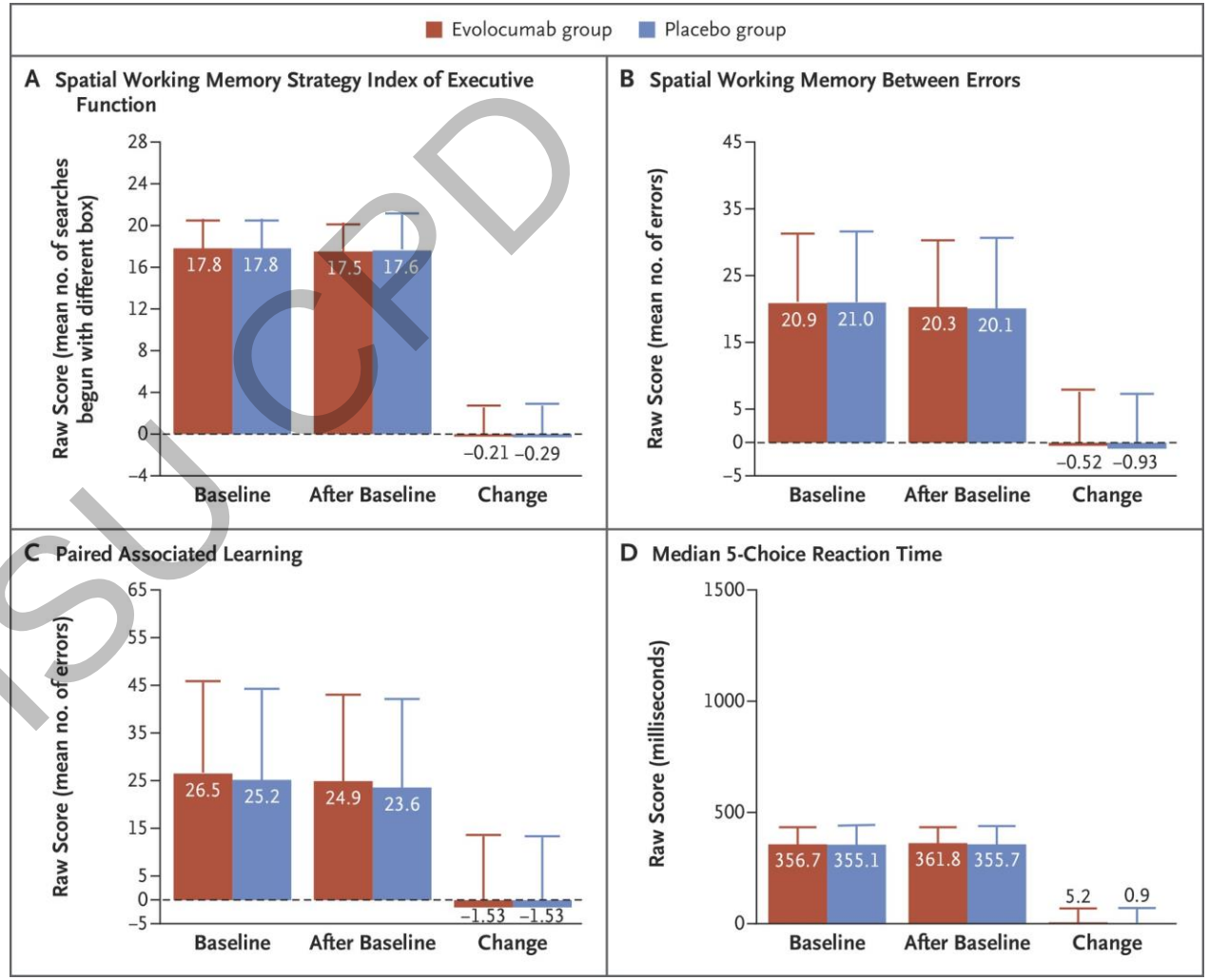
"There is no lower limit of LDL cholesterol that is known to be unsafe." European Society of Cardiology, 2019

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EBBINGHAUS

Cognitive Function in a Randomized Trial of Evolocumab

Primary and Secondary Cambridge Neuropsychological Test Automated Battery (CANTAB) End Points



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Table 2. Changes in CANTAB End Points and Global Composite Score of CANTAB End Points, Stratified According to Lowest-Attained LDL Cholesterol Level (Full-Analysis Population).

Table 2. Changes in CANTAB End Points and Global Composite Score of CANTAB End Points, Stratified According to Lowest-Attained LDL Cholesterol Level (Full-Analysis Population).*

End Point	Lowest-Attained LDL Cholesterol Level				
	Evolocumab Group			Placebo Group	
	<25 mg/dl (N=661)	*25–39 mg/dl (N=206)*	*≥40 mg/dl (N=115)*	*25–39 mg/dl (N=13)*	*≥40 mg/dl (N=969)*
Primary end point: executive function (spatial working memory strategy index of executive function raw score)†					
No. of patients with data	639	199	103	12	924
Change in score over time	−0.2±2.7	−0.3±2.9	−0.4±2.6	0.7±2.2	−0.4±3.0
Secondary end points					
Working memory (spatial working memory between-errors raw score)‡					
No. of patients	639	199	103	12	924
Change in score over time	−0.5±8.7	0.2±9.6	−0.8±8.1	0.4±9.1	−0.6±8.3
Episodic memory (paired associates learning raw score adjusted)§					
No. of patients	638	199	103	12	919
Change in score over time	−0.3±14.5	−0.6±12.3	−1.0±12.9	−3.4±18.0	−0.2±14.6
Psychomotor speed (median 5-choice reaction time raw score)¶					
No. of patients	632	199	102	12	914
Change in score (in milliseconds) over time	5.5±55.7	1.4±66.2	7.8±54.6	0.3±65.1	1.8±60.3
Exploratory end point: global composite score of CANTAB end points‖					
No. of patients	638	199	103	12	922
Change in z score over time	0.02±0.44	0.02±0.42	0.03±0.40	−0.02±0.44	0.04±0.47

* Plus–minus values are means ±SD changes from baseline over time (i.e., the difference between the mean score at baseline and the mean

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Very low (< 30 mg/dL) LDL-C Levels

Benefits

- Coronary atherosclerotic plaque regression
- Statistically significant reduction in the composite of:
  - Cardiovascular death
  - Myocardial infarction
  - Ischemic stroke
  - Coronary revascularization
  - Unstable angina
- Cardiovascular clinical benefit increases monotonically with lowering LDL-C levels wit no observed benefit plateau

Potential Side effects

- New onset diabetes mellitus, possible association.
- Hemorrhagic (intraparenchymal) stroke; possible association.
- Cataract; unclear if there is a true association.
- No data to support any association with cancer, hepatobiliary toxicity, neurocognitive impairment, hypogonadism, hematuria

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There is a paucity of data on the benefits and safety of attaining and maintaining LDL-C < 15 mg/dL over the long term

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Thank You!

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