



THE UNIVERSITY OF BRITISH COLUMBIA

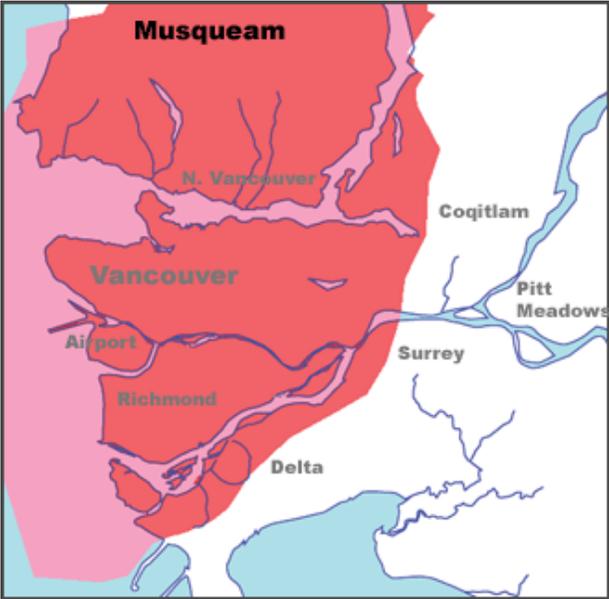
CV Risk Stratification in the Young

More than just risk scores

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We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html



PROGRAM DISCLOSURE OF COMMERCIAL SUPPORT

I have/do not have relationships with for-profit and not-for-profit organizations over the past two years:

NATURE OF RELATIONSHIP	NAME OF THE FOR-PROFIT OR NOT-FOR-PROFIT ORGANIZATION	DESCRIPTION OF RELATIONSHIP
Any direct financial payments including receipt of honoraria	HLS Therapeutics, Sanofi, Amgen	Honoraria
Membership on advisory boards or speakers' bureaus	Novo Nordisk, Ultragenyx, HLS Therapeutics, Novartis	Advisory board
Funded grants of clinical trials	None	
Patents on a drug, product or device	None	
All other investments/relationship that could be seen as having the potential to influence the content of the educational activity	None	

I have not received any financial support for today's talk

1. Review the CCS dyslipidemia screening recommendations across the lifespan
2. Review CCS guideline-based statin indicated conditions
3. Discuss lipid management considerations beyond LDL

CASE PRESENTATION

Mr. Risk

- 54M previously healthy, referred for chest pain
- No known cardiovascular risk factors. No medications.
- Family history unknown (patient adopted)
- BP 122/71mmHg, otherwise normal cardiovascular exam

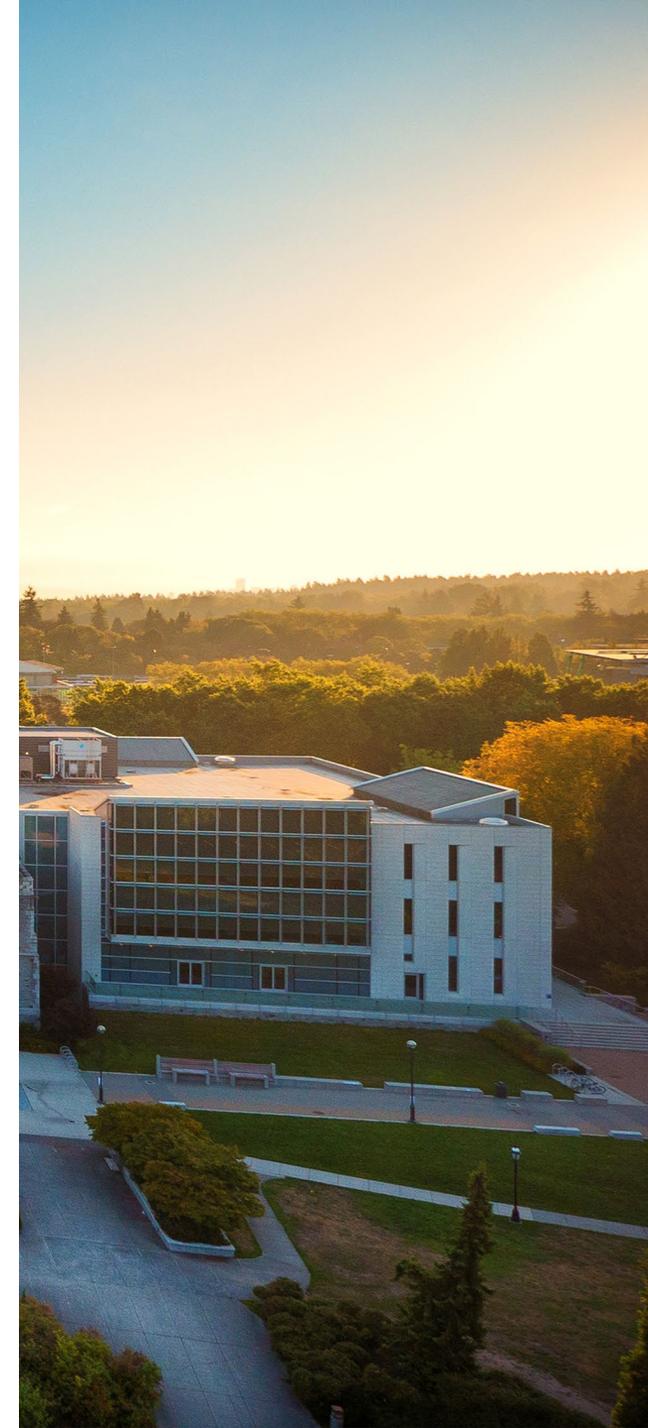
Investigations

Test	Value
Hb	121
Plt	184
Cr	108
GFR	67
HbA1c	5.6%
Cholesterol	5.34
LDL	3.71
HDL	1.29
Non-HDL	4.05
Triglycerides	0.74



Framingham Risk Score 9% (low risk)

CCS Dyslipidemia Guidelines 2021



Society Guidelines

2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults

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Arden R. Barry, PharmD,^d Patrick Couture, MD, PhD,^e Natalie Dayan, MD,^f
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Alexander A. Leung, MD,^m Eva Lonn, MD,ⁿ G.B. John Mancini, MD,^o Priya Manjoo, MD,^p
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Rick Ward, MD,^v and Wendy Wray, RN, MScN^w

TERMINOLOGY

Atherosclerotic cardiovascular disease (ASCVD)

- All forms of atherosclerotic disease – acute coronary syndromes, coronary artery disease on imaging, prior revascularization, stroke/TIA, carotid stenosis, peripheral artery disease, abdominal aneurysmal disease

Primary prevention

- Efforts aimed at preventing or delaying the onset of ASCVD

Secondary prevention

- Efforts to treat known ASCVD



WHO TO SCREEN

Table 1. Who to screen for dyslipidemia in adults at risk

Who to screen

Men 40 years of age or older; women 40 years of age or older (or postmenopausal)

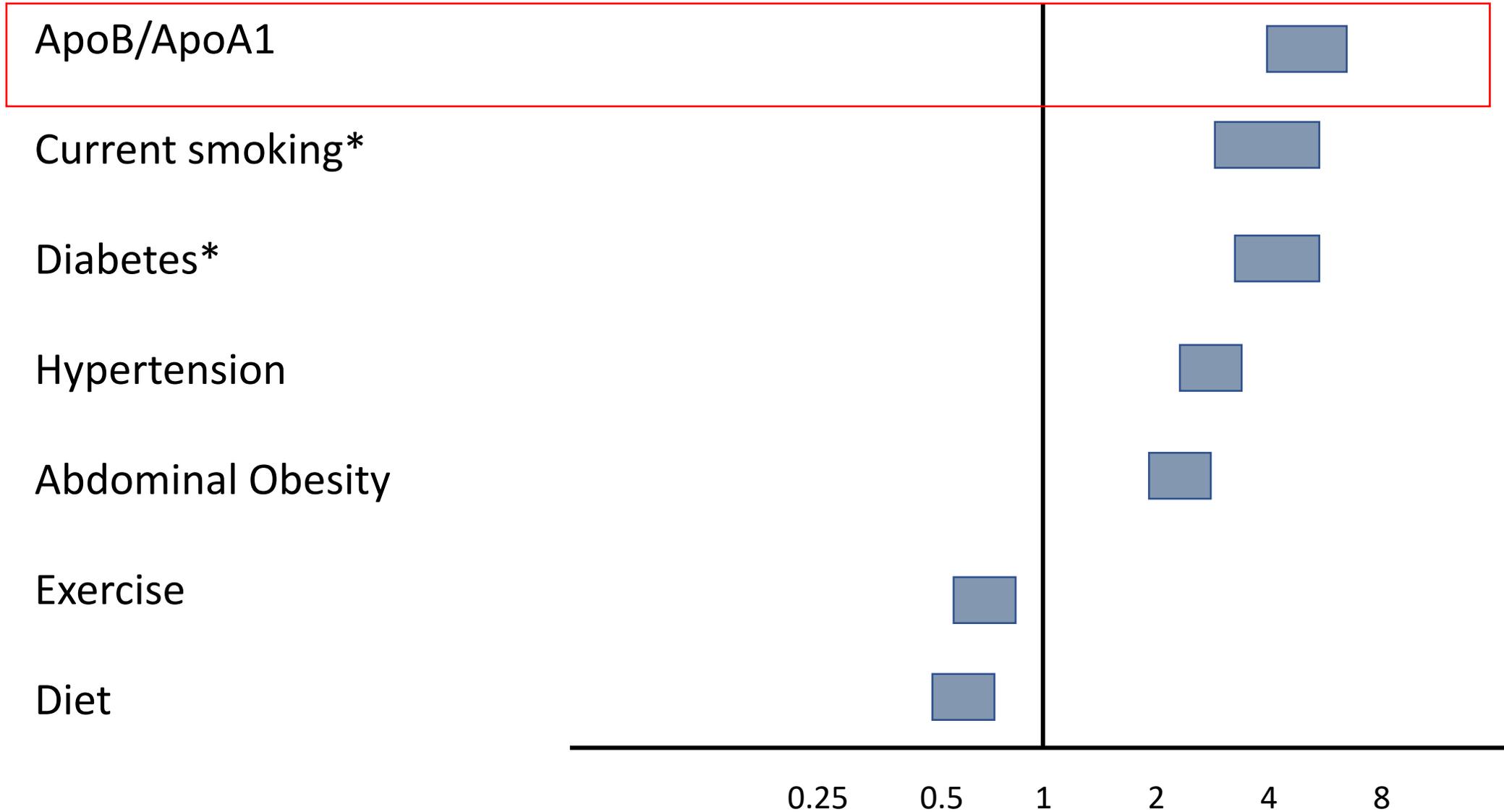
- Consider earlier in ethnic groups at increased risk such as South Asian or indigenous individuals

All patients with any of the following conditions, regardless of age

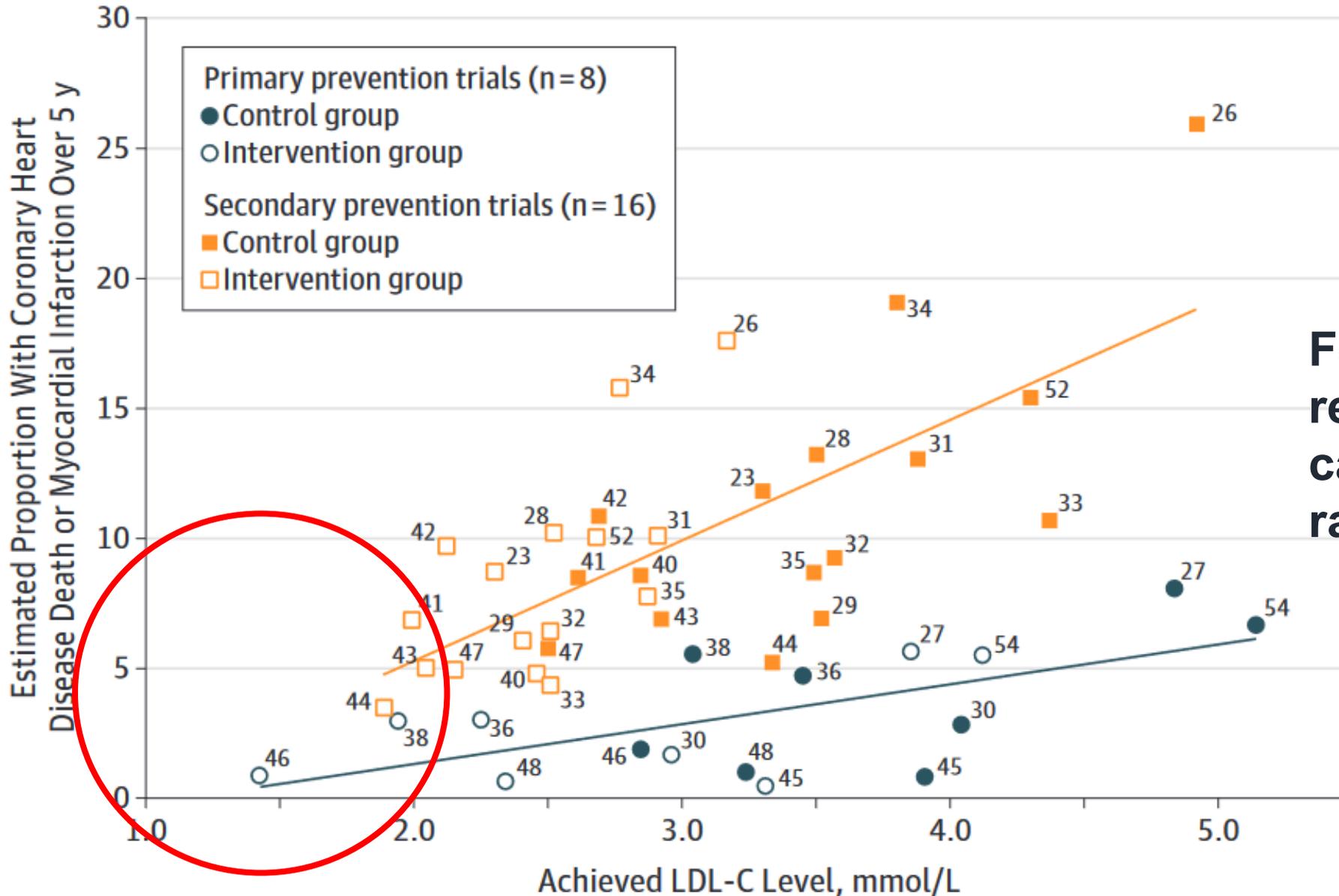
- Clinical evidence of atherosclerosis
 - Abdominal aortic aneurysm
 - Diabetes mellitus
 - Arterial hypertension
 - Current cigarette smoking
 - Stigmata of dyslipidemia (corneal arcus, xanthelasma, xanthoma)
 - Family history of premature CVD*
 - Family history of dyslipidemia
 - CKD (eGFR ≤ 60 mL/min/1.73 m² or ACR ≥ 3 mg/mmol)
 - Obesity (BMI ≥ 30)
 - Inflammatory diseases (RA, SLE, PsA, AS, IBD)
 - HIV infection
 - Erectile dysfunction
 - COPD
 - History of hypertensive disorder of pregnancy
-



RISK FACTORS



LOWER IS BETTER...LOWEST IS BEST?



For every 1mmol/L reduction in LDL, we can reduce CV event rate by **~20-22%**

Silverman MG *et al.* JAMA. 2016.

HOW TO SCREEN

Table 2. How to screen for dyslipidemia in adults at risk

How to screen

For all

- History and physical examination
- Standard lipid profile*: TC, LDL-C, HDL-C, non-HDL-C,[†] TG
- FPG or A1c
- eGFR
- Lipoprotein(a)—once in patient's lifetime, with initial screening

Optional

- ApoB
 - Urine ACR (if eGFR <60 mL/min/1.73 m², hypertension, or diabetes)
-



HOW TO SCREEN

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-



A NOTE ABOUT TRIGLYCERIDES...

If triglycerides ≥ 1.5 mmol/L

- LDL calculation is inaccurate
- Preferable to follow non-HDL or ApoB

To fast or not to fast...

- Non-fasting lipids can be used for most adults for screening
- If interested in triglyceride counts, should be a fasting panel (e.g. in patients with a TG >4.5 mmol/L historically)



CV RISK ASSESSMENTS

Framingham Risk Score

- Estimation of 10-year cardiovascular risk

Vascular age, Lifetime ASCVD Risk estimator



CardioRisk Calculator™

Simple Framingham Risk Score

new Dyslipidemia Risk Calculator

Criteria for Diagnosing Familial Hypercholesterolemia

Imputed LDL-C Calculator

Cholesterol Drug Dosage Chart

% LDL-C Reduction Calculator

Diagnosis of apoB Dyslipoproteinemias

new Alternate LDL-C Calculator (for high TG)



FRAMINGHAM RISK

Some caveats and limitations

- Framingham risk score predicts **10-year** risk
- The description of the original score may not be applicable to all populations
 - Based on study in Framingham, Massachusetts
 - Original population was 100% European ancestry
- Young patients were under-represented



OTHER CLINICAL RISK STRATIFICATION TOOLS

AHA ASCVD Risk Estimator (ie. Pooled cohort equation)

<https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/>



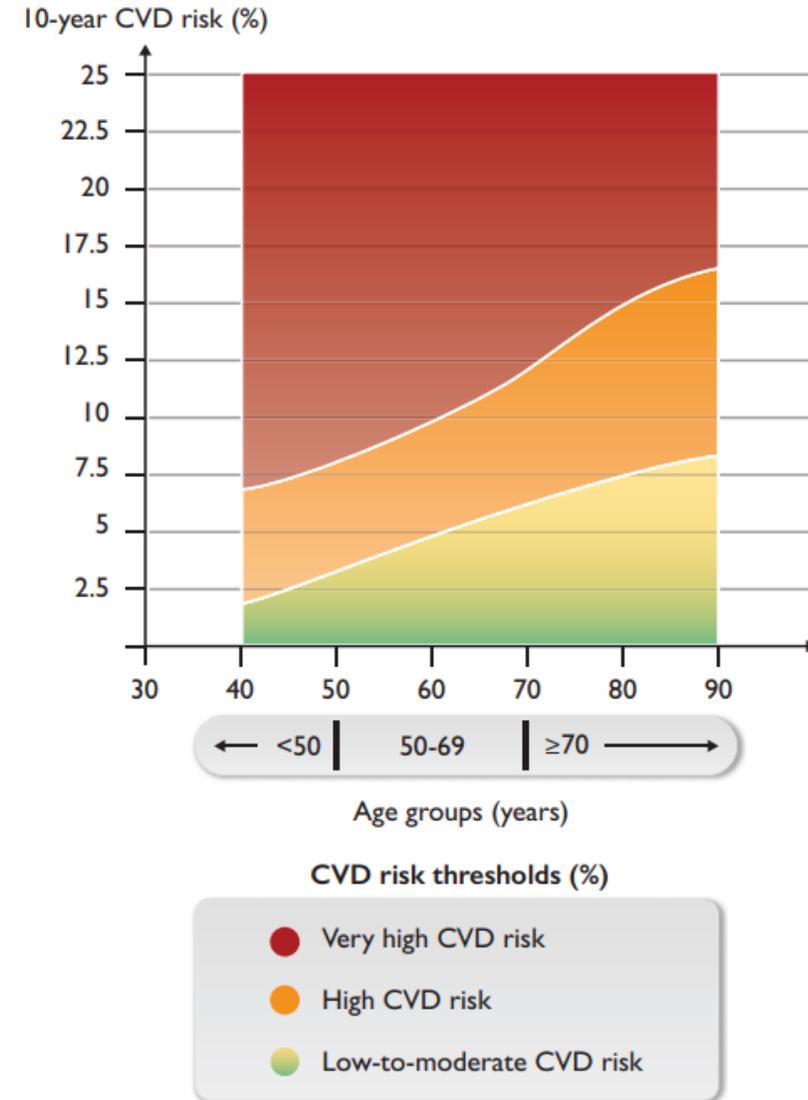
SCORE2 and SCORE2-OP

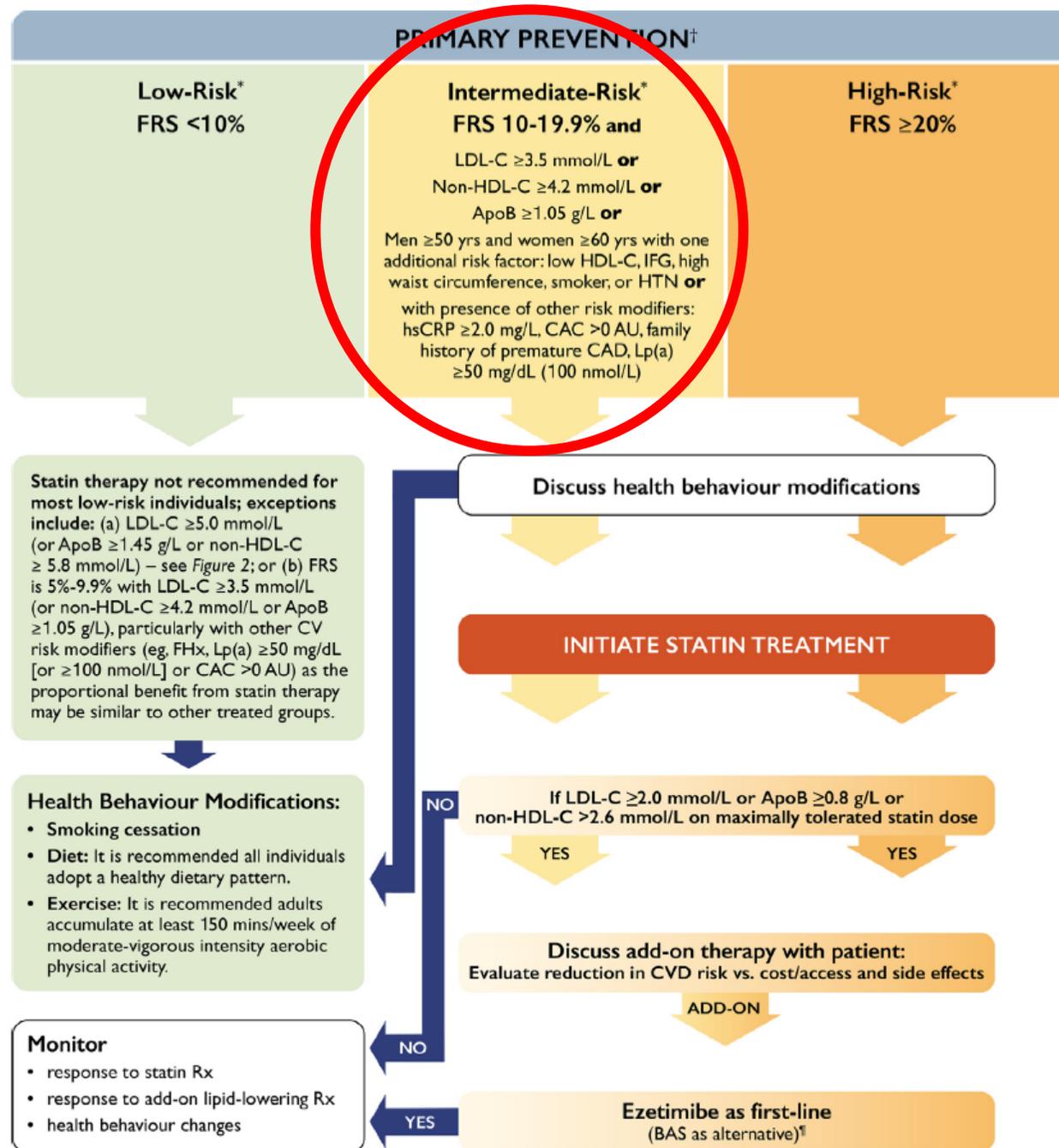
<https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts>

AN EXCERPT FROM THE EUROPEANS

Table 5 Cardiovascular disease risk categories based on SCORE2 and SCORE2-OP in apparently healthy people according to age

	<50 years	50 – 69 years	≥70 years ^a
Low-to-moderate CVD risk: risk factor treatment generally not recommended	<2.5%	<5%	<7.5%
High CVD risk: risk factor treatment should be considered	2.5 to <7.5%	5 to <10%	7.5 to <15%
Very high CVD risk: risk factor treatment generally recommended ^a	≥7.5%	≥10%	≥15%





Intermediate-Risk*

FRS 10-19.9% and

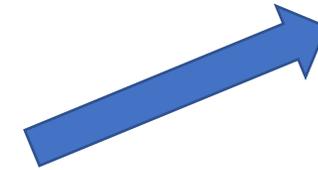
LDL-C ≥ 3.5 mmol/L **or**

Non-HDL-C ≥ 4.2 mmol/L **or**

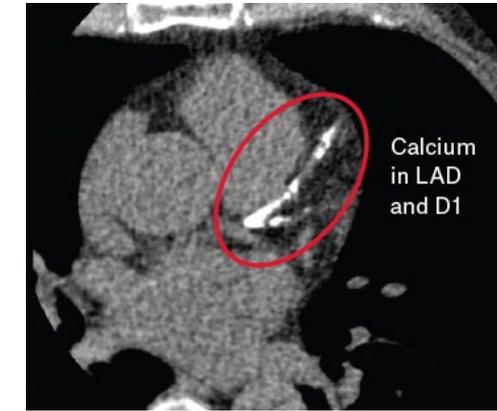
ApoB ≥ 1.05 g/L **or**

Men ≥ 50 yrs and women ≥ 60 yrs with one additional risk factor: low HDL-C, IFG, high waist circumference, smoker, or HTN **or**

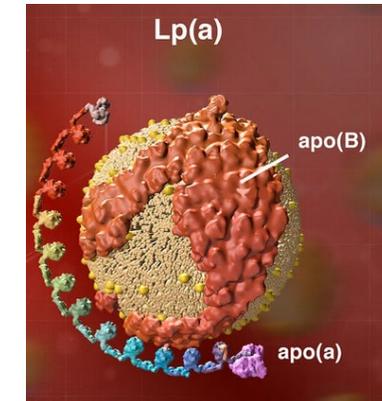
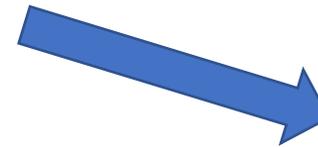
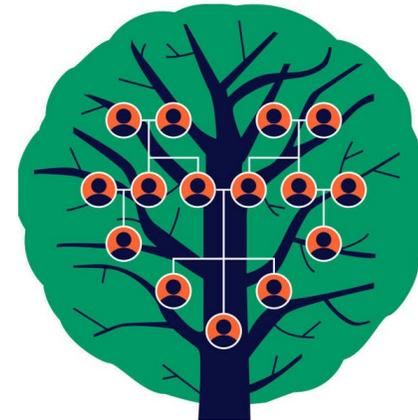
with presence of other risk modifiers:
hsCRP ≥ 2.0 mg/L, CAC > 0 AU, family history of premature CAD, Lp(a) ≥ 50 mg/dL (100 nmol/L)



Calcium scoring



Family History



CORONARY ARTERY CALCIUM

- Low dose CT used to individualize cardiac risk stratification
- Non-contrasted study
- Assess and quantitates the calcified atherosclerotic disease in coronary arteries
- Main utility and indication is for use in **asymptomatic** patients for risk stratification and decision making
- There is no defined role for serial calcium scoring individuals already treated with statins
- CAC = 0 is associated with an extremely favorable risk profile



CT CORONARY ANGIOGRAM

- ECG-gated contrasted study to assess coronary anatomy
- Assesses both the calcified and noncalcified portions of CAD, and in some instances, flow
- Main utility is to assess coronary anatomy in **symptomatic** patients
- When used in asymptomatic patients, has not been shown to add incremental value in prognosis



1. Review the CCS dyslipidemia screening recommendations across the lifespan
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3. Discuss lipid management considerations beyond LDL

STATIN INDICATED CONDITIONS

LDL ≥ 5.0 mmol/L

(or ApoB ≥ 1.45 g/L or non-HDL-C ≥ 5.8 mmol/L)
(familial hypercholesterolemia or genetic dyslipidemia)

Most patients with diabetes:

- Age ≥ 40 y
- Age ≥ 30 y & DM $\times \geq 15$ y duration
- Microvascular disease

Chronic Kidney Disease

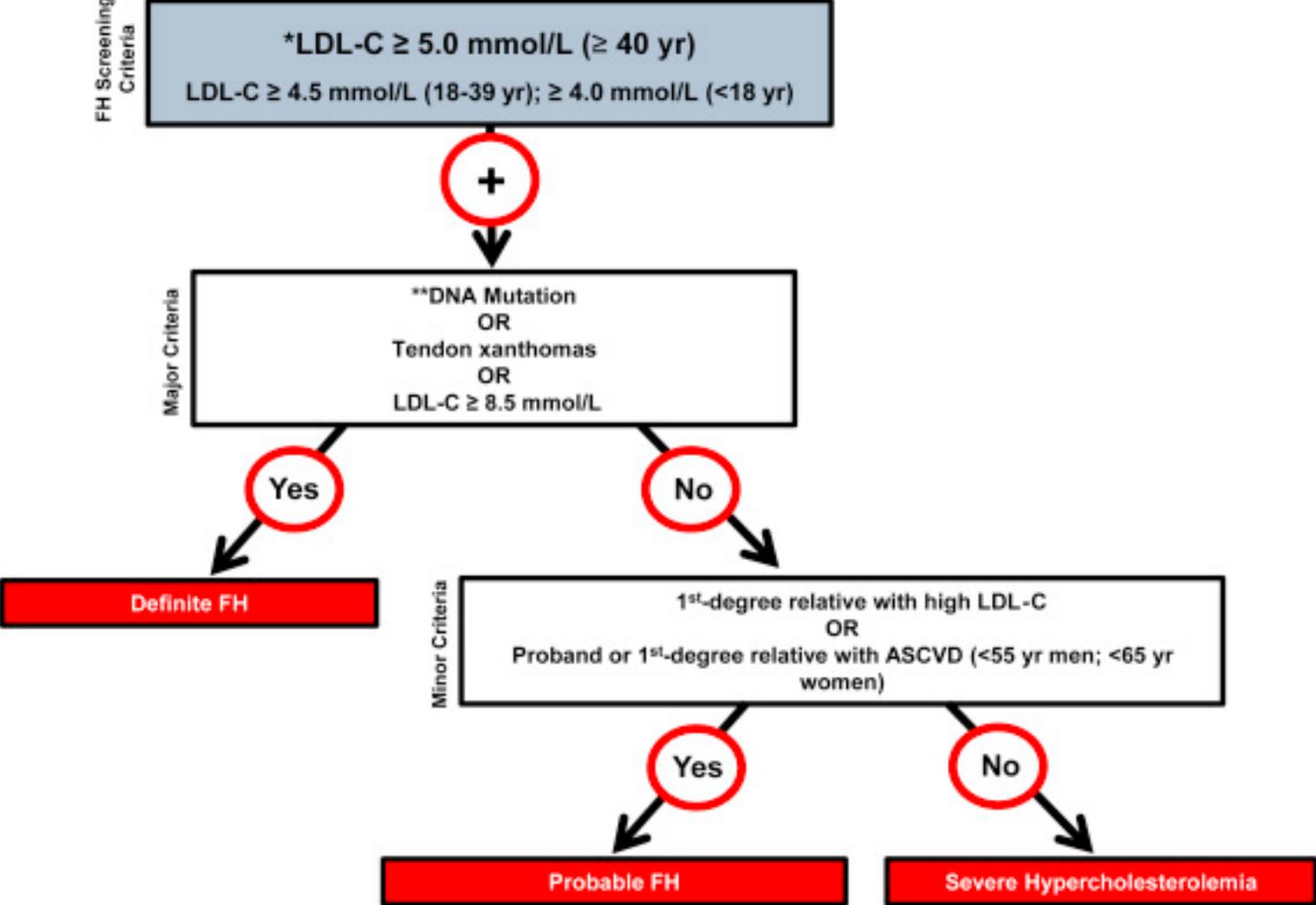
- Age ≥ 50 y and eGFR < 60 mL/min/1.73 m² or ACR > 3 mg/mmol

Atherosclerotic Cardiovascular Disease (ASCVD):

- Myocardial infarction (MI), acute coronary syndromes (ACS)
- Stable angina, documented coronary artery disease using angiography
- Stroke, TIA, documented carotid disease
- Peripheral arterial disease, claudication, and/or ABI < 0.9
- Abdominal aortic aneurysm (AAA) -- abdominal aorta > 3.0 cm or previous aneurysm surgery

Review/Discuss health behavioural modifications (refer to Figure 1)

HETEROZYGOUS FH



HETEROZYGOUS FH

A. Simon Broome Registry

Criteria

1. A plasma measurement of either:
 Total cholesterol > 7.5 mmol/L (adult patient) or > 6.7 mmol/L (child aged < 16 years)
 Low-density lipoprotein cholesterol > 4.9 mmol/L (adult patient) or > 4.0 mmol/L (child aged < 16 years)
2. Tendon xanthomas in the patient or any of the patient's first- or second-degree relatives
3. DNA-based evidence in the patient of mutation in *LDLR* or other FH-related gene
4. Family history of myocardial infarction before the age of:
 50 Years, in any first- or second-degree relative
 60 Years, in any first-degree relative
5. Family history of plasma total cholesterol > 7.5 mmol/L in any first- or second-degree relative

B. Dutch Lipid Clinic Network

Points	Criteria	Diagnosis
1	First-degree relative with premature cardiovascular disease or LDL-C > 95th percentile, or personal history of premature peripheral or cerebrovascular disease, or LDL-C between 4.01 and 4.89 mmol/L (155 and 189 mg/dL)	Definite FH (≥ 8 points)
2	First-degree relative with tendinous xanthoma or corneal arcus, or First-degree relative child (< 18 years) with LDL-C > 95th percentile, or personal history of coronary artery disease	
3	LDL-C between 4.91 and 6.44 mmol/L (190 and 249 mg/dL)	Probable FH (6-7 points)
4	Presence of corneal arcus in patient younger than 45 years of age	
5	LDL-C between 6.46 and 8.51 mmol/L (250 and 329 mg/dL)	
6	Presence of a tendon xanthoma	Possible FH (3-5 points)
8	LDL-C > 8.53 mmol/L (330 mg/dL), or functional mutation in the <i>LDLR</i> gene	

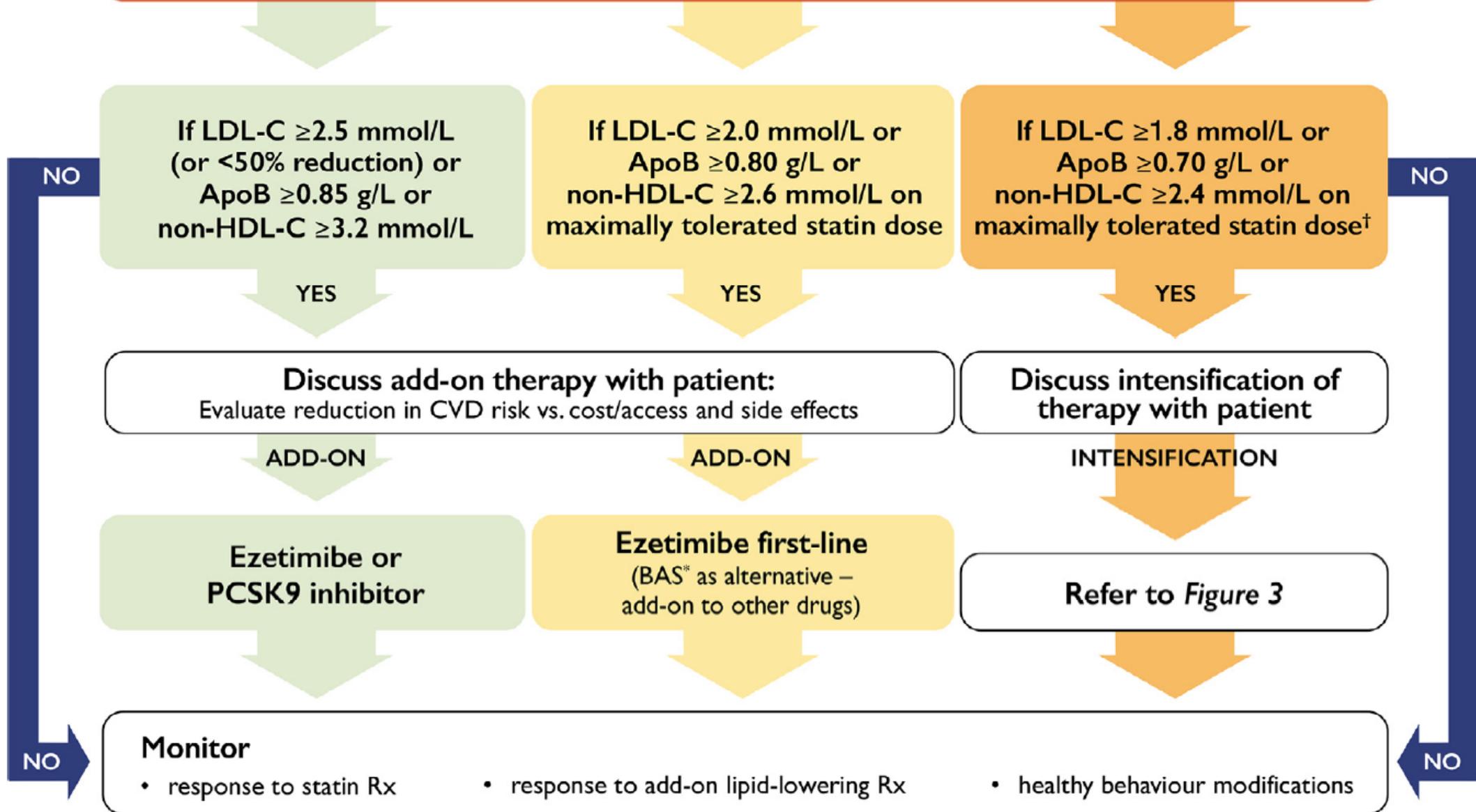
HETEROZYGOUS FH

Epidemiology and prognosis

- Very common monogenic condition with autosomal dominance
- 1 in 250-500 affected depending on population
- Frequently underdiagnosed and undertreated
- Untreated FH has a 20-fold increased lifetime risk coronary disease
- Untreated men ~50% risk of fatal or nonfatal coronary event by age 50
- Untreated women ~30% risk of by age 60



INITIATE STATIN TREATMENT



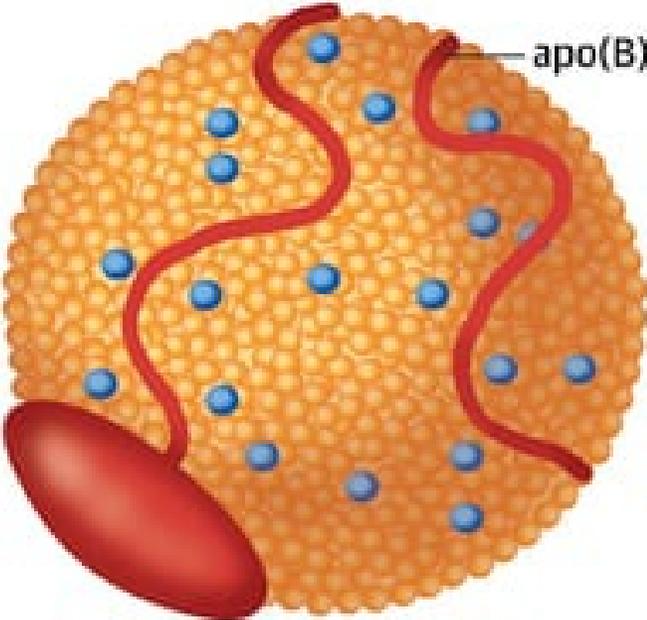
Treatment	Average LDL-C reduction
Moderate intensity statin	~ 30%
High intensity statin	~ 50%
High intensity statin + ezetimibe	~ 65%
PCSK9 inhibitor	~60%
PCKS9 inhibitor + high intensity statin	~ 75%
PCKS9 inhibitor + high intensity statin + ezetimibe	~ 85%



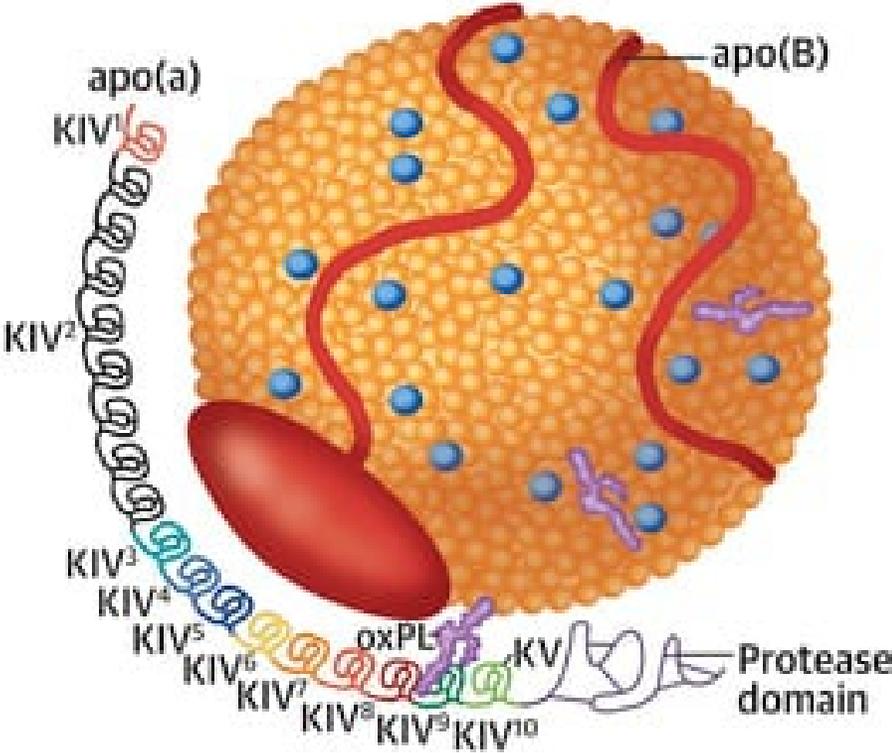
1. Review the CCS dyslipidemia screening recommendations across the lifespan
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3. Discuss lipid management considerations beyond LDL

LIPOPROTEIN (A)

LDL-C



Lp(a)



LIPOPROTEIN (A)

Genetics

- Predominantly (>90%) genetically determined by variability in *LPA*

Ethnicity

- Impacted by ethnicity
- Chinese < White Caucasian < South Asian < Black



LIPOPROTEIN (A)

Measurement units

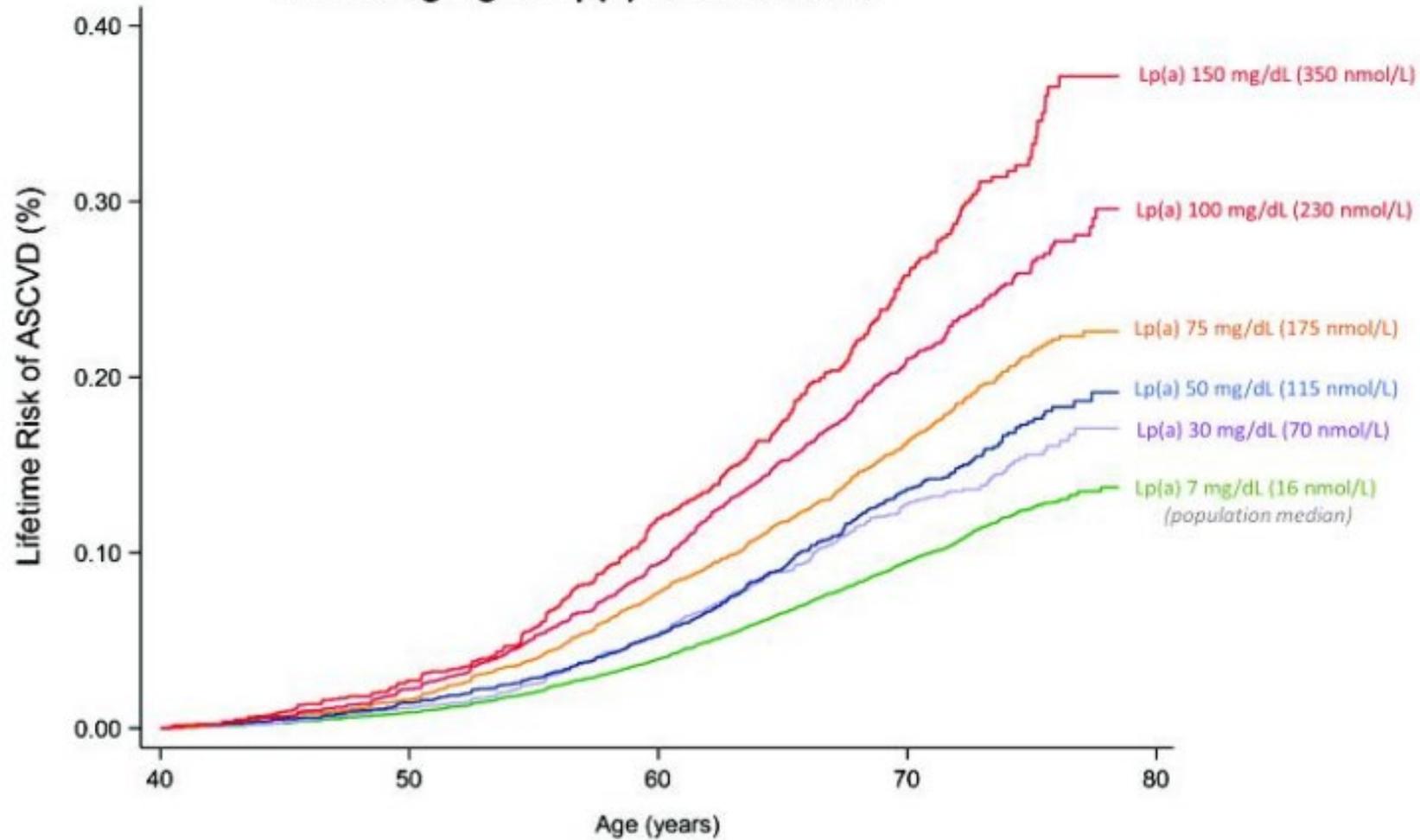
- Usually reported as either mg/dL (or mg/L) or nmol/L



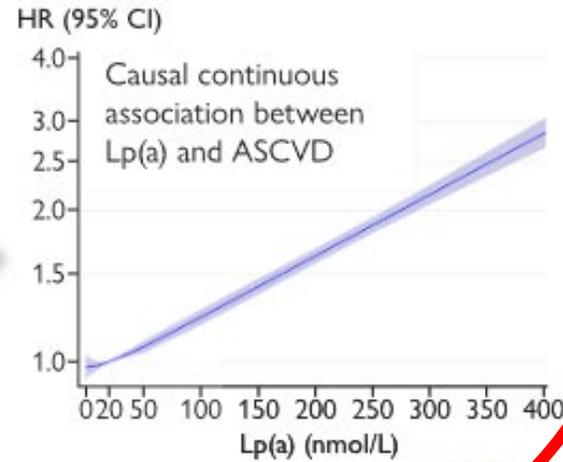
mg/dL	mg/L	nmol/L	Risk equivalent
30	300	75	
50	500	125	Diabetes
100	1000	250	
180	1800	450	HeFH

E

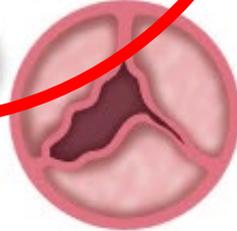
Lifetime risk for major cardiovascular events with increasing higher Lp(a) concentrations



2022 EAS Consensus on Lp(a)



New risk factor for aortic valve stenosis



Not a risk factor for venous thrombosis



Very low Lp(a) may associate with type 2 diabetes



EAS

Lp(a) should be measured at least once in adults

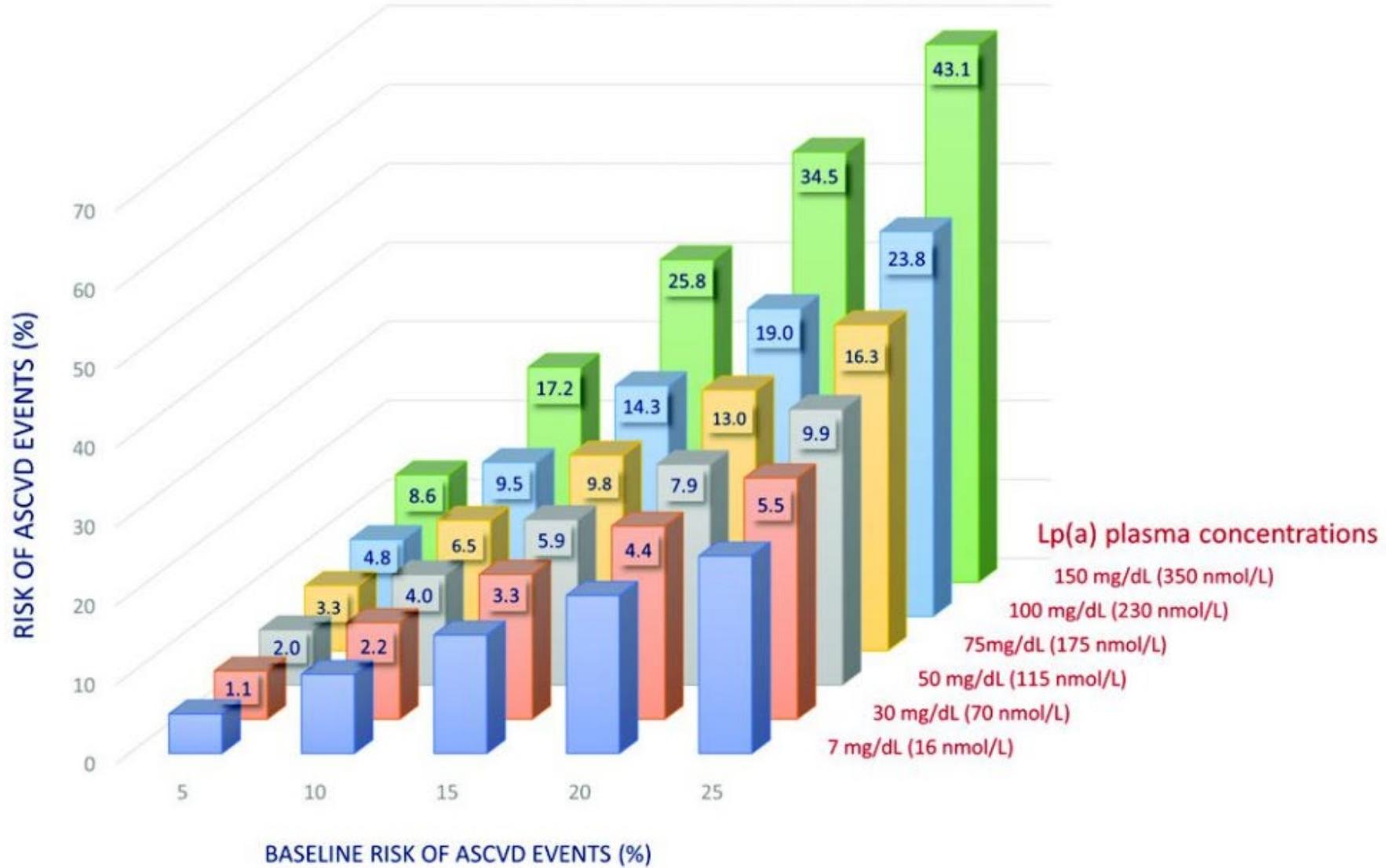
Interpretation of Lp(a) concentration in the context of absolute global CVD risk

Intensified risk factor management by lifestyle modification and medications

Specific Lp(a)-lowering therapies in phase II/III trials



A



B

	Total CV risk (SCORE) %	Untreated Lp(a) concentrations					
		< 10 mg/dL < 25 nmol/L	10 to <30 mg/dL 25 to <75 nmol/L	30 to <50 mg/dL 75 to <125 nmol/L	50 to <75 mg/dL 125 to <188 nmol/L	75 to <100 mg/dL 188 to <250 nmol/L	≥100 mg/dL ≥250 nmol/L
Primary Prevention	< 1 low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
	≥1 to <5, or moderate-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
	≥5 to <10, or high-risk	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
	≥10, or at very-high risk due to a risk condition	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
Secondary Prevention	Very-high-risk	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)



B Intensification of LDL-C reduction needed to reduce the global cardiovascular risk to a similar extent as the risk attributable to elevated Lp(a) depending on age at which LDL-C reduction is initiated

Lp(a) nmol/L	Δ Lp(a) compared to median	Lp(a) percentile	HR for MCVE due to increased Lp(a)	Intensification of LDL-C reduction (nmol/L) needed to mitigate the increased risk caused by Lp(a)			
				Begin age 30y	Begin age 40y	Begin age 50y	Begin age 60 y
320	300	99	2.56	1.2 mmol/L	1.4 mmol/L	1.7 mmol/L	2.3 mmol/L
270	250	97.5	2.19	1.0 mmol/L	1.2 mmol/L	1.5 mmol/L	1.9 mmol/L
220	200	93.5	1.87	0.8 mmol/L	0.9 mmol/L	1.2 mmol/L	1.5 mmol/L
170	150	90	1.60	0.6 mmol/L	0.7 mmol/L	0.9 mmol/L	1.1 mmol/L
120	100	82.5	1.37	0.4 mmol/L	0.5 mmol/L	0.6 mmol/L	0.8 mmol/L
70	50	75	1.17	0.2 mmol/L	0.2 mmol/L	0.3 mmol/L	0.4 mmol/L
20	ref.	50	ref.	ref.	ref.	ref.	ref.

WHAT COMES NEXT?

Pelacarsen

- Antisense oligonucleotide
- Dosed once a month

Olpasiran

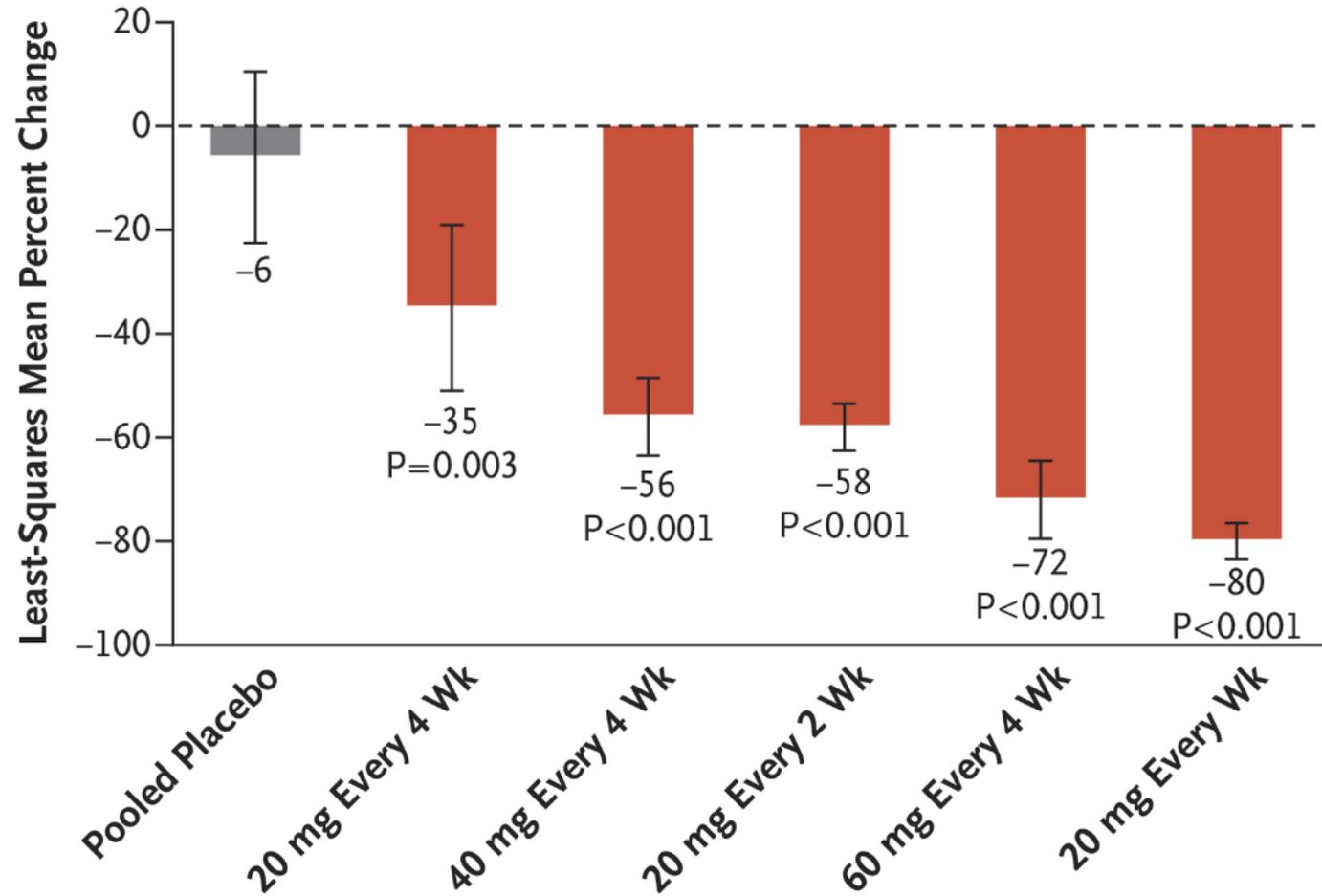
- Small interfering RNA
- Dose every 3 months



PELACARSEN

Lipoprotein(a) Reduction in Persons with Cardiovascular Disease.
N Engl J Med. 2020 Jan 16;382(3):244-255.

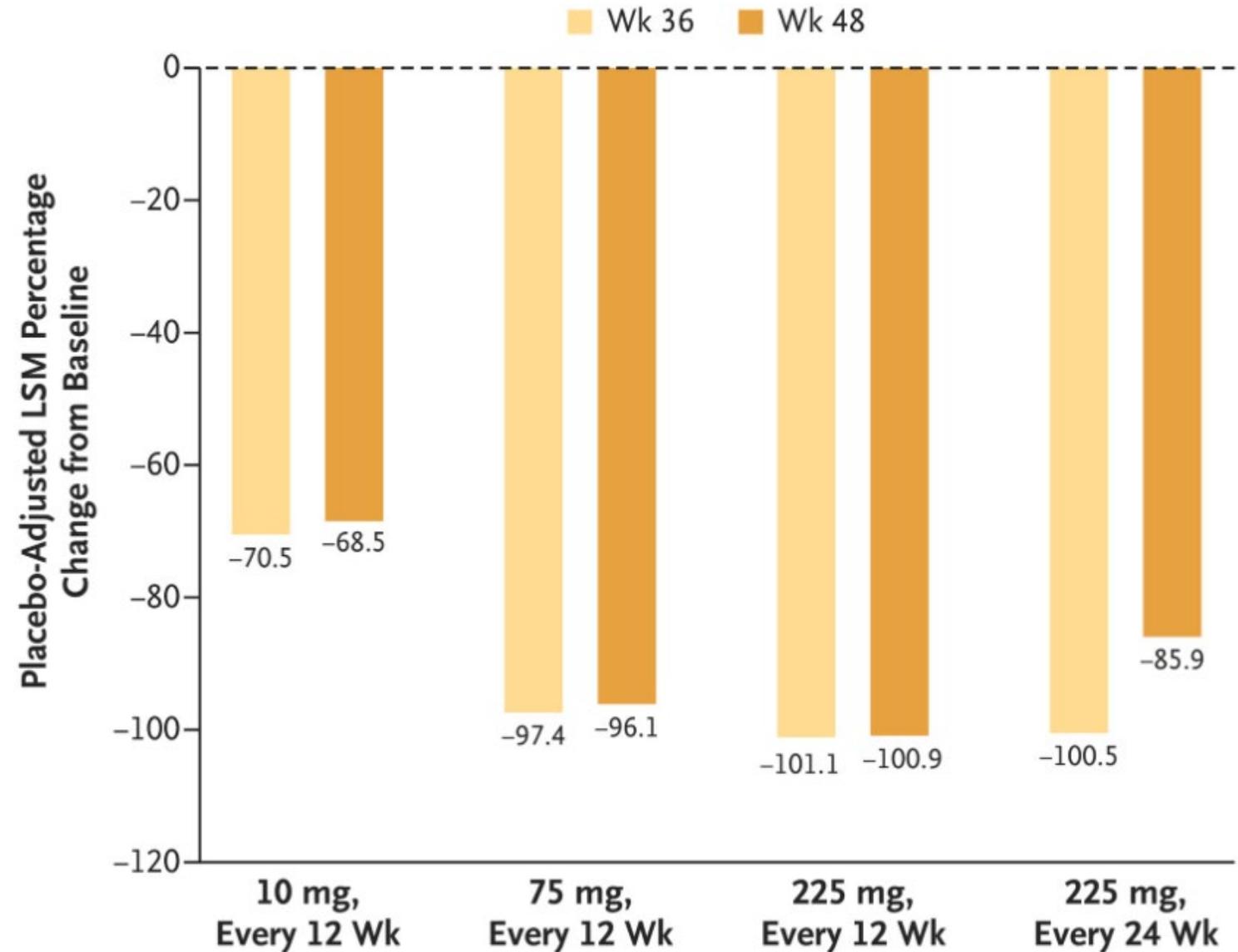
A Change from Baseline to PAT in Lipoprotein(a) Level



OLPASIRAN

Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease. N Engl J Med. 2022 Nov 17;387(20):1855-1864.

B Placebo-Adjusted Change in Lipoprotein(a) Concentration



WHAT COMES NEXT?

Pelacarsen

- Antisense oligonucleotide
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Olpasiran

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CV Outcomes trials

OCEAN (a) Outcomes trial

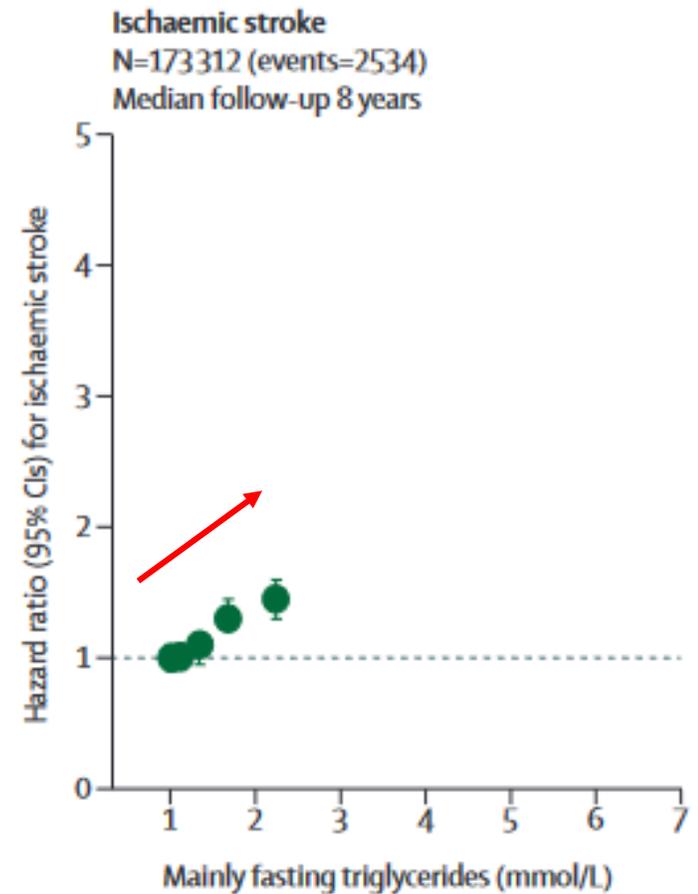
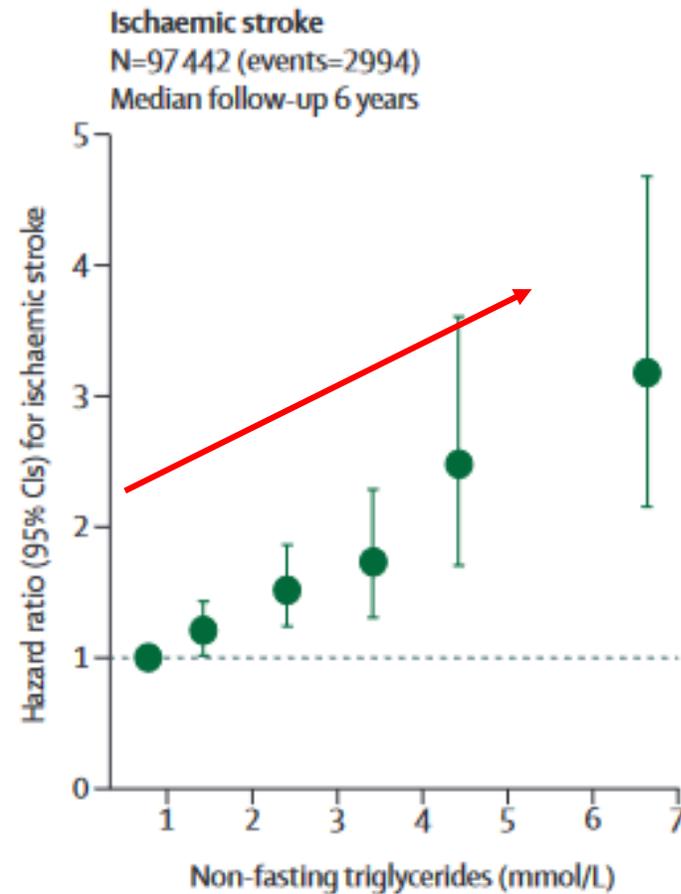
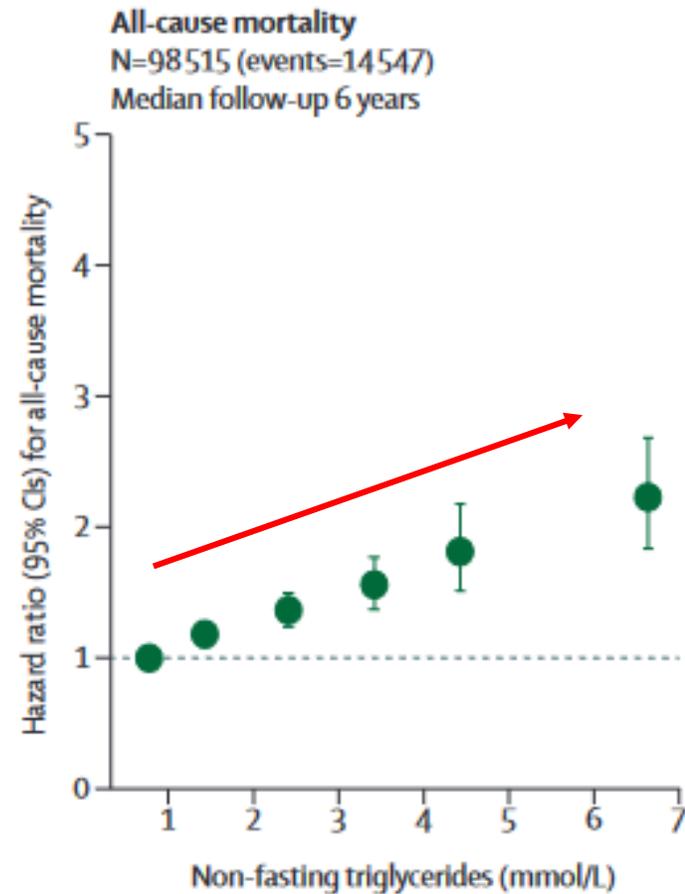
- Estimated completion 2026

Lp(a) HORIZON Trial

- Enrollment complete, results this year

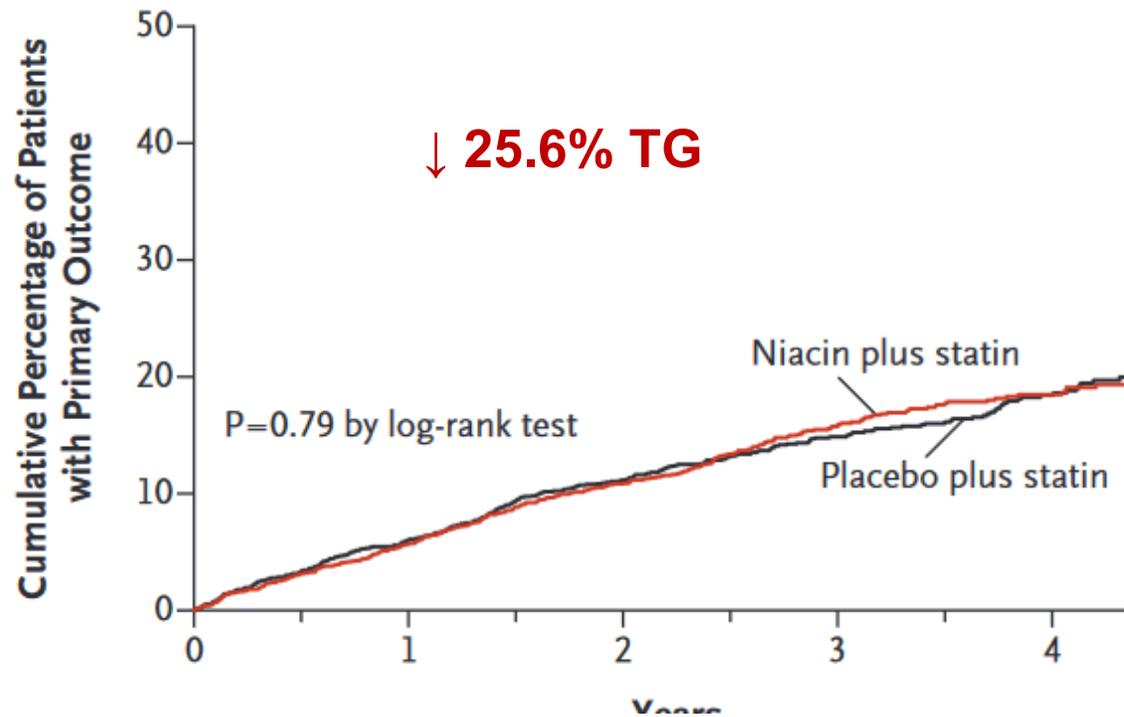


TRIGLYCERIDES AND VASCULAR DISEASE

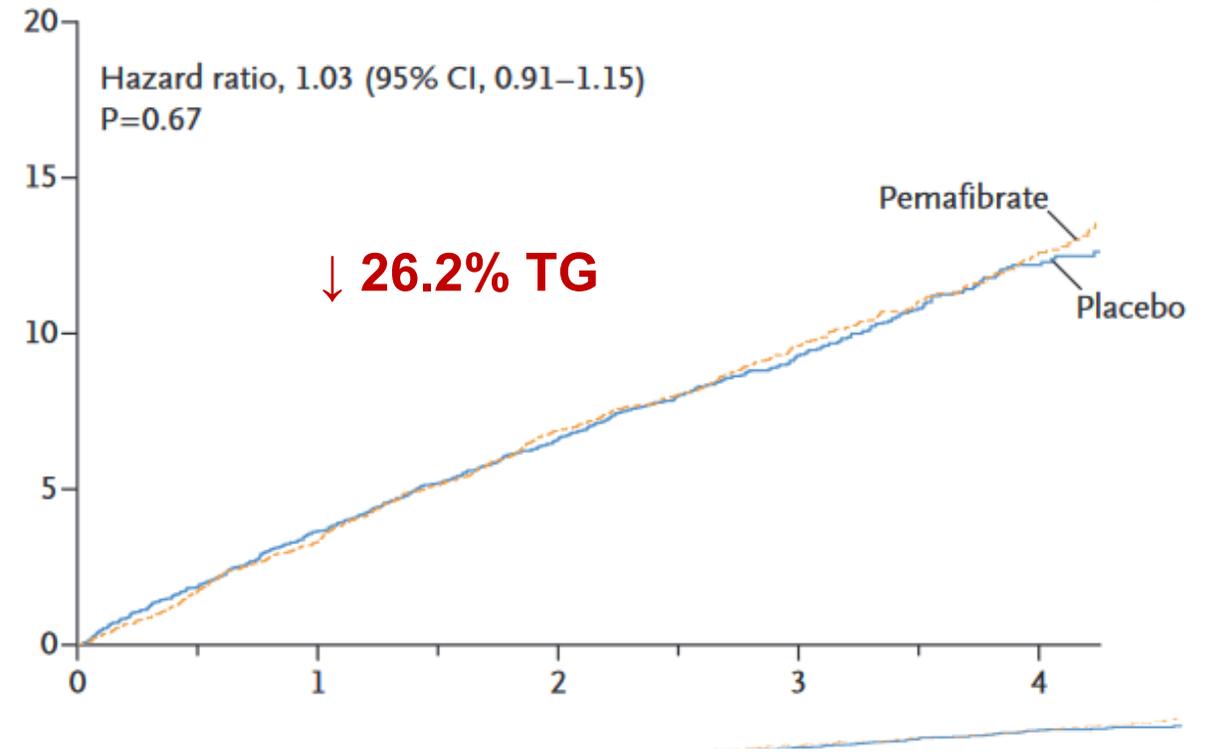


TRIGLYCERIDES AND VASCULAR DISEASE

AIM-HIGH. NEJM 2011.



PROMINENT. NEJM 2022.



TRIGLYCERIDES AND VASCULAR DISEASE

Triglycerides and risk

- High TG has been relegated to being considered more of a risk marker than a direct causal risk factor
- Patients with an elevated TG are felt to be at greater risk, but lowering TG in isolation probably does not translate to improved outcomes

Practical points

- TG >10mmol/L deserves different considerations as patient is at risk for pancreatitis
- If TG > 1.5mmol/L, calculated LDL value is not valid



ICOSAPENT ETHYL

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

JANUARY 3, 2019

VOL. 380 NO. 1



Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

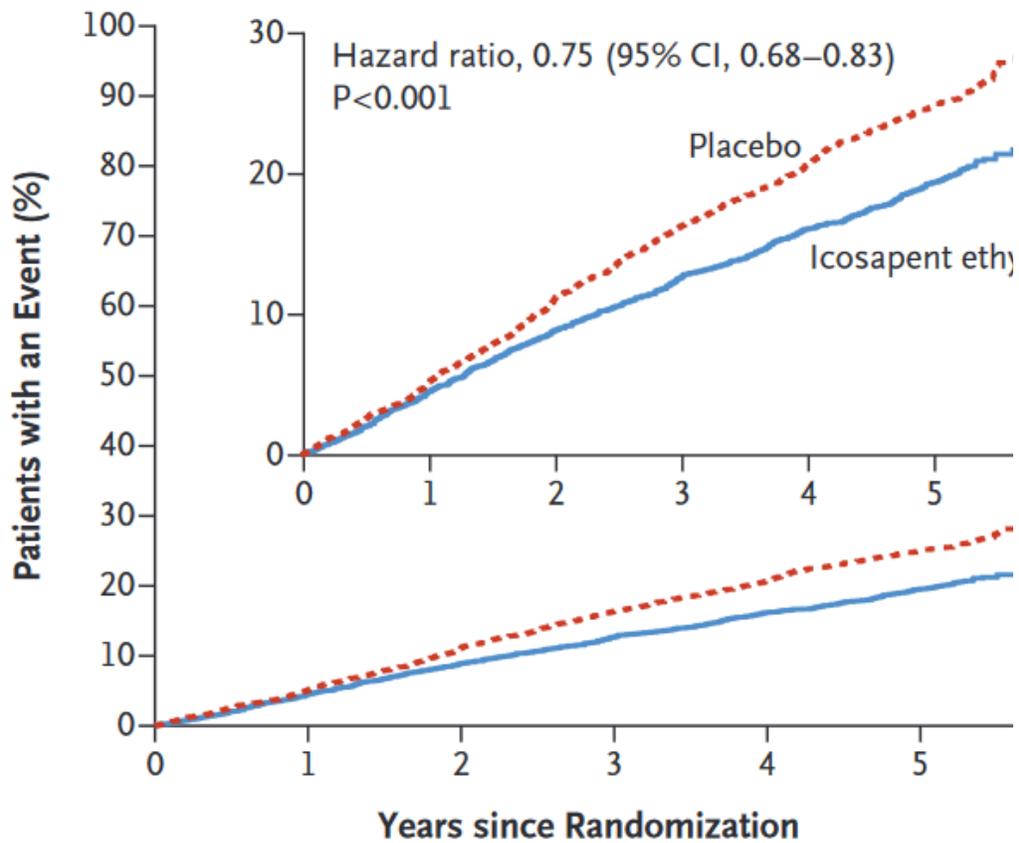
Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D.,
Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D.,
Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D.,
for the REDUCE-IT Investigators*

ICOSAPENT ETHYL

- REDUCE-IT (NEJM 2019)
 - 8179 patients with CVD or DM + risk factors (age, smoking, HTN, CKD etc.) with **fasting TG 1.52-5.63 mmol/L**
 - Randomized to IPE vs. placebo
 - 70.7% enrolled were secondary prevention
 - 29.3% primary prevention
 - Primary endpoint: CV death*, MI*, nonfatal stroke*, coronary revasc*, hospitalization for UA*
 - Secondary endpoint: CV death, MI, stroke

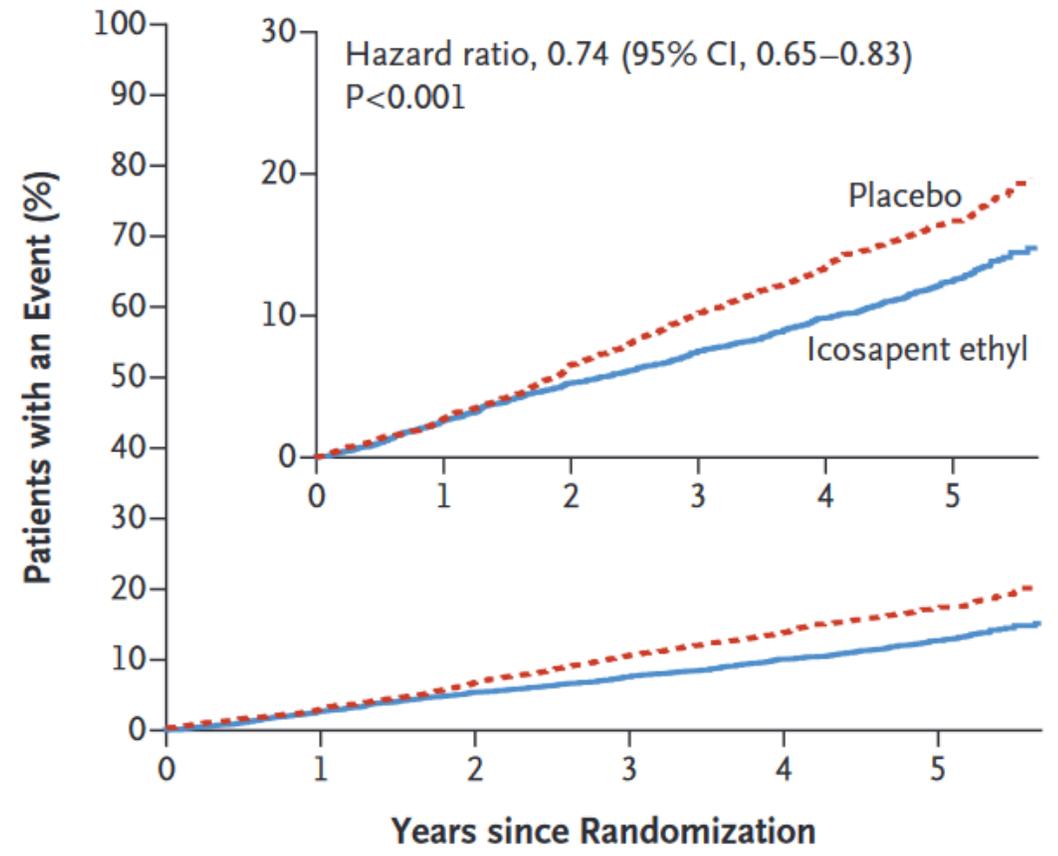


A Primary End Point



No. at Risk	0	1	2	3	4	5
Placebo	4090	3743	3327	2807	2347	1358
Icosapent ethyl	4089	3787	3431	2951	2503	1430

B Key Secondary End Point



No. at Risk	0	1	2	3	4	5
Placebo	4090	3837	3500	3002	2542	1487
Icosapent ethyl	4089	3861	3565	3115	2681	1562

~ 20% ↓
in TG

For up-to-date criteria and forms, please check: www.gov.bc.ca/pharmacarespecialauthority

Fax requests to 1-800-609-4884 (toll free) OR mail requests to: PharmaCare, Box 9652 Stn Prov Govt, Victoria, BC V8W 9P4
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If PharmaCare approves this Special Authority request, approval is granted solely for the purpose of covering prescription costs. PharmaCare approval does not indicate that the requested medication is, or is not, suitable for any specific patient or condition.

Forms with information missing will be returned for completion. If no prescriber fax or mailing address is provided, PharmaCare will be unable to return a response.

If you have received this fax in error, please write MISDIRECTED across the front of the form and fax toll-free to 1-800-609-4884, then destroy the pages received in error.

SECTION 1 – PRESCRIBER INFORMATION

Name and Mailing Address	
[Blank]	
College ID (use ONLY College ID number)	Phone Number (include area code)
[Blank]	[Blank]
CRITICAL FOR A TIMELY RESPONSE →	Prescriber's Fax Number
	[Blank]

SECTION 2 – PATIENT INFORMATION

Patient (Family) Name	
[Blank]	
Patient (Given) Name(s)	
[Blank]	
Date of Birth (YYYY / MM / DD)	Date of Application (YYYY / MM / DD)
[Blank]	[Blank]
CRITICAL FOR PROCESSING →	Personal Health Number (PHN)
	[Blank]

SECTION 3 – MEDICATION COVERAGE

ICOSAPENT ETHYL: 9901-0418

Icosapent ethyl 1g capsule (up to 4g daily)

SECTION 4 – CRITERIA FOR INITIAL COVERAGE: INDEFINITE

Approval subject to ALL of the criteria below being met (mark boxes and complete blanks as applicable):

- A. Patient is 45 years of age or greater.
- B. Patient has established cardiovascular disease requiring secondary prevention.
- C. Patient is currently receiving maximally tolerated statin therapy for a minimum of 4 weeks, targeted to achieve a low-density lipoprotein cholesterol (LDL-C) lower than 1.8 mmol/L for secondary prevention.
- D. Patient has a fasting triglyceride between 1.70 mmol/L and 5.59 mmol/L measured within the 3-month period immediately preceding treatment initiation with icosapent ethyl.
Triglyceride _____ mmol/L Lab Date (YYYY/MM/DD) _____
- E. Patient has a LDL-C between 1.01 mmol/L and 2.59 mmol/L measured within the 3-month period immediately preceding treatment initiation with icosapent ethyl.
LDL _____ mmol/L Lab Date (YYYY/MM/DD) _____

OR

- Patient's LDL-C cannot be calculated due to high fasting triglyceride.



CASE RESOLUTION

Mr. Risk

- Exercise stress test performed
 - ST elevation and chest pain reproduced on ETT
 - Admitted to hospital
- Found to have severe proximal LAD lesion, treated with a stent
- Subsequent LP (a) testing: **838mg/L (210 nmol/L)**





Questions?