The 2021 CCS dyslipidemia guidelines

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Disclosure / Conflict of Interest

George Thanassoulis MD MSc FRCPC

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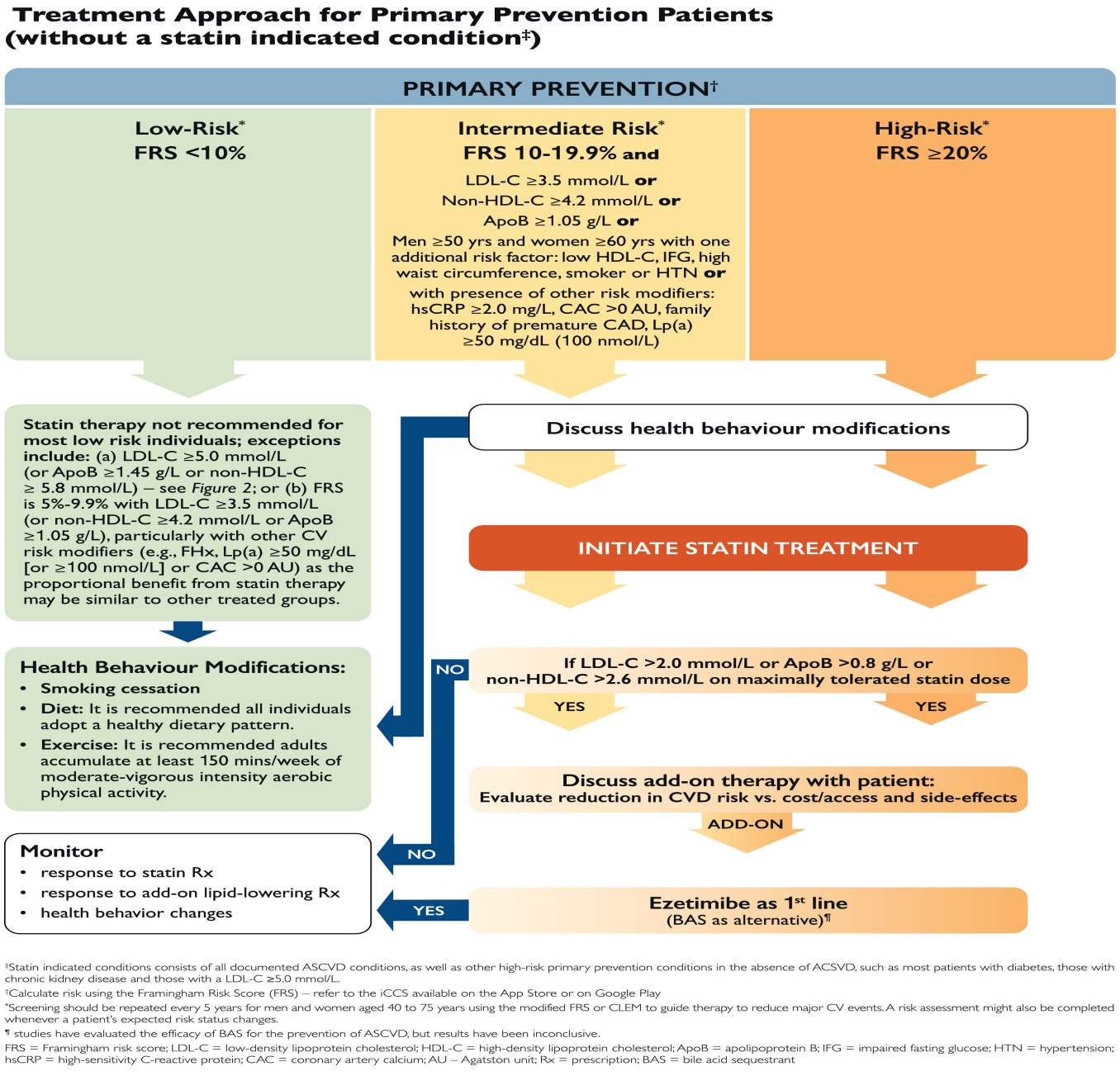
Objectives

1. Overview the new 2021 recommendations for the management of dyslipidemia

2. Discuss the role of non-statin therapies in the management of patients with dyslipidemia

3. Review how the new recommendations affect management through case-based learning

Overview of 2021 Guidelines



‡Statin indicated conditions consists of all documented ASCVD conditions, as well as other high-risk primary prevention conditions in the absence of ACSVD, such as most patients with diabetes, those with chronic kidney disease and those with a LDL-C ≥5.0 mmol/L.

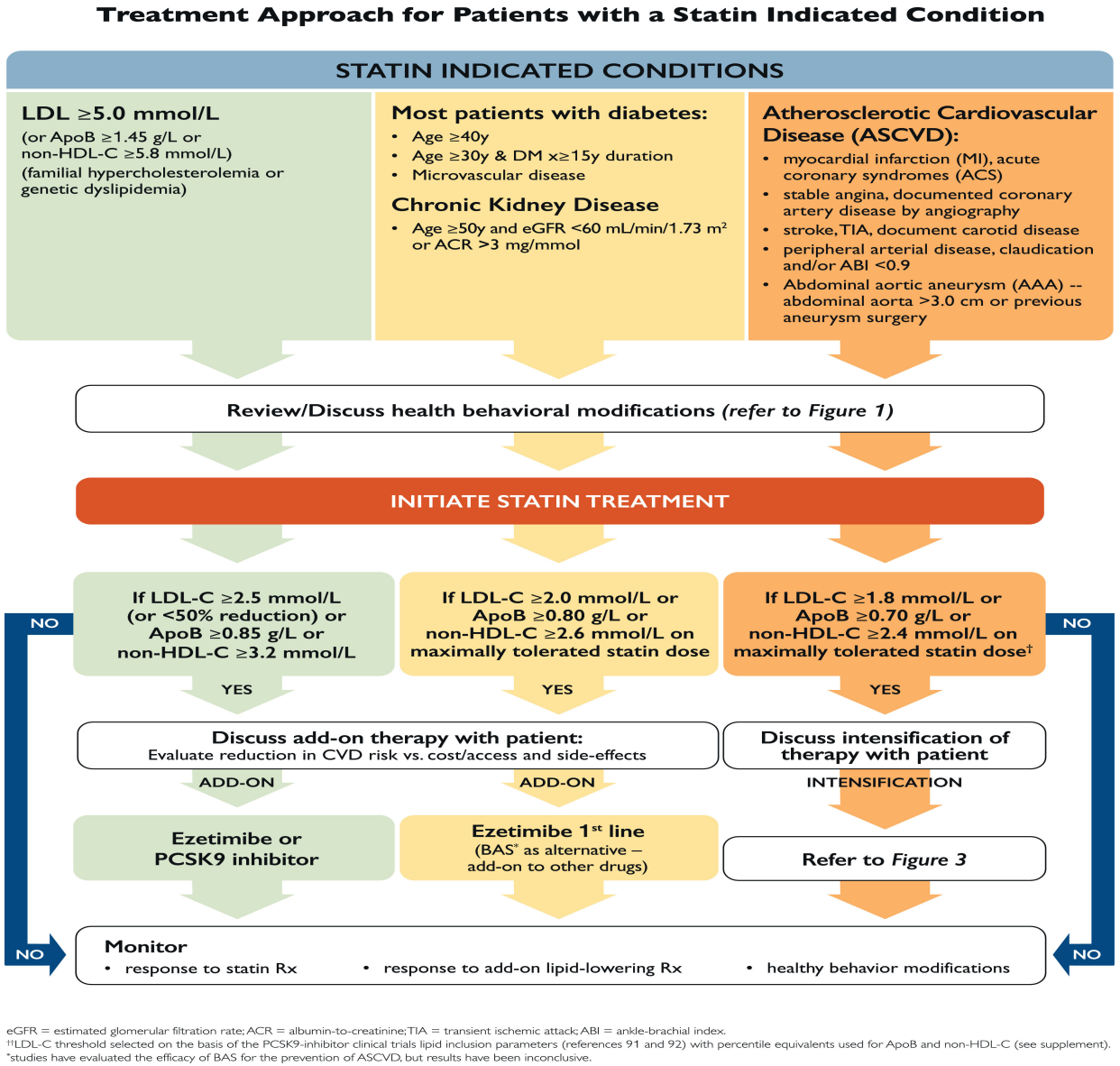
†Calculate risk using the Framingham Risk Score (FRS) – refer to the iCCS available on the App Store or on Google Play

*Screening should be repeated every 5 years for men and women aged 40 to 75 years using the modified FRS or CLEM to guide therapy to reduce major CV events. A risk assessment might also be completed whenever a patient's expected risk status changes.

¶ studies have evaluated the efficacy of BAS for the prevention of ASCVD, but results have been inconclusive.

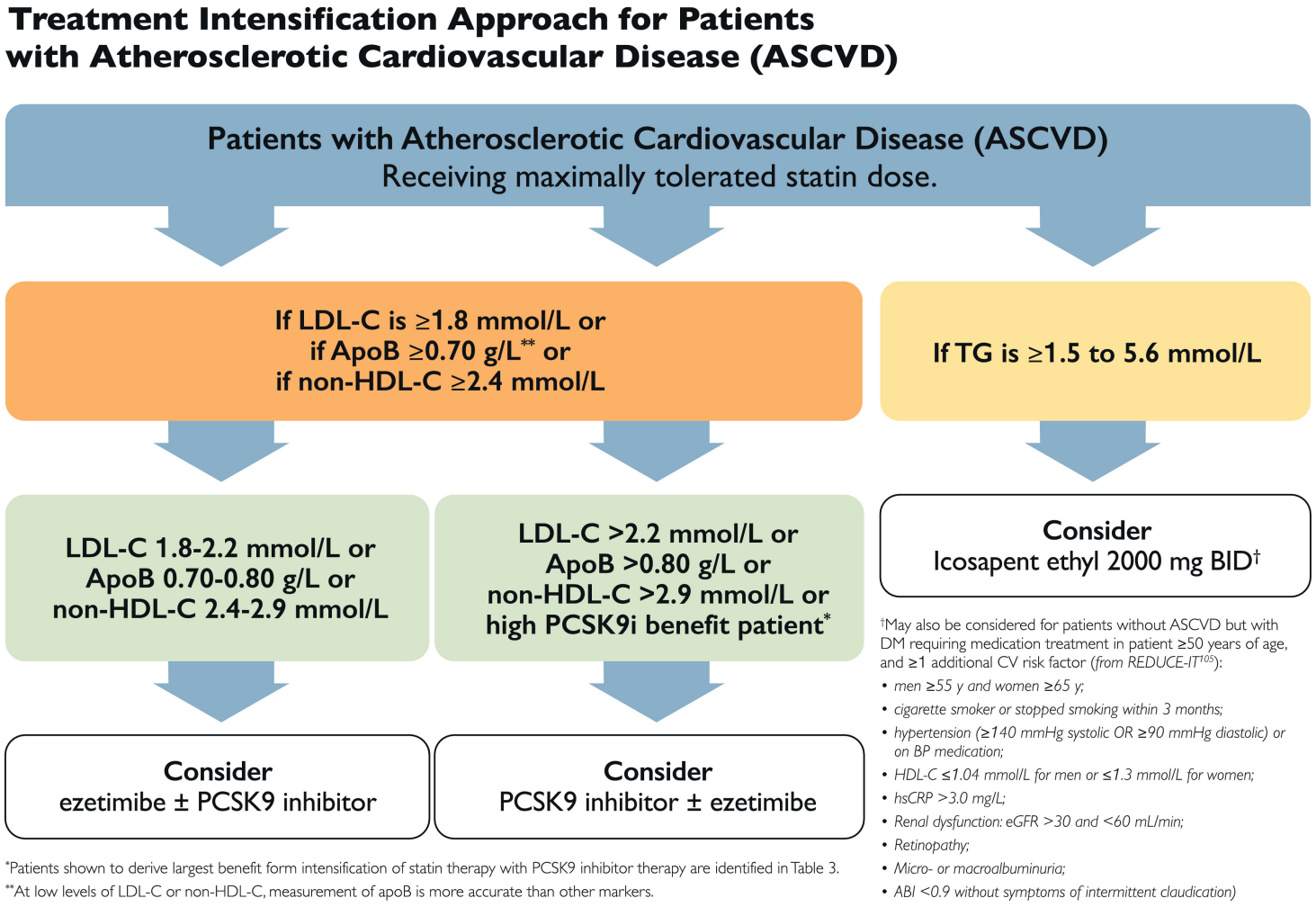
FRS = Framingham risk score; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; ApoB = apolipoprotein B; IFG = impaired fasting glucose; HTN = hypertension; hsCRP = high-sensitivity C-reactive protein; CAC = coronary artery calcium; AU – Agatston unit; Rx = prescription; BAS = bile acid sequestrant

Overview of 2021 Guidelines



eGFR = estimated glomerular filtration rate; ACR = albumin-to-creatinine; TIA = transient ischemic attack; ABI = ankle-brachial index.
††LDL-C threshold selected on the basis of the PCSK9-inhibitor clinical trials lipid inclusion parameters (references 91 and 92) with percentile equivalents used for ApoB and non-HDL-C (see supplement).
*studies have evaluated the efficacy of BAS for the prevention of ASCVD, but results have been inconclusive.

Overview of 2021 Guidelines



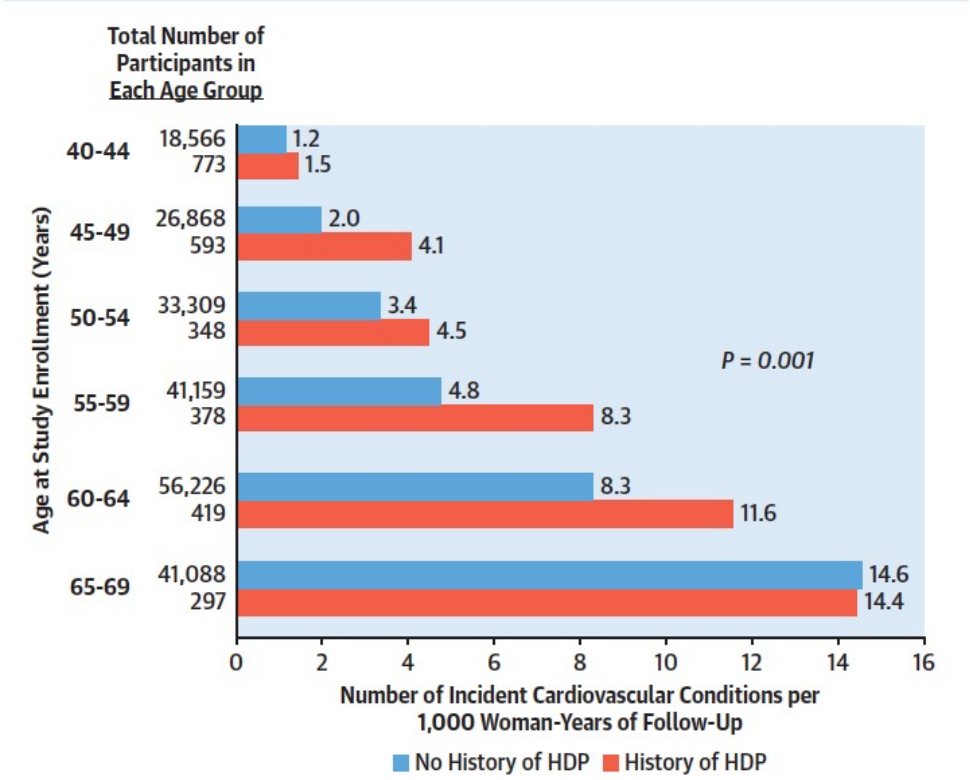
PICO #1

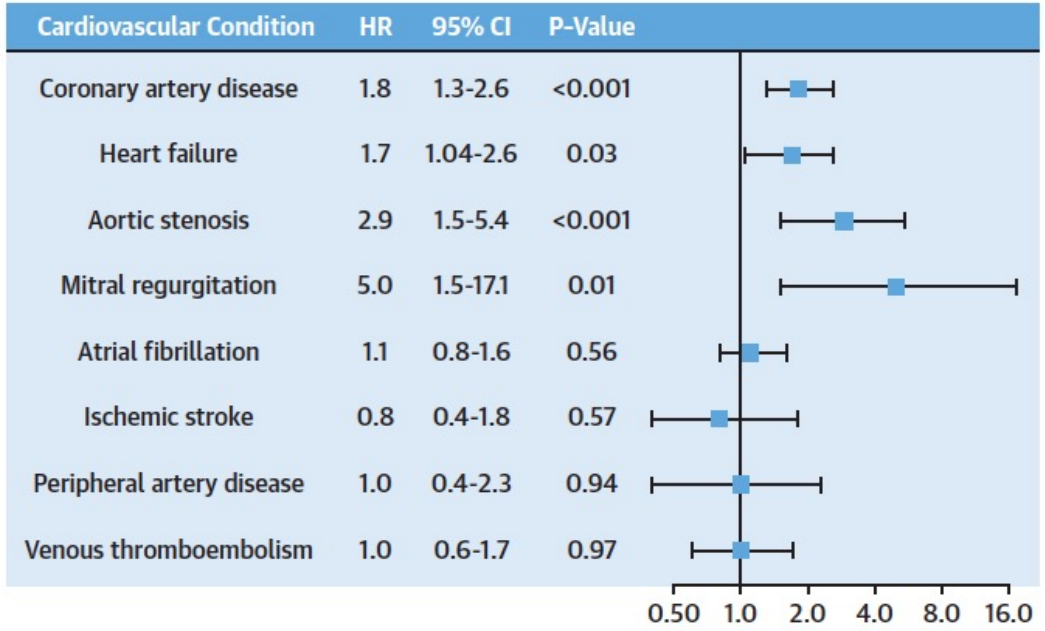
Do pregnancy-related conditions (hypertensive disorders of pregnancy and other related complications) identify women at increased risk of premature cardiovascular disease warranting lipid screening?

2021 CCS Dyslipidemia Guidelines

1. Among **women who have had a pregnancy complication** such as hypertensive disorders of pregnancy, gestational diabetes, pre-term birth, stillbirth, low birthweight infant, or placental abruption, **we recommend screening with a complete lipid panel in the late postpartum period**, since these women have a higher risk of premature CVD and stroke with onset 10-15 years after index delivery. (Strong Recommendation; Moderate Quality Evidence).
2. We **recommend counselling women** who have any of these pregnancy-related complications of the increased lifetime risk of ASCVD, and reinforcing the importance of healthy behaviours
3. To assist with decisions about lipid-lowering pharmacotherapy in this patient population, **we recommend favouring CV age, over 10-year risk calculators** (Strong Recommendation; Low Quality Evidence)

Pregnancy-related complications increase CV risk





Honigsberg M et al JACC 2020

PICO #2

Can consideration of lipoproteins, such as triglyceride-rich lipoproteins, apolipoprotein B and/or lipoprotein(a) improve risk assessment?

2021 CCS Dyslipidemia Guidelines

- **We recommend that for any patient with triglycerides > 1.5 mmol/L, non-HDL-C or ApoB be used instead of LDL-C** as the preferred lipid parameter for screening (Strong Recommendation, High-Quality Evidence).

2021 CCS Dyslipidemia Guidelines

1. **We recommend measuring Lp(a) level once in a person's lifetime** as a part of the initial lipid screening. (Strong Recommendation; High Quality Evidence).

2. For all patients in the setting of primary prevention **with a Lp(a) ≥50 mg/dL (or ≥100 nmol/L)**, **we recommend earlier and more intensive health behaviour modification counselling and management of other ASCVD risk factors** (Strong recommendation; Expert consensus).

2021 CCS Dyslipidemia Guidelines

Need to consider ALL atherogenic lipoprotein particles not ONLY LDL-C

- **Non-HDL-C (indirect measure)**
- **ApoB (direct measure)**

- **ApoB > non-HDL-C >> LDL-C**

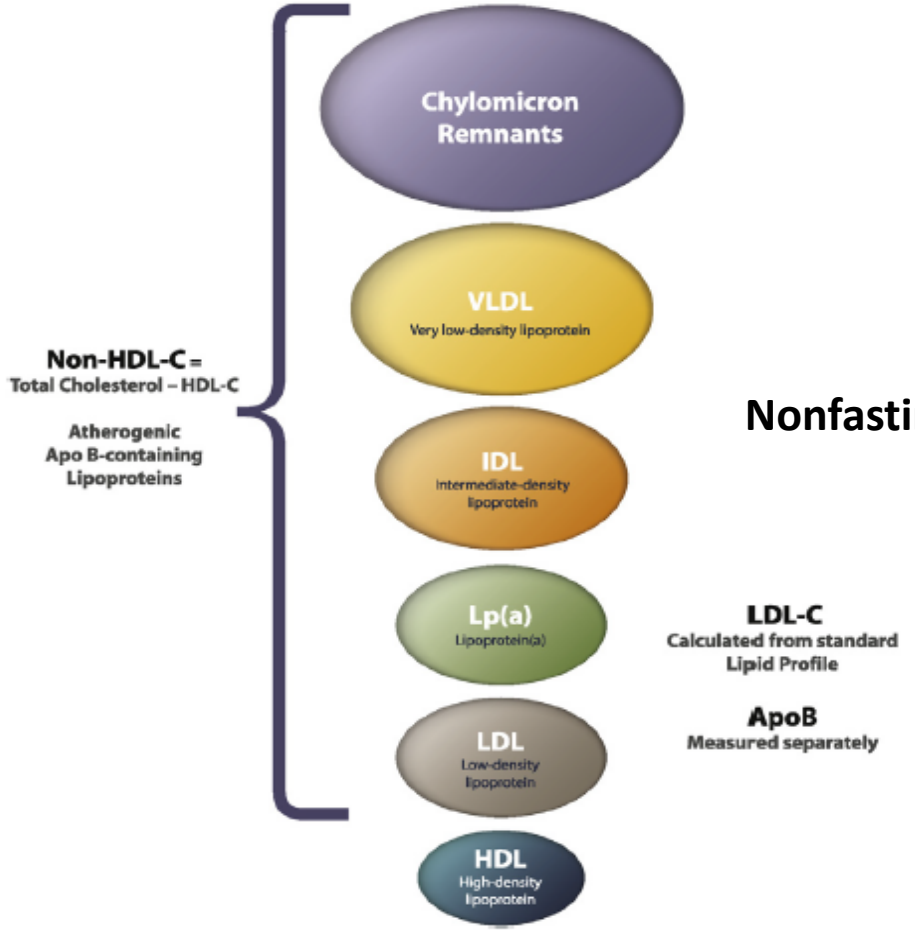


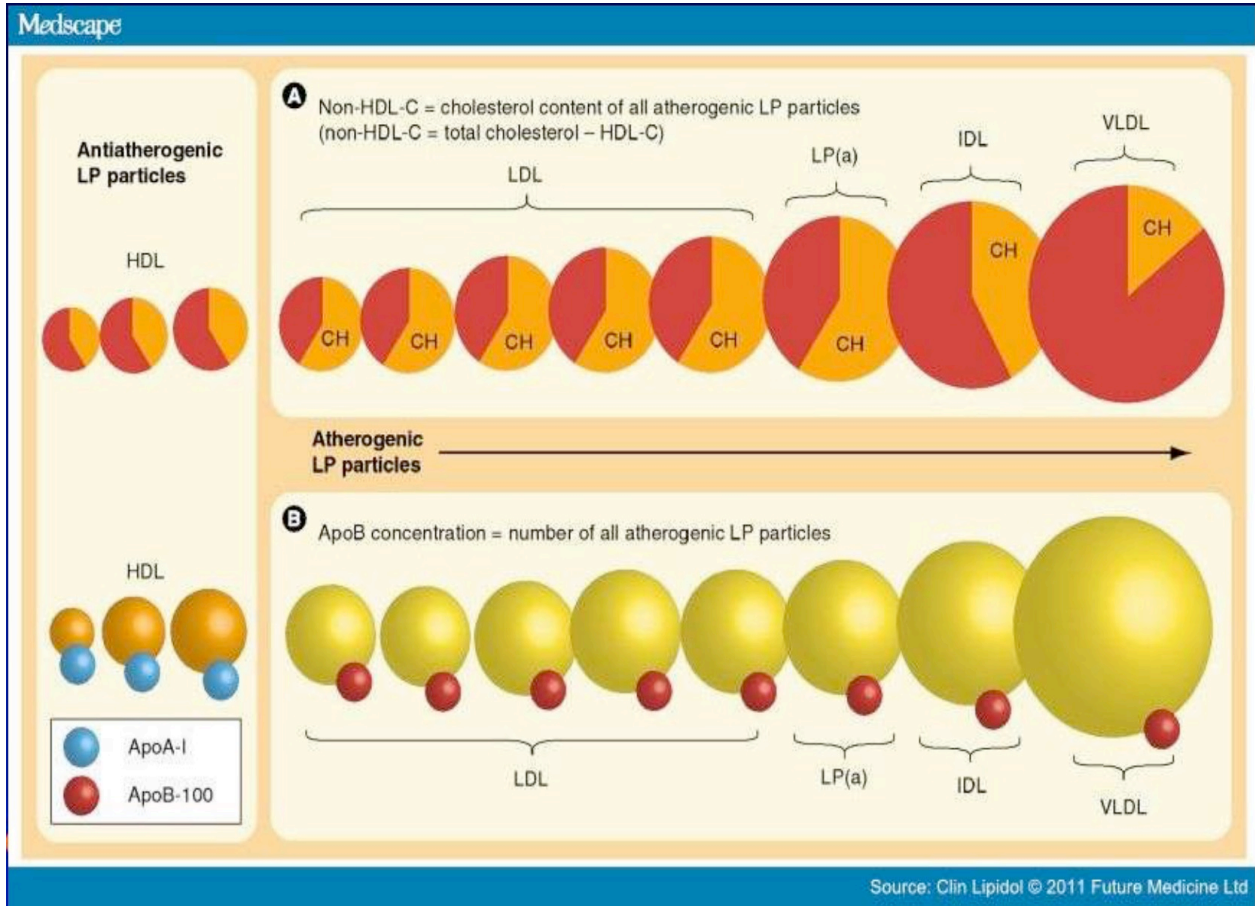
Figure 3. Non-HDL-cholesterol measures cholesterol in all atherogenic lipoproteins. ApoB, apolipoprotein B; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LP(a), lipoprotein(a); VLDL, very low-density lipoprotein.

Nonfasting lipid testing

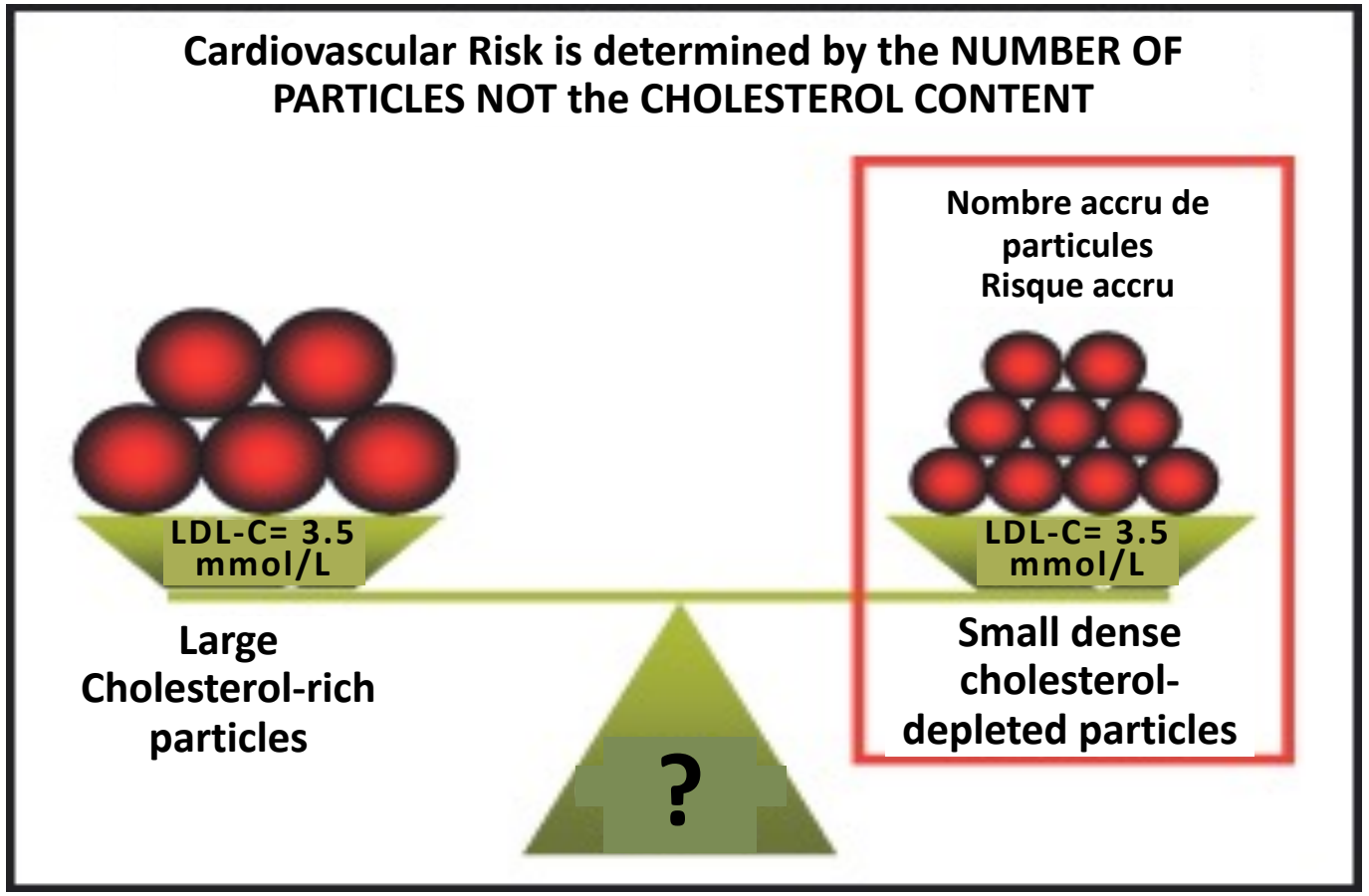
Anderson TJ, Gregoire J, Pearson GJ, et al. *Can J Cardiol* 2016;32:1263-1282.

Apolipoprotein-B

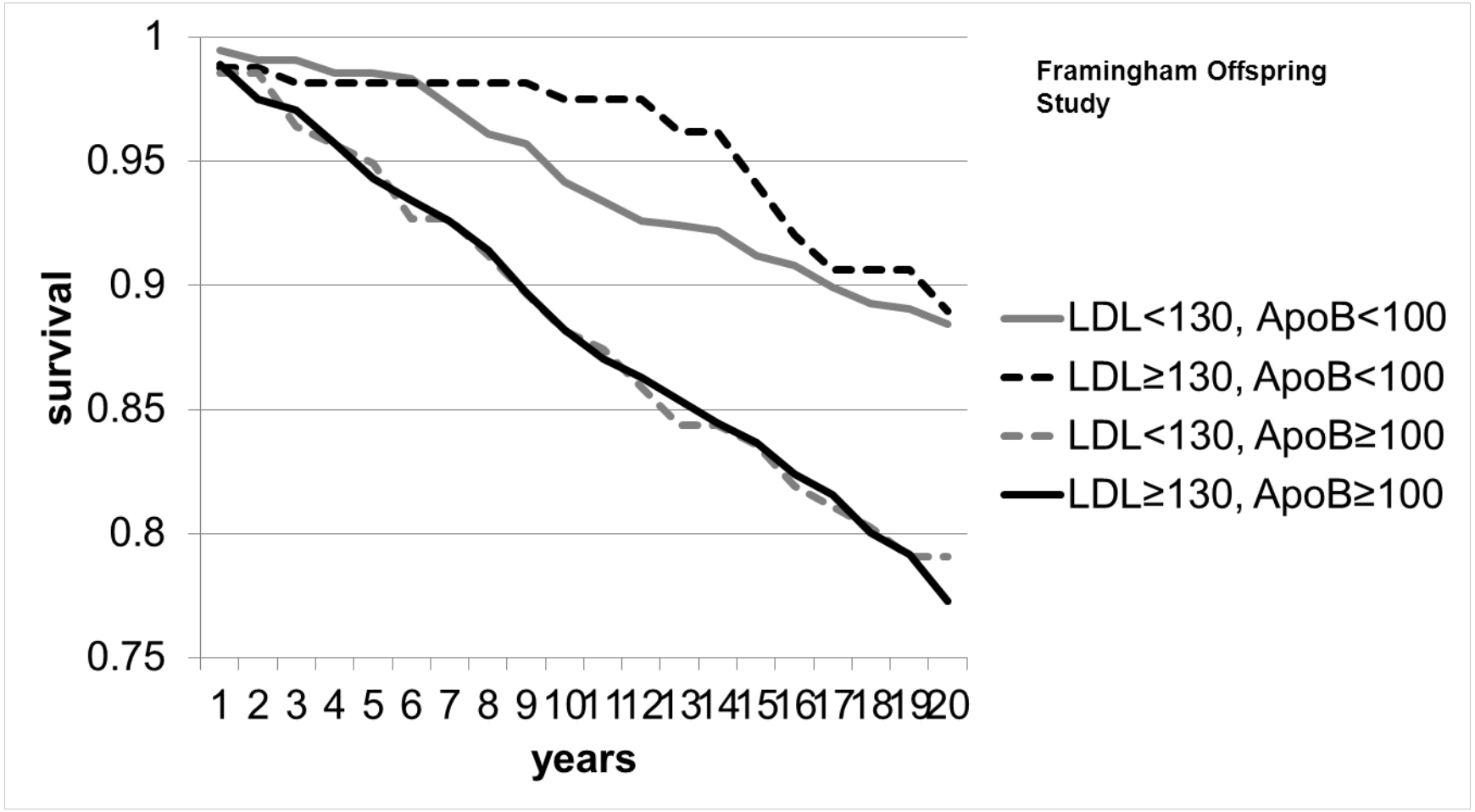
- Each of the atherogenic lipid particles (*LDL, Lp(a), IDL, VLDL*) contain 1 molecule of Apo-B
- serum concentration of Apo-B reflects the total number of these particles in the circulation
- Measuring apo-B provides information about the number and total atherogenicity of the lipid profile



High apoB = danger

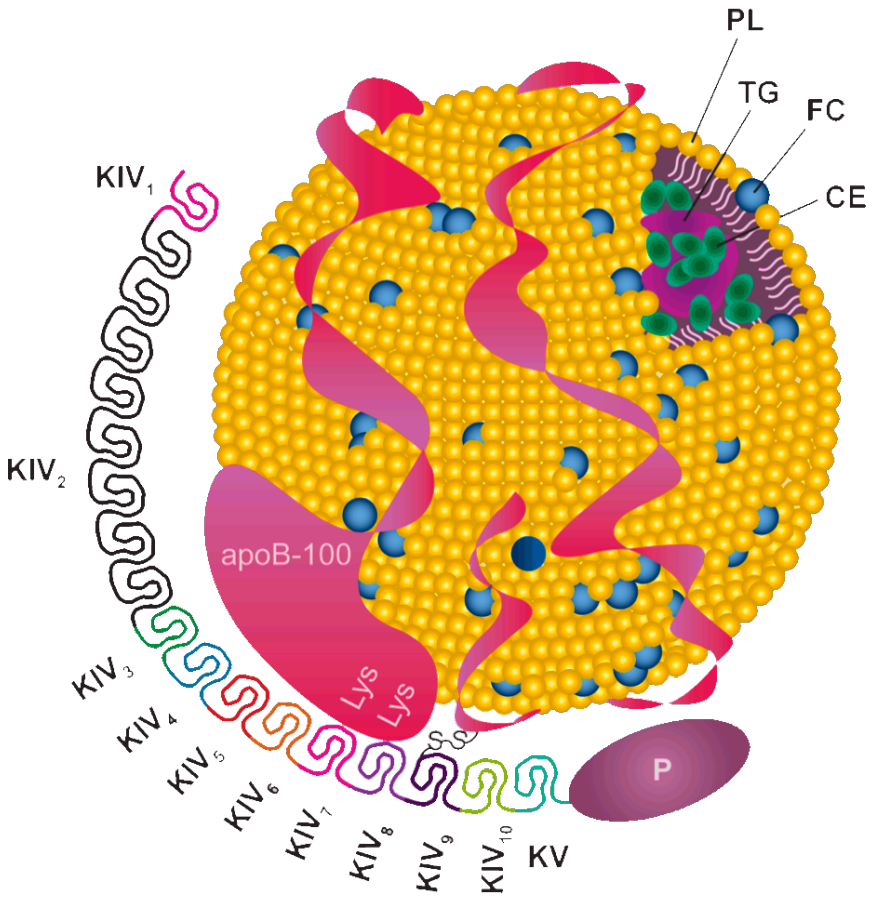


Risk tracks ApoB - always



Pencina MJ, Eur J Prev Card 2015

Lipoprotein(a)



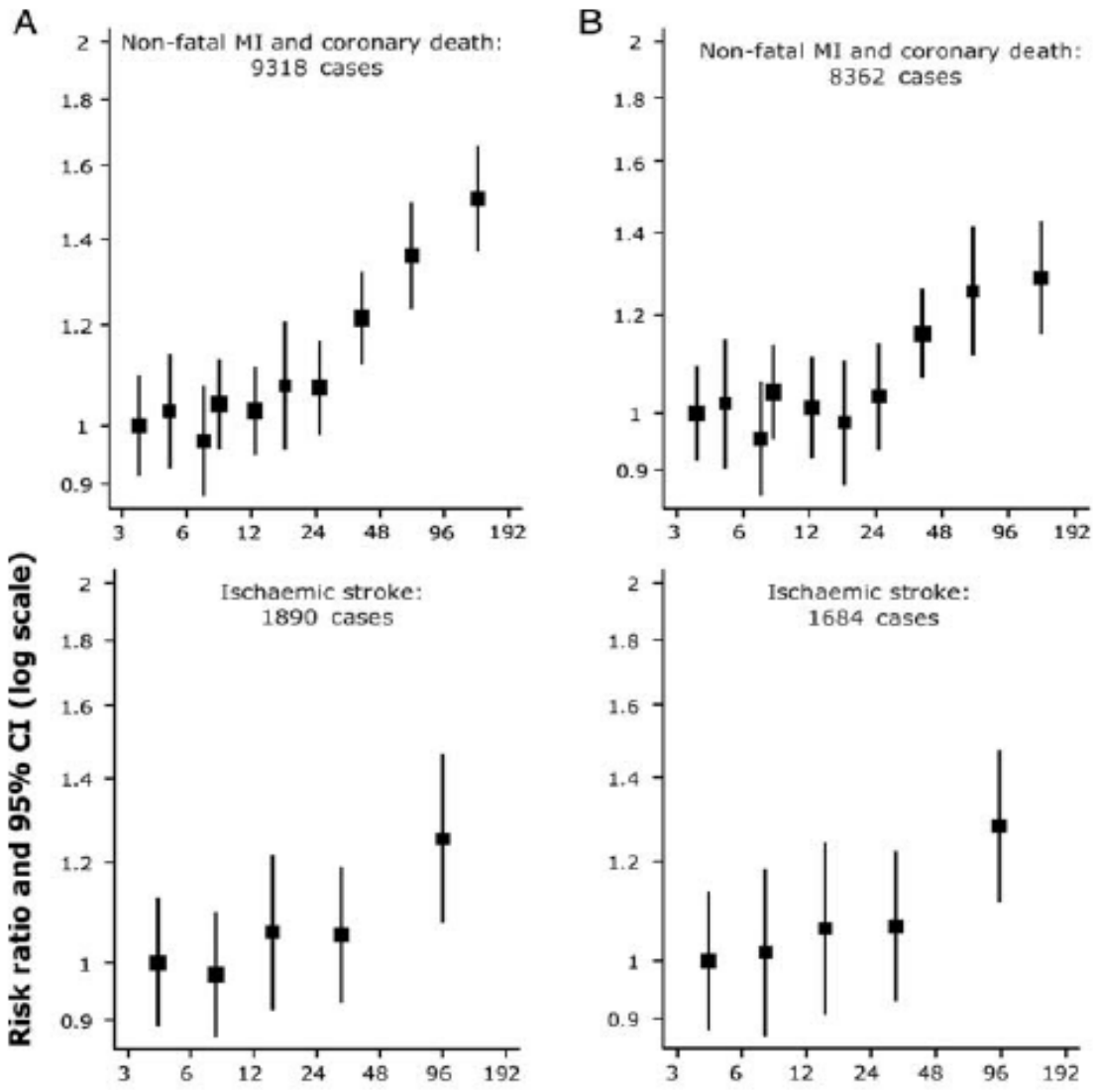
- LDL-like particle with a Apolipoprotein (a) covalently bound to Apolipoprotein-B
- Lp(a) levels are explained by genetics
  - Number of repeats in KIV-2 is inversely correlated to plasma levels
  - SNPs in Lp(a) are associated with plasma levels

Lipoprotein(a)

- Increased Lp(a) is associated with MI, ischemic stroke, aortic stenosis and mortality

- Risk increases starting at ≥30 mg/dL and becomes clinically significant ≥ 50 mg/dL

- **Some individuals with extreme levels (> 180 mg/dL) may have a prognosis similar to htz FH**



Erqou et al *JAMA* 2009

Lipoprotein (a) and Risk of Recurrent CVD

- Compared with individuals with Lp(a)<10 mg/dL (18 nmol/L), the multifactorially adjusted MACE incidence rate ratios were:
  - 1.28 (1.03–1.58) for 10 to 49 mg/dL
  - 1.44 (1.12–1.85) for 50 to 99 mg/dL
  - 2.14 (1.57–2.92) for ≥100 mg/dL
- High concentrations of Lp(a) are associated with high risk of recurrent CVD in individuals from the general population

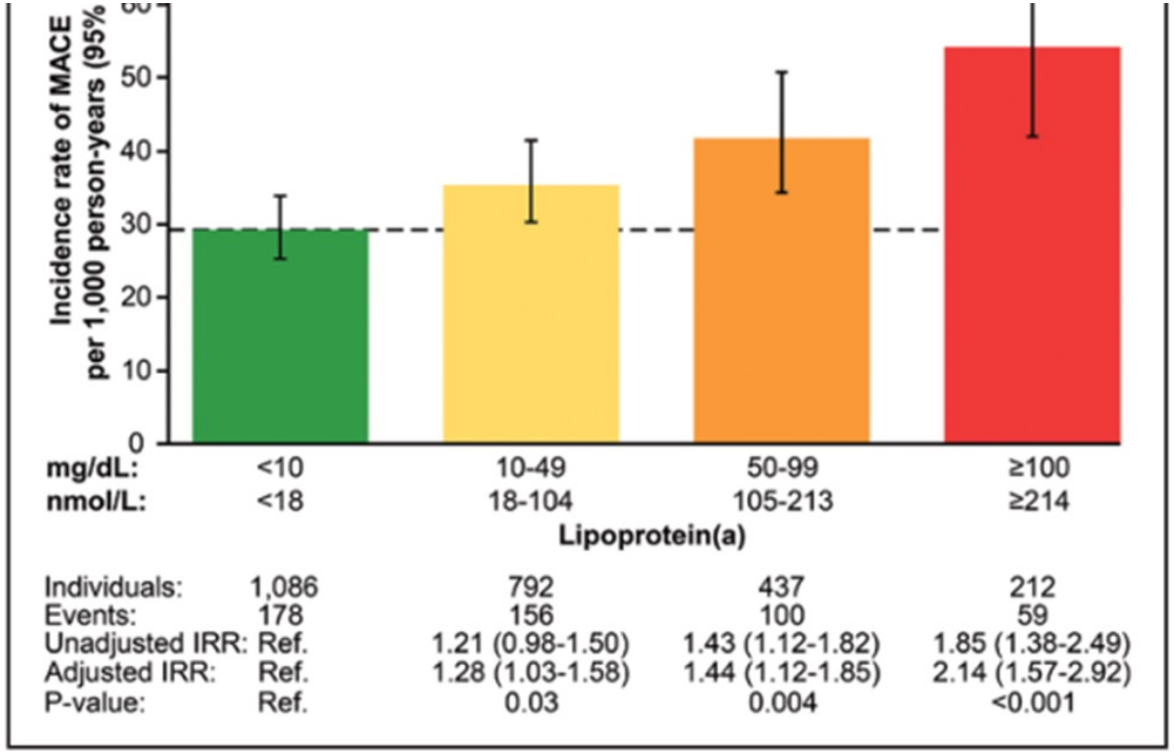


Figure 1. Absolute risk of major adverse cardiovascular event (MACE) according to concentrations of Lp(a) (lipoprotein[a]).

Arterioscler Thromb Vasc Biol 2020;40(1):255-266.

Future Lp(a) therapy

Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study

Sotirios Tsimikas, Nicholas J Viney, Steven G Hughes, Walter Singleton, Mark J Graham, Brenda F Baker, Jennifer L Burkey, Qingqing Yang, Santica M Marcovina, Richard S Geary, Rosanne M Crooke, Joseph L Witztum

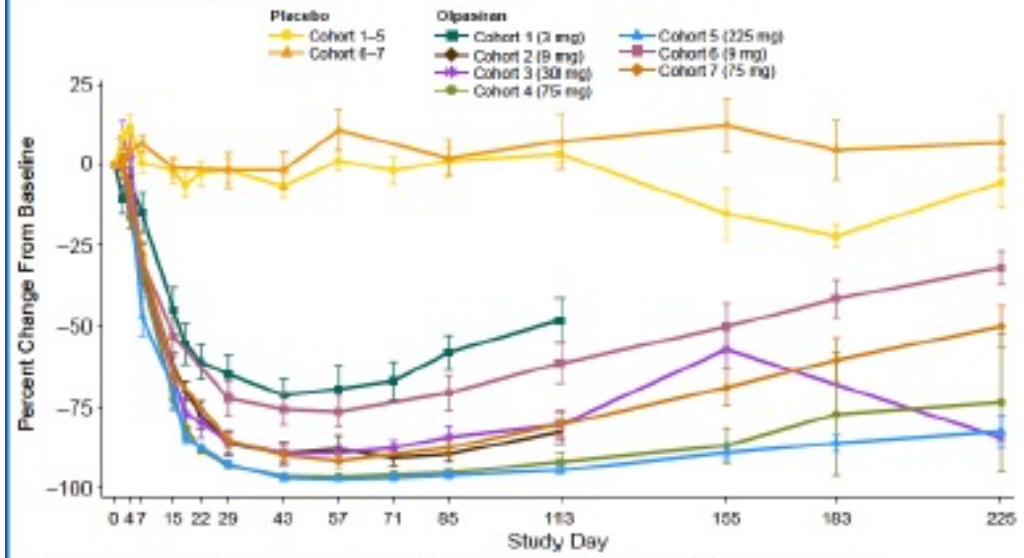
Safety, Tolerability, and Efficacy of Single-dose AMG 890, a Novel siRNA Targeting Lp(a), in Healthy Subjects and Subjects With Elevated Lp(a)

Michael J Koren,[1] Patrick Maurice Moriarty,[2] Joel Neutel,[3] Seth J Baum,[4] Martha Hernandez-Illas,[5] Howard S Weintraub,[6] Jennifer Hellawell,[7] Tracy Varrieur,[8] Winnie Sohn,[9] Huei Wang,[10] Mary Elliott-Davey,[11] Helina Kassahun,[9] Gerald F Watts[12†]

[1]Jacksonville Center for Clinical Research, Jacksonville, FL; [2]University of Kansas Medical Center, Kansas City, KS; [3]Orange County Research Center, Tustin, CA; [4]Excel Medical Clinical Trials, Boca Raton, FL; [5]QPS MRA, Miami, FL; [6]NYU Langone Medical Center, New York, NY; [7]Amgen, South San Francisco, CA; [8]Amgen, Cambridge, MA; [9]Amgen, Thousand Oaks, CA; [10]Amgen, Newbury Park, CA; [11]Amgen Ltd, Cambridge; [12]University of Western Australia, Perth, Australia

[†]Current affiliation, School of Medicine, University of Western Australia, Department of Cardiology, Royal Perth Hospital, Perth, Australia

Figure 2. Lp(a) Percent Change from Baseline After a Single Dose of Placebo or Olpasiran



Baseline values are the mean of screening and day 1 pre-dose values. If only 1 value was available, that value was used as the baseline value.
As-is data snapshot date: 21Oct2020

PICO #3

In primary prevention, what is the evidence for CAC to improve risk assessment? Specifically, should low CAC (or CAC=0) be used to avoid statin therapy in select individuals?

2021 CCS Dyslipidemia Guidelines

1. **We suggest that CAC screening using computed tomography imaging may be considered for asymptomatic adults ≥ 40 years and at intermediate risk (FRS 10%- 20%)** for whom treatment decisions are uncertain (Strong Recommendation, Moderate-Quality Evidence).
2. We recommend that **CAC screening using computed tomography imaging not be undertaken for**: (1) high-risk individuals; (2) patients receiving statin treatment; or (3) most asymptomatic, low-risk adults (Strong Recommendation; Moderate-Quality Evidence).
3. **We suggest that CAC screening may be considered for a subset of low-risk individuals > 40 years with a family history of premature ASCVD** (men < 55 years; women ≤†65 years) in addition to identifying known **genetic causes of CAD** such as elevated Lp(a) or FH. (Weak Recommendation; Low-Quality Evidence).

Case Discussion
- Screening and Primary Prevention -

Case 1 Mrs. Tremblay

55F for CV risk assessment

2 prior pregnancies – 2 healthy daughters

Developed hypertension during both pregnancies.

BP 135/85 mm HG

BMI 29/m2, normal blood glucose/Hgba1C

TC 5.9 mmol/L

HDL-C 1.2

TG 3.0 mmol/L

LDL-C 3.3 mmol/L

FRS– 5% risk of CV event in 10 years

Case 1 Mrs. Tremblay

Which of the following is **the most appropriate statement**:

1. She is at low-risk for CV events. No further management needed.
2. She is at high-risk for CV events. Start lipid-lowering therapy with high-dose statin.
3. Her risk is likely underestimated. Consider total atherogenic burden and other risk factors for better risk assessment.
4. Her risk is likely underestimated. Would recommend exercise stress testing and coronary artery calcium scan.

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Case 1 Mrs. Tremblay

59F for risk assessment

2 prior pregnancies – 2 healthy daughters

Developed hypertension during both pregnancies

BP 135/85 mm HG

BMI 29 kg/m2

TC 5.9 mmol/L

HDL-C 1.2 mmol/L

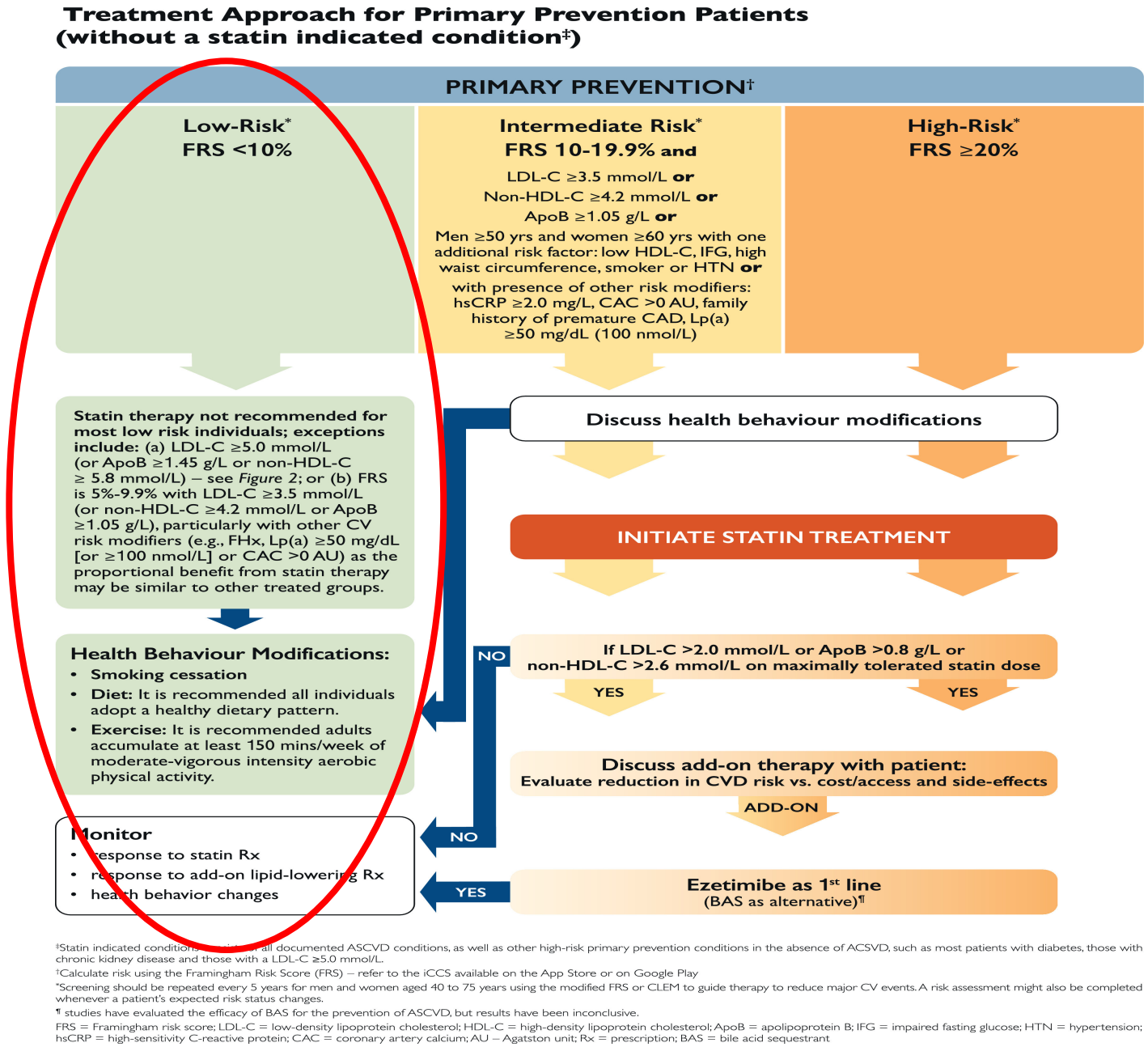
TG 3.0 mmol/L

LDL-C 3.3 mmol/L

FRS– 5% risk of CV event in 10 years

Non-HDL-C 4.7 mmol/L!
apoB 1.25!
Lp(a) 120 nmol/L!

Overview of 2021 Guidelines



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PICO #4

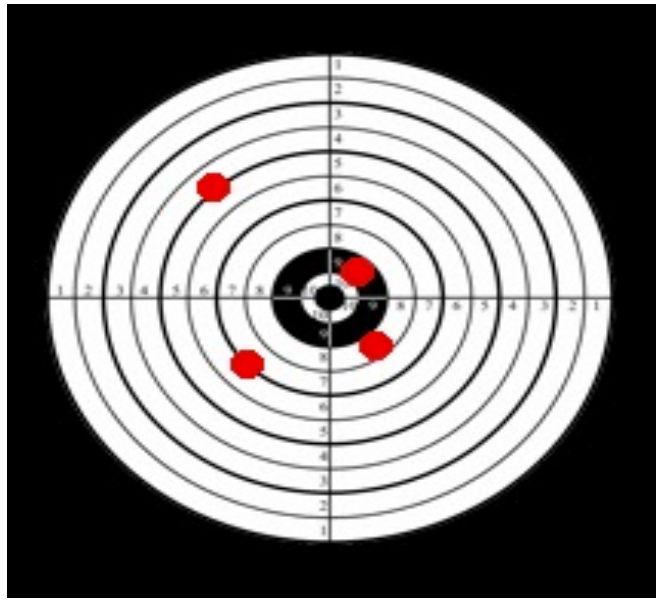
In adults already receiving or intolerant to statins, what is the role of other lipid-modulating drugs compared with placebo reduce CVD events?

PICO #5

In secondary prevention,
what is the most appropriate lipid/lipoprotein threshold for intensification of therapy?

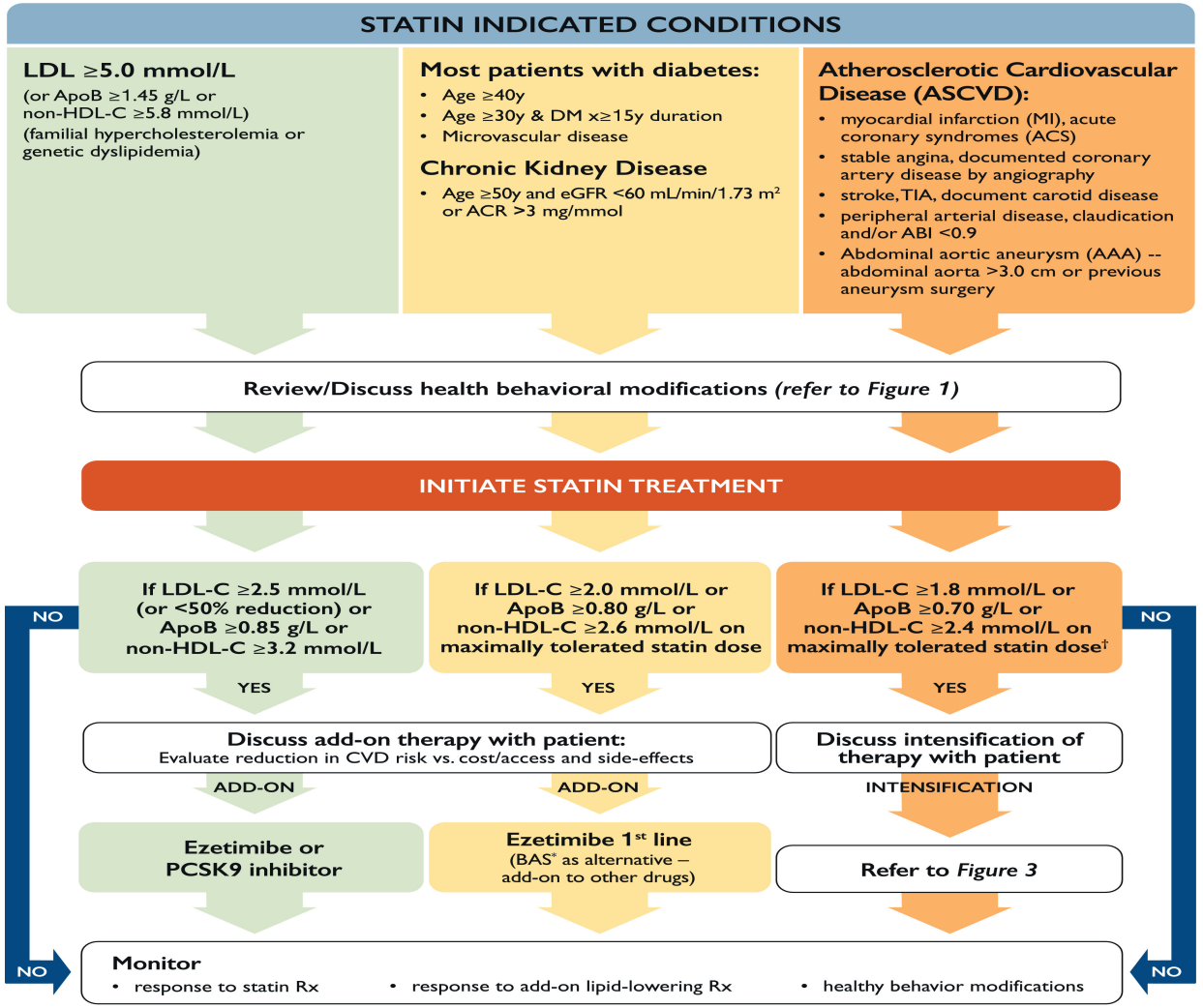
LDL-targets vs treatment intensification thresholds?

- Lower LDL is better
  - ”close-enough” is not good enough
  - WHO should we treat intensively?
- Evidence-based
  - Thresholds based on RCTs
- Actionable
  - ?less clinical inertia



Intensification threshold

Treatment Approach for Patients with a Statin Indicated Condition



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†‡LDL-C threshold selected on the basis of the PCSK9-inhibitor clinical trials lipid inclusion parameters (references 91 and 92) with percentile equivalents used for ApoB and non-HDL-C (see supplement).
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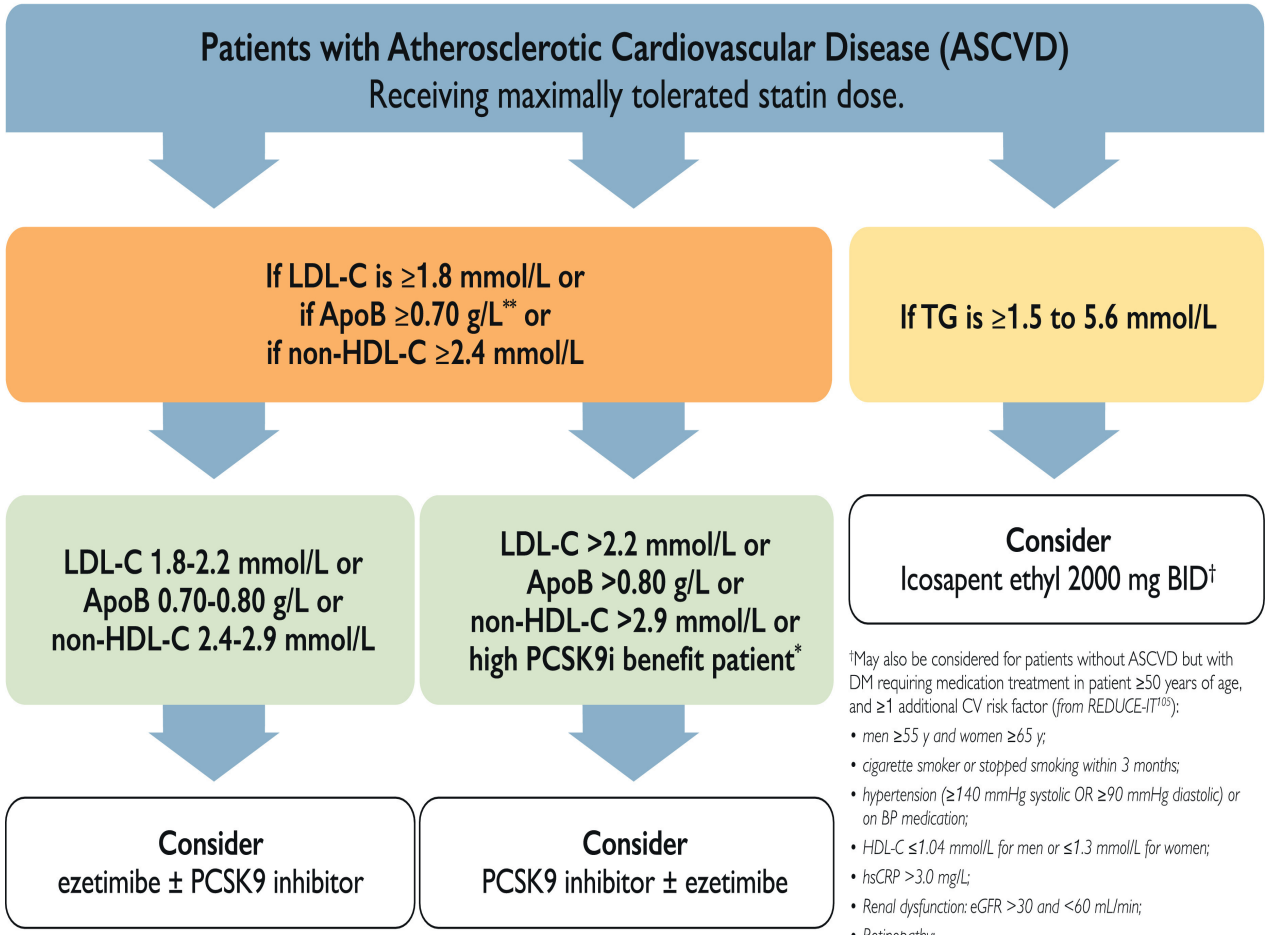
2021 CCS Dyslipidemia Guidelines

1. **We recommend use of high-intensity statin therapy in addition to appropriate health behaviour modifications for all secondary prevention CVD patients**. For patients who do not tolerate a high-intensity statin, we recommend the maximally tolerated statin dose (Strong Recommendation; High-Quality Evidence).

2021 CCS Dyslipidemia Guidelines

2. **We recommend intensification of lipid-lowering therapy with ezetimibe and/or PCSK9 inhibitor therapy for all secondary prevention CVD patients in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L)** on maximally tolerated statin dose. (Strong recommendation; High Quality Evidence). If ezetimibe is used initially and LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) PCSK9 inhibitor therapy is recommended.
3. **We recommend intensification of lipid-lowering therapy with a PCSK9 inhibitor (evolocumab or alirocumab) – with or without the addition of ezetimibe – for secondary CV prevention patients shown to derive the largest benefit from PSCK9 inhibitor therapy in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L)** on maximally tolerated statin dose. Refer to Figure 3. (Strong Recommendation; Moderate-Quality Evidence).

Treatment Intensification Approach for Patients with Atherosclerotic Cardiovascular Disease (ASCVD)



*Patients shown to derive largest benefit form intensification of statin therapy with PCSK9 inhibitor therapy are identified in Table 3.

**At low levels of LDL-C or non-HDL-C, measurement of apoB is more accurate than other markers.

†May also be considered for patients without ASCVD but with DM requiring medication treatment in patient ≥50 years of age, and ≥1 additional CV risk factor (*from REDUCE-IT*[105]):

- *men ≥55 y and women ≥65 y;*
- *cigarette smoker or stopped smoking within 3 months;*
- *hypertension (≥140 mmHg systolic OR ≥90 mmHg diastolic) or on BP medication;*
- *HDL-C ≤1.04 mmol/L for men or ≤1.3 mmol/L for women;*
- *hsCRP >3.0 mg/L;*
- *Renal dysfunction: eGFR >30 and <60 mL/min;*
- *Retinopathy;*
- *Micro- or macroalbuminuria;*
- *ABI <0.9 without symptoms of intermittent claudication)*

Table 3: Secondary prevention patients shown to derive the largest benefit from intensification of statin therapy with the addition of a PCSK9 inhibitor

Recent acute coronary event (ACS) • hospitalized index ACS to 52 weeks post index ACS
Clinically evident ASCVD and any of the following: i. diabetes mellitus or metabolic syndrome ii. polyvascular disease (vascular disease in ≥2 arterial beds) iii. symptomatic PAD iv. recurrent MI v. MI in the past 2 years vi. previous CABG surgery vii. LDL-C ≥ 2.6 mmol/L or heterozygous FH viii. lipoprotein (a) ≥ 60 mg/dL (120 nmol/L)

ASCVD = atherosclerotic cardiovascular disease; PAD = peripheral arterial disease; MI = myocardial infarction; CABG = coronary artery bypass graft; LDL-C = low density lipoprotein cholesterol; FH = familial hypercholesterolemia

2021 CCS Dyslipidemia Guidelines

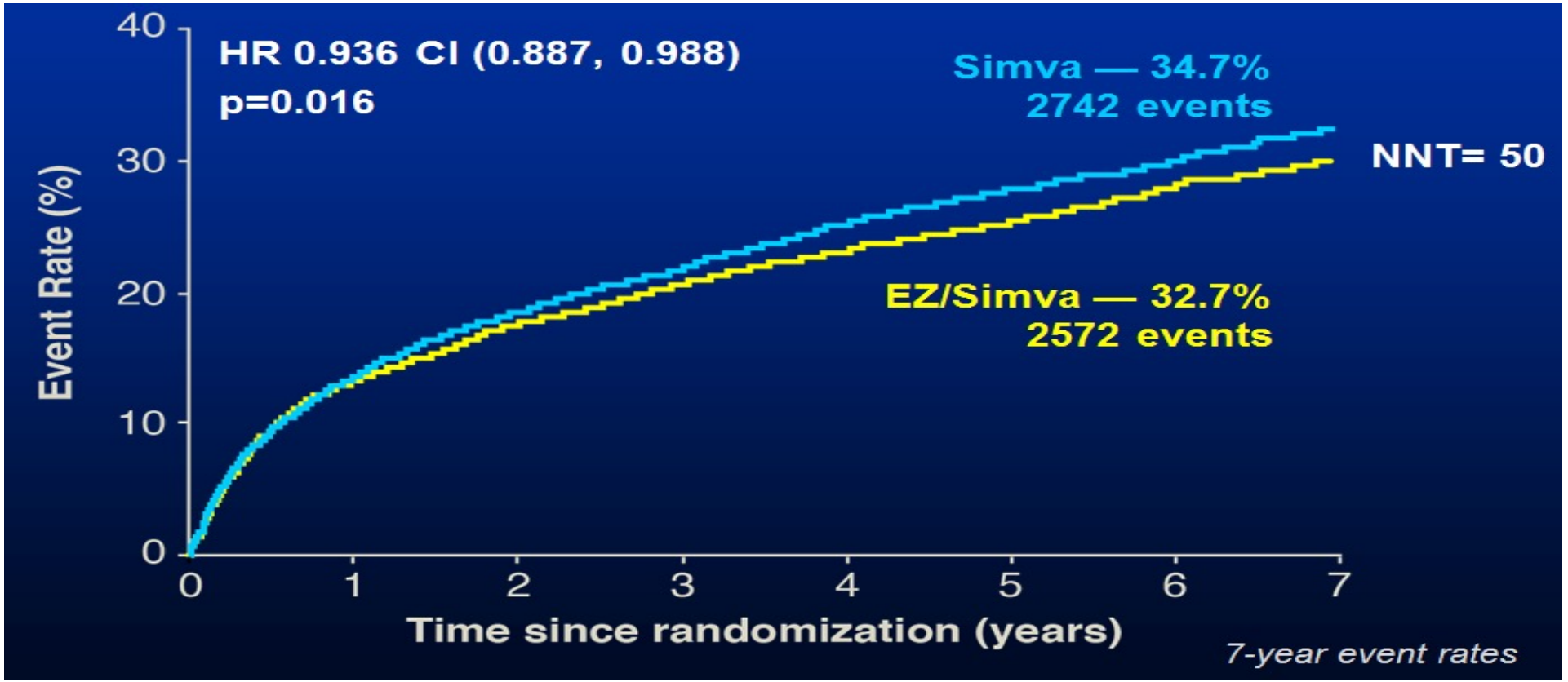
1. **We recommend the use of icosapent ethyl to lower the risk of CV events in patients with ASCVD, or with diabetes and ≥1 CVD risk factors, who have an elevated fasting triglyceride level of 1.5-5.6 mmol/L** despite treatment with maximally tolerated statin therapy (Strong Recommendation; High-Quality Evidence).

2021 CCS Dyslipidemia Guidelines

1. **We recommend the use of a PCSK9 inhibitor (alirocumab or evolocumab) to lower LDL-C in patients with heterozygous FH without clinical ASCVD whose LDL-C remains above the threshold** (i.e., LDL-C ≥2.5 mmol/L or < 50% reduction from baseline; or Apo-B≥ 0.85 mg/dL or non-HDL-C ≥ 3.2 mmol/L)) despite maximally tolerated statin therapy with or without ezetimibe therapy (Strong Recommendation; High-Quality Evidence).
2. **We recommend the use of a PCSK9 inhibitor (alirocumab or evolocumab) for patients with heterozygous FH and ASCVD whose LDL-C remains above the threshold ≥ 1.8 mmol/L** (or ApoB ≥ 0.7 mg/dL or non-HDL-C ≥ 2.4 mmol/L) despite maximally tolerated statin therapy, with or without ezetimibe. (Strong Recommendation; High-Quality Evidence).

IMPROVE-IT

18,144 patients within 10 days post ACS (N=18144); LDL>1.3 mmol/L; not on LLT < 3.2 mmol/L; on LLT < 2.6 mmol/L
Primary endpoint: CV death, MI, UAP requiring rehospitalization, coronary revascularization (≥30 days), or stroke



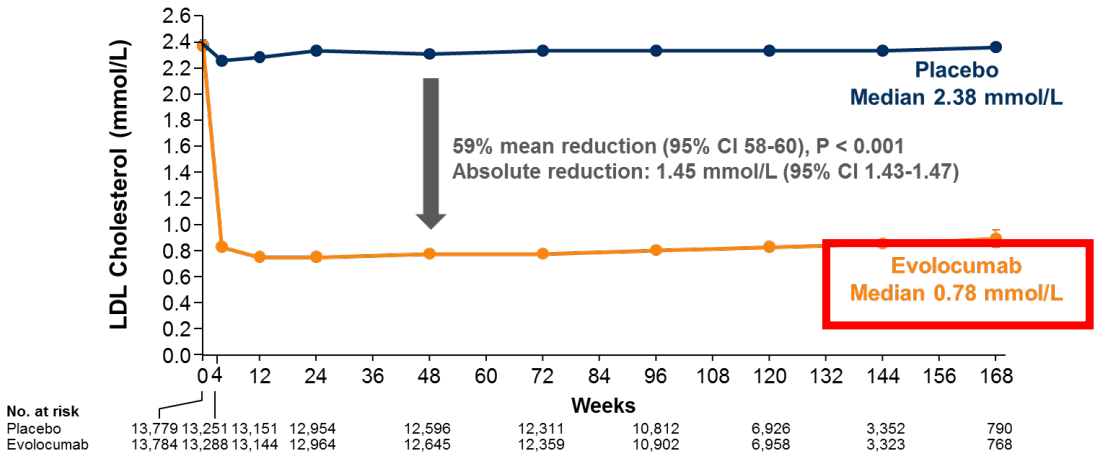
Mean LDL-C at 1 year: 1.4 mmol/L for simvastatin/ezetimibe vs 1.8 mmol/L for simvastatin alone

Cannon C. N Engl J Med 2015;372:2387-97

FOURIER

27,564 patients with history of CVD event (chronic stable ASCVD) plus additional RFs;
Fasting LDL-C ≥ 1.8 mmol/L or non-HDL-C C ≥2.6 mmol/L
Primary Endpoint: CV death, MI, stroke, hosp. for UA, or coronary revasc

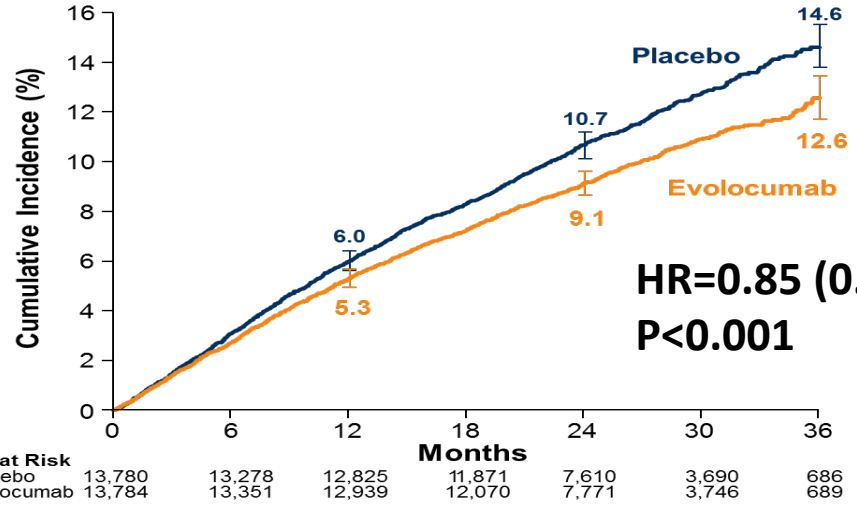
Median LDL-C Levels Over Time: All Patients



LDL-C was significantly reduced in the evolocumab group (median: 0.78 mmol/L) including 42% who achieved levels ≤ 0.65 mmol/L vs < 0.1% in the placebo group

Data shown are median values with 95% confidence intervals in the two arms; ITT.
Sabatine MS, et al . *N Engl J Med.* [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

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



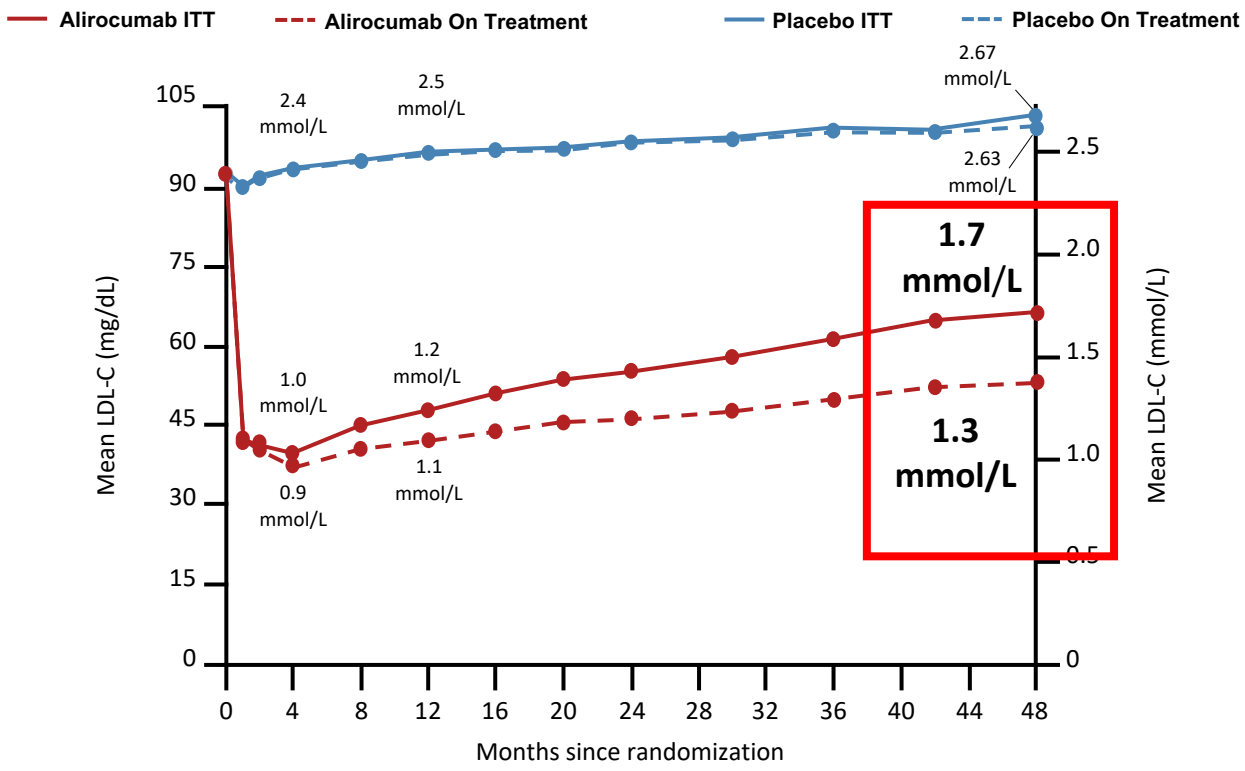
HR 0.85 (95% CI 0.79 to 0.92); *P* < 0.001

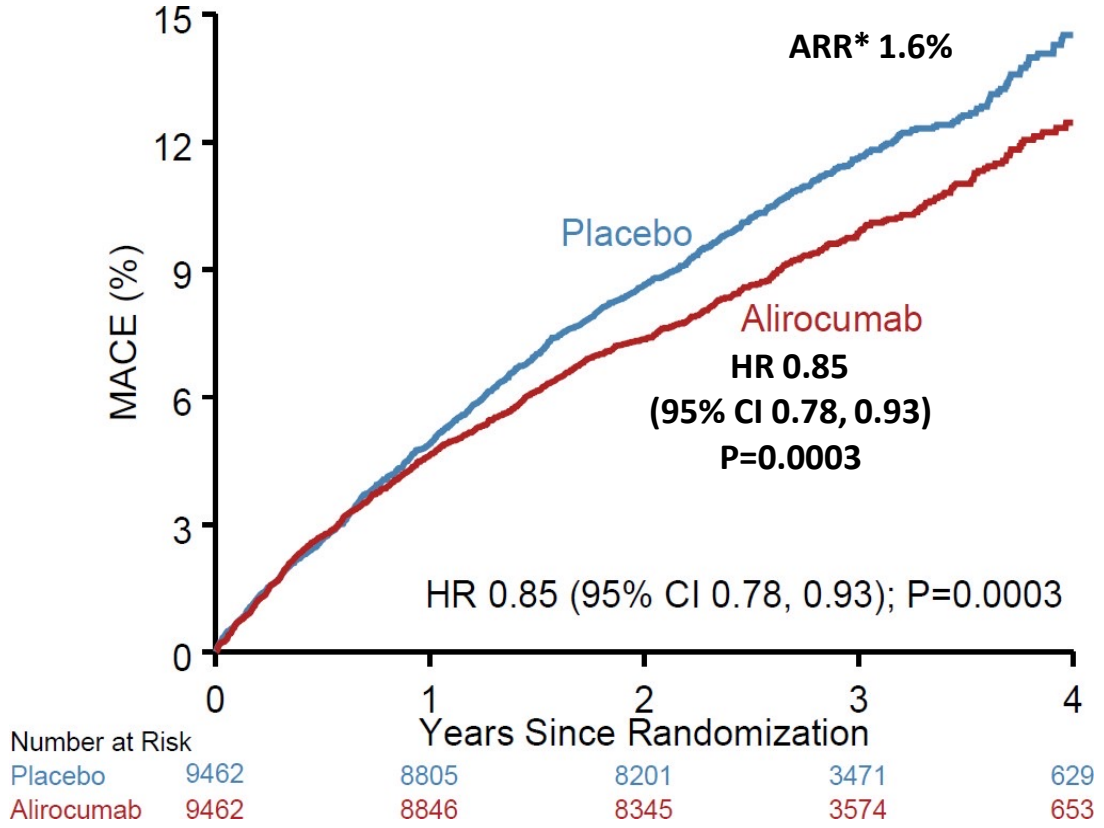
CV = Cardiovascular; MI = Myocardial infarction; UA = Unstable angina; HR = Hazard ratio
Sabatine MS, et al . *N Engl J Med.* [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Sabatine M. N Engl J Med 2017 ;376(18):1713-1722

ODYSSEY OUTCOMES

18,924 post ACS patients (1-12 months); LDL-C ≥ 1.8 mmol/L or non-HDL ≥ 2.6 mmol/L or apo B ≥ 80 mg/dL
Primary Outcome: CHD death, non-fatal MI, fatal or non-fatal stroke, UAP requiring hospitalization





Schwarz GG. N Engl J Med 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

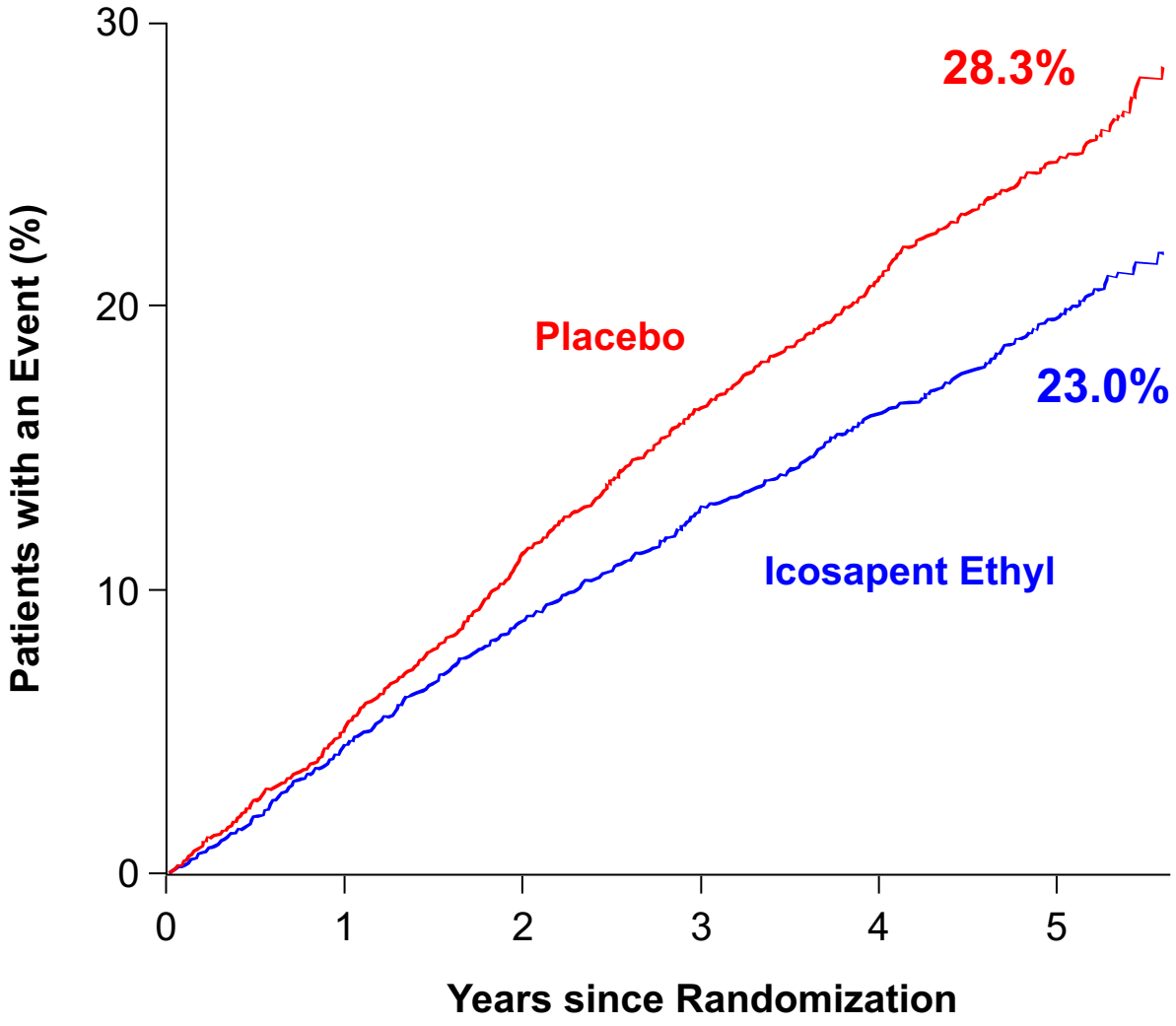
Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

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*

Bhatt DL, et al. *N Engl J Med* 2019;3880:11-22.

Primary End Point:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

RRR = 24.8%

ARR = 4.8%

NNT = 21 (95% CI, 15–33)

P=0.00000001

PICO #6

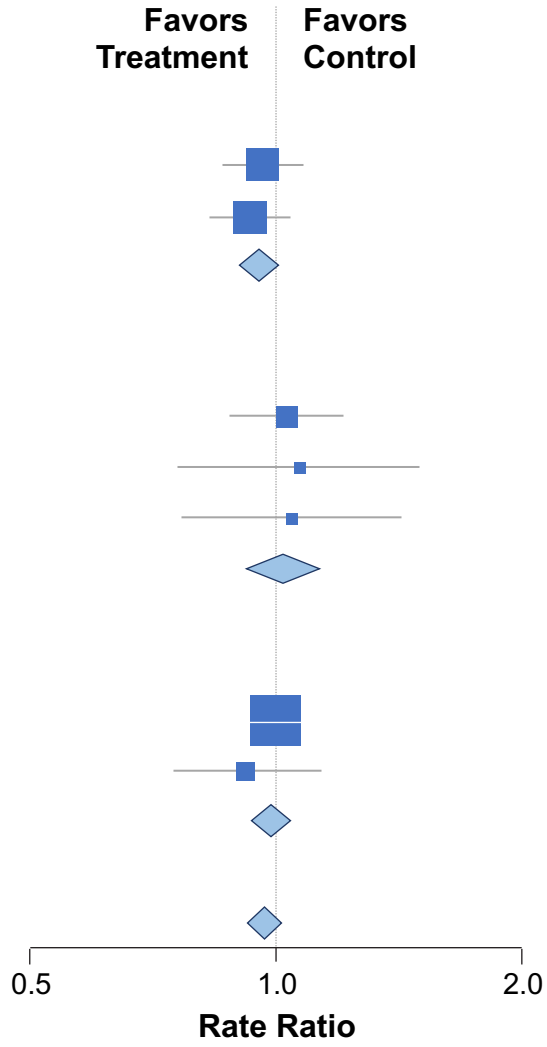
In primary and secondary prevention, what is the evidence for CV benefit of omega-3 from:
(i) dietary sources, or
(ii) OTC formulations/supplements?

2021 CCS Dyslipidemia Guidelines

1. **We do not recommend the use of over-the-counter omega-3 polyunsaturated fatty acids supplements (marketed as natural health products in Canada) to reduce CVD risk** (Strong Recommendation; High-Quality Evidence).

Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

Source	No. of Events (%)		Rate Ratios (CI)
	Treatment	Control	
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87–1.08)
Coronary heart disease	1301 (3.3)	1394 (3.6)	0.93 (0.83–1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90–1.01)
			P=.12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88–1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76–1.51)
Unclassified/other	142 (0.4)	135 (0.3)	1.05 (0.77–1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93–1.13)
			P=.60
Revascularization			
Coronary	3044 (9.3)	3040 (9.3)	1.00 (0.93–1.07)
Noncoronary	305 (2.7)	330 (2.9)	0.92 (0.75–1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94–1.04)
			P=.60
Any major vascular event	5930 (15.2)	6071 (15.6)	0.97 (0.93–1.01)
			P=.10



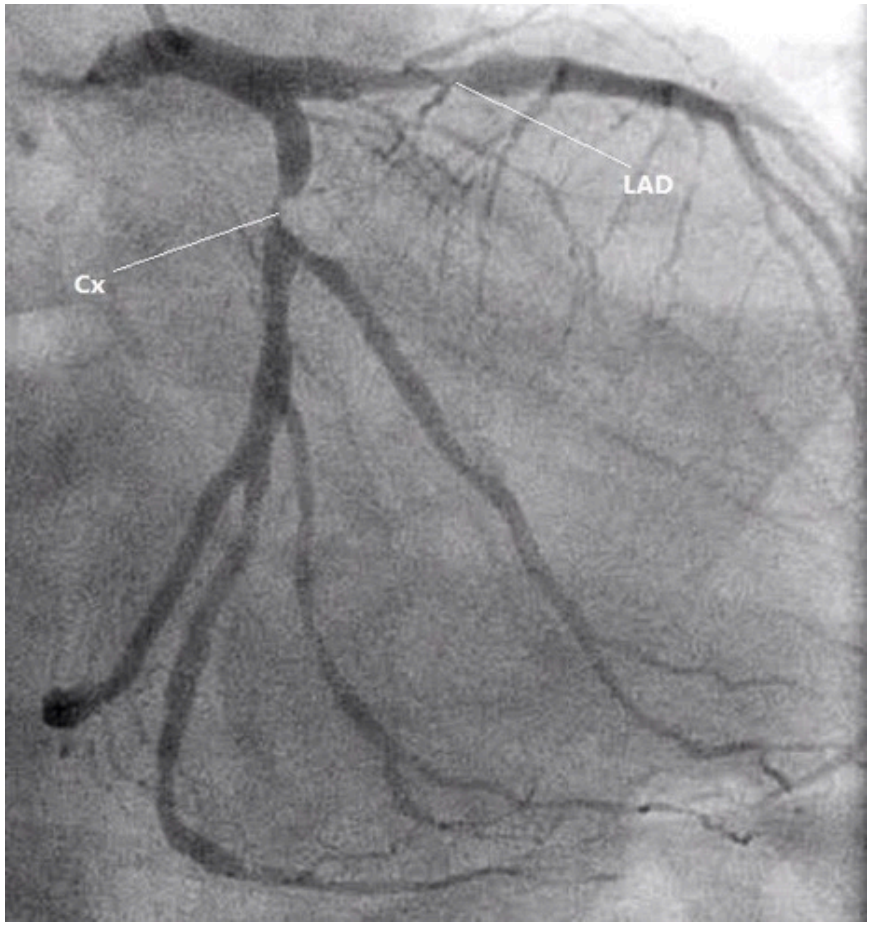
Aung T, Halsey J, Kromhout D, et al. *JAMA Cardiol* 2018;3:225-234.

Case
- Treatment intensification and Secondary Prevention -

Case: Mr. Young

- 54 yrs old, non-smoker, 6 months post-ACS, stented pLAD + pCIRC

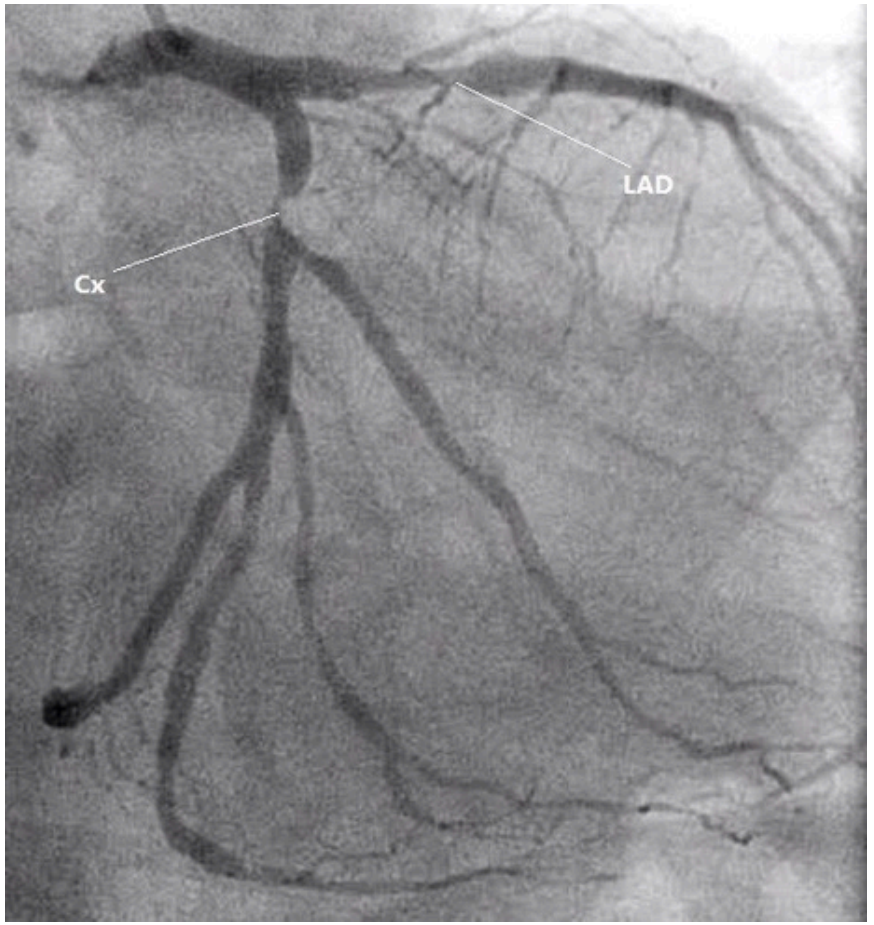
- BMI = 27 kg/m^2
- BP 130/80
- No diabetes
- TC = 3.8 mmol/L
- HDL-C = 1.2 mmol/L
- TG = 1.6 mmol/L
- LDL-C = 1.8 mmol/L (on atorvastatin 80 mg + ezetimibe daily)



Case: Mr. Young

- 54 yrs old, non-smoker, 1 month post-ACS, stented pLAD + pCIRC

- BMI = 27 kg/m^2
- BP 130/80
- No diabetes
- TC = 3.8 mmol/L
- HDL-C = 1.2 mmol/L
- TG = 1.6 mmol/L
- LDL-C = 1.8 mmol/L (on atorvastatin 80 mg + ezetimibe daily)
- apoB = 0.85 g/L
- Lp(a) = 100 mg/dL



Case 1 Mrs. Tremblay

Which of the following is **the most appropriate statement**:

1. This patient is young and therefore not at high-risk. No additional therapy is needed.
2. This patient is young and at high-risk but is near LDL-C target. No additional therapy is needed.
3. This patient is young and at high-risk. He would have been eligible for PCSK9i trial and likely shown high-benefit from therapy. Recommend PCSK9i.
4. This patient is young and at high-risk. He would have been eligible for IPE trial which showed a large benefit. Recommend IPE.
5. This patient is young and at high-risk. Recommend PCSK9i+IPE.

Case 1 Mrs. Tremblay

Which of the following is **the most appropriate statement**:

1. This patient is young and therefore not at high-risk. No additional therapy is needed.
2. This patient is young and at high-risk but is near LDL-C threshold. No additional therapy is needed.
3. This patient is young and at high-risk. He would have been eligible for PCSK9i trial and likely shown high-benefit from therapy. Recommend PCSK9i.
4. This patient is young and at high-risk. He would have been eligible for IPE trial which showed a large benefit. Recommend IPE.
5. This patient is young and at high-risk. Recommend PCSK9i+IPE.

Questions?