Lipid management using the 2021 CCS Dyslipidemia Guidelines

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Disclosures

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- **Industry relations**: Novartis, Sanofi, Amgen, Ionis, Servier, Silence

Objectives

At the conclusion of this session, participants will be able to:

- Recognize the major changes in the new guidelines and how they impact on the care of patients with dyslipidemia
- Apply the recent 2021 dyslipidemia guidelines to the management of patients with common lipid disorders in primary care
- Integrate the use of apolipoproteinB, non-HDL-C amd lipoprotein(a) into their practice

1: Who to Screen for Risk of ASCVD?

A. Men ≥40 yrs old; Women ≥40 yrs old or postmenopausal
   - consider screening at younger age in Indigenous and South Asian ethnic groups

B. Patient at any age with:

a. Clinical ASCVD
b. Abdominal aortic aneurysm (AAA)
c. Diabetes mellitus
d. Arterial hypertension
e. Current smoking
f. Chronic Kidney Disease
g. Family history of premature CVD in first degree relative (male <55 yrs old; female <65 yrs old)
h. Family history of dyslipidemia (**including elevated Lp(a), especially ≥50 mg/dL or ≥100 nmol/L**)
i. Stigmata of dyslipidemia: tendinous xanthomas (also corneal arcus, xanthelasmas if <45 yrs old)
j. Evidence of preclinical ASCVD (e.g. CACS or carotid ultrasound abnormalities)
k. Chronic obstructive pulmonary disease (COPD)
l. Obesity (BMI ≥30 kg/m^2)
m. Inflammatory diseases (e.g., RA, SLE, PsA, AS, IBD)
n. HIV/AIDS
o. Erectile dysfunction
p. Pregnancy-related complications (hypertensive disease of pregnancy, gestational diabetes, pre-term birth, stillbirth, low birthweight infant, placental abruption)

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2. How to Screen for ASCVD Risk?

B. How to Screen for Dyslipidemia

- For all patients:
  - history and physical examination
  - standard lipid profile[†]*:* TC, LDL-C, HDL-C, non-HDL-C[*], TG
    - [†]Non-fasting lipid testing is recommended in most adults for screening; however, for individuals with a history of TGs >4.5 mmol/L, fasting lipid levels are recommended.
    - *it is now generally preferable to follow non-HDL-C or ApoB levels over LDL-C when interpreting lipid results, particularly when TG is ≥1.5 mmol/L*
  - eGFR
  - **lipoprotein(a) -- once in patient's lifetime, with initial screening**

- Optional:
  - Apolipoprotein B (ApoB)
  - Urine ACR (if eGFR <60 mL/min/1.73 m^2, hypertension, or diabetes)

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**

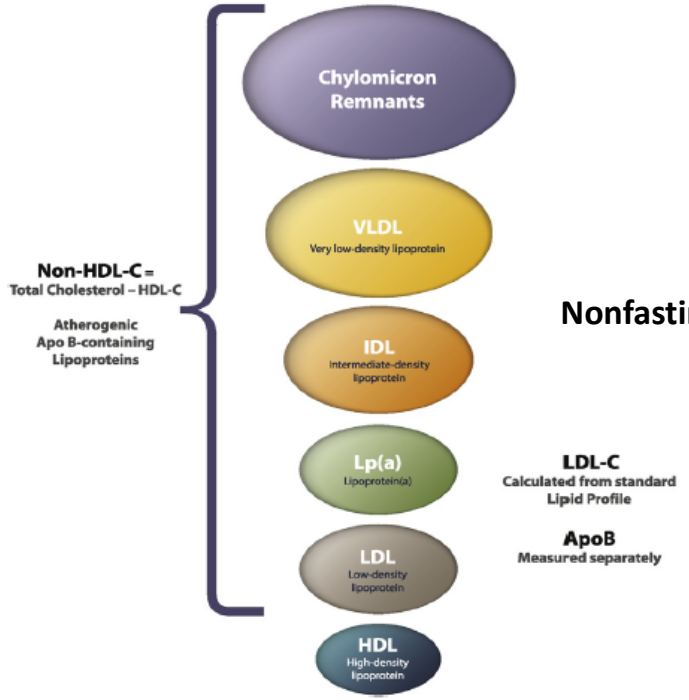

Figure 3. Non-HDL-cholesterol measures cholesterol in all atherogenic lipoproteins. ApoB, apolipoprotein B; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LP(a), lipoprotein(a); VLDL, very low-density lipoprotein.

Nonfasting lipid testing

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

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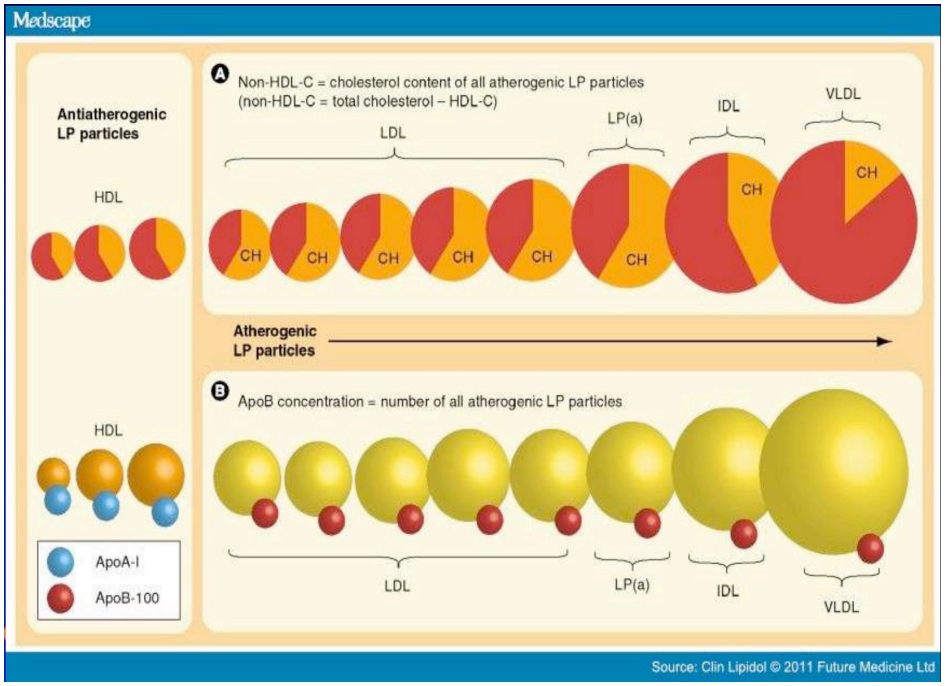
Apolipoprotein-B

- 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



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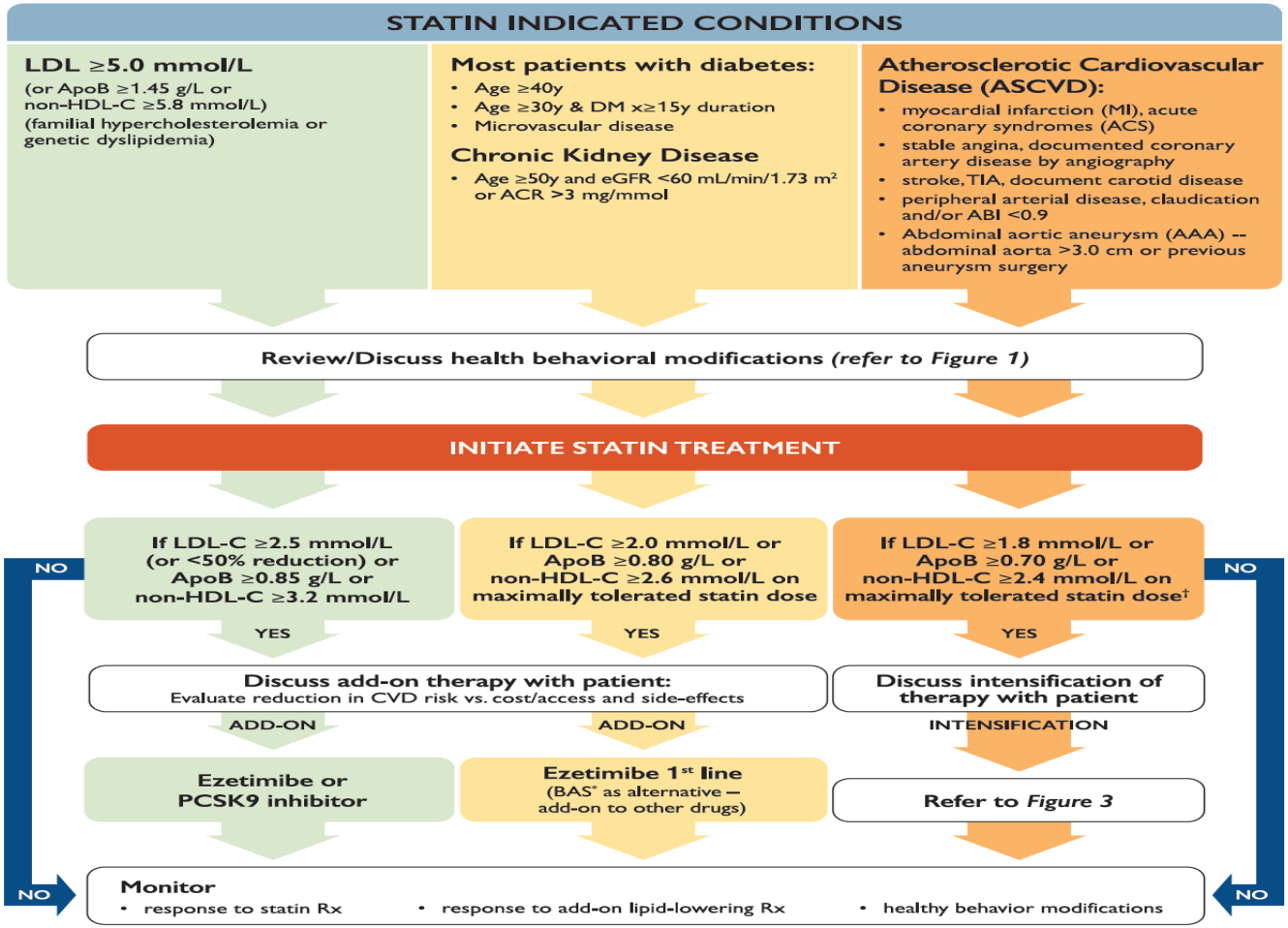
Treatment Approach for Patients with a Statin-Indicated Condition



Pearson GJ, Thanassoulis G, et al. Can J Card 2021. Online March 26, 2021. DOI:https://doi.org/10.1016/j.cjca.2021.03.016

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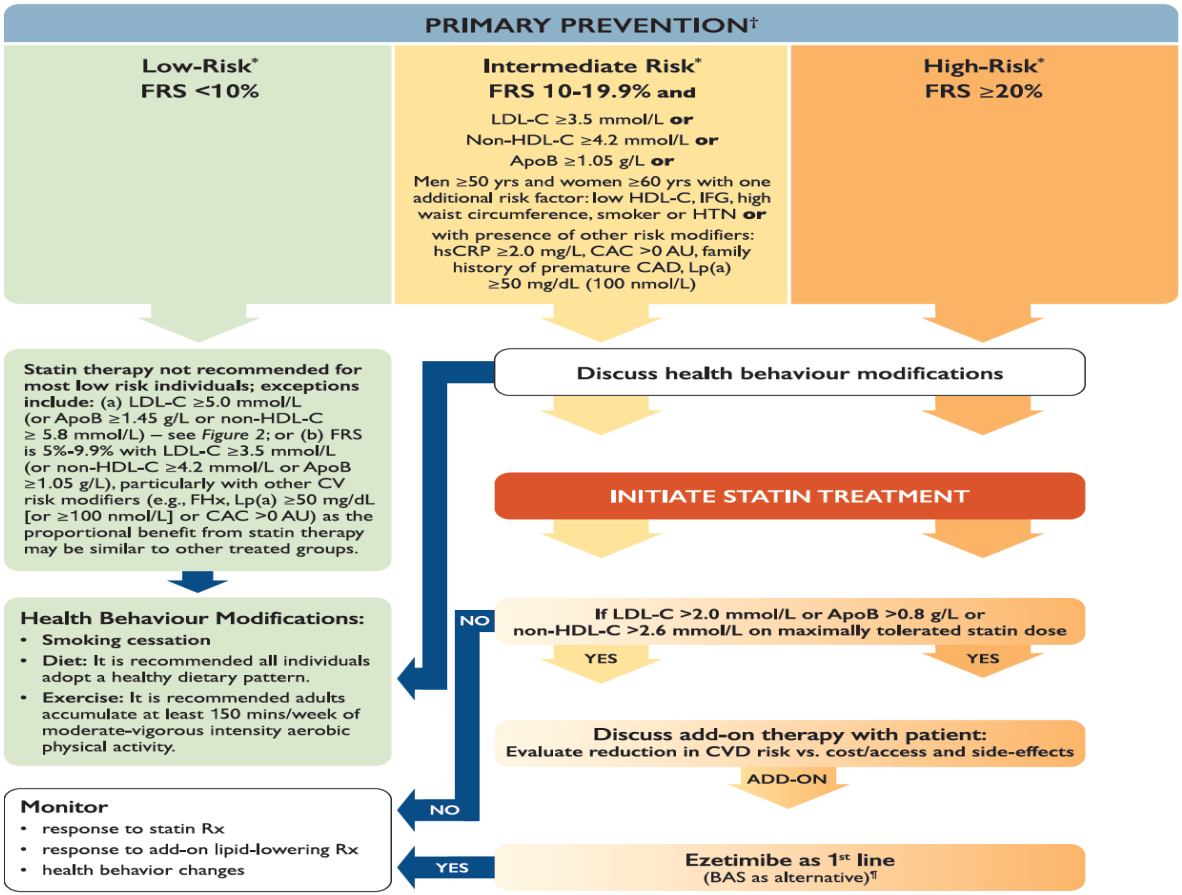
Treatment Approach for Primary Prevention Patients (without a statin-indicated condition)



Pearson GJ, Thanassoulis G, et al. Can J Card 2021. Online March 26, 2021. DOI:https://doi.org/10.1016/j.cjca.2021.03.016

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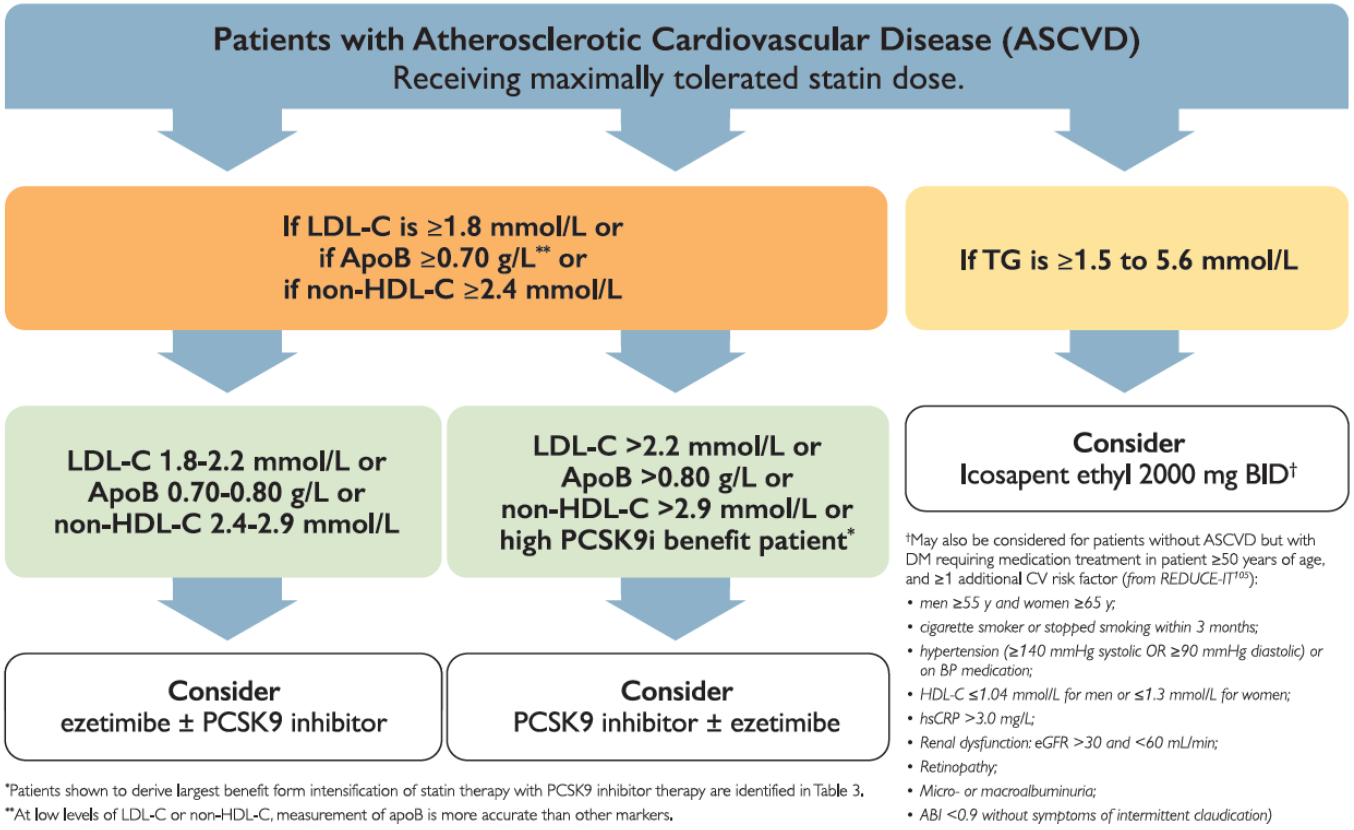
Treatment Intensification Approach for Patients with ASCVD



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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).

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Workshop
Primary prevention and risk stratification

Case 1: Mr. Hy. Risc

- 44 years old, non-smoker

- BMI = 26 kg/m^2
- BP 130/80 mm Hg
- No diabetes or CKD or CVD
- Total cholesterol = 5.9 mmol/L
- HDL cholesterol = 1.0 mmol/L
- TG = 1.7
- LDL-C = 4.1

1. What is the first step in managing this patient?

a) Establish that he has no statin-indicated condition and calculate CV risk
b) Order EST to evaluate for CAD
c) Start statins
d) Recommend nutritionist consultation
e) Refer to cardiologist

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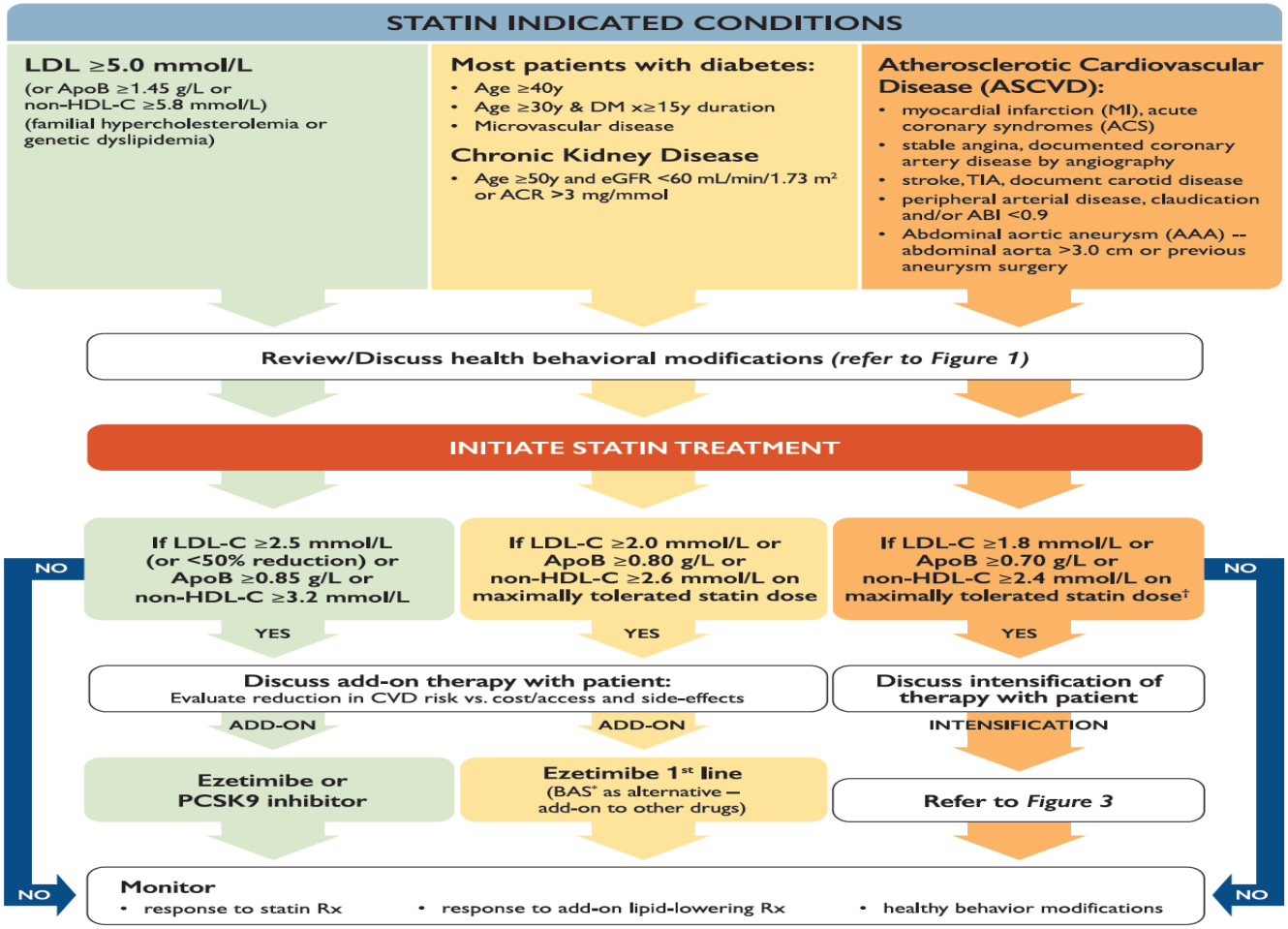
Treatment Approach for Patients with a Statin-Indicated Condition



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Mr. Hy Risc

Estimation of 10-year risk of total cardiovascular disease in men (Framingham Heart Study)

POINTS	Age	HDL-C	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic	
–2		>1.6		<120				
–1		1.3-1.6						
0	30-34	1.2-1.3	<4.1	120-129	<120	NO	NO	
1		0.9-1.2	4.1-5.2	130-139				
2	35-39	<0.9	5.2-6.2	140-159	120-129			
3			6.2-7.2	160+	130-139		YES	
4			>7.2		140-159	YES		
5	40-44				160+			
6								
7	45-49							
8	50-54							
9								
10	55-59							
11	60-64							
12								
13	65-69							
14	70-74							
15	75+							TOTAL POINTS
Points Allotted								

Adapted from reference 33. HDL-C High-density lipoprotein cholesterol; SBP Systolic blood pressure

Cardiovascular disease risk for men

Points	Risk, %	Points	Risk, %	Points	Risk, %
–3 or less	<1	5	3.9	13	15.6
–2	1.1	6	4.7	14	18.4
–1	1.4	7	5.6	15	21.6
0	1.6	8	6.7	16	25.3
1	1.9	9	7.9	17	29.4
2	2.3	10	9.4	18+	>30
3	2.8	11	11.2		
4	3.3	12	13.3		

44 years old

BMI = 28 kg/m2

BP 130/80 mm Hg

Non-smoker, no diabetes

Total cholesterol = 5.9 mmol/L
HDL cholesterol = 1.0 mmol/L
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What's his risk?

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9 pts = 8% risk of CV event in 10 years (low risk)

What is his vascular age?

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What is his vascular age? 51-52

2. What is the next step in managing this patient?

a) Discuss the patient's low Framingham risk and congratulate him for maintaining his CV risk low
b) Emphasize lifestyle measures for optimal CV health: smoking cessation, exercise, healthy diet and weight control.
c) Start ECASA 81 mg die
d) Start ezetimibe 10 mg die
e) Start amlodipine 2.5 mg po die

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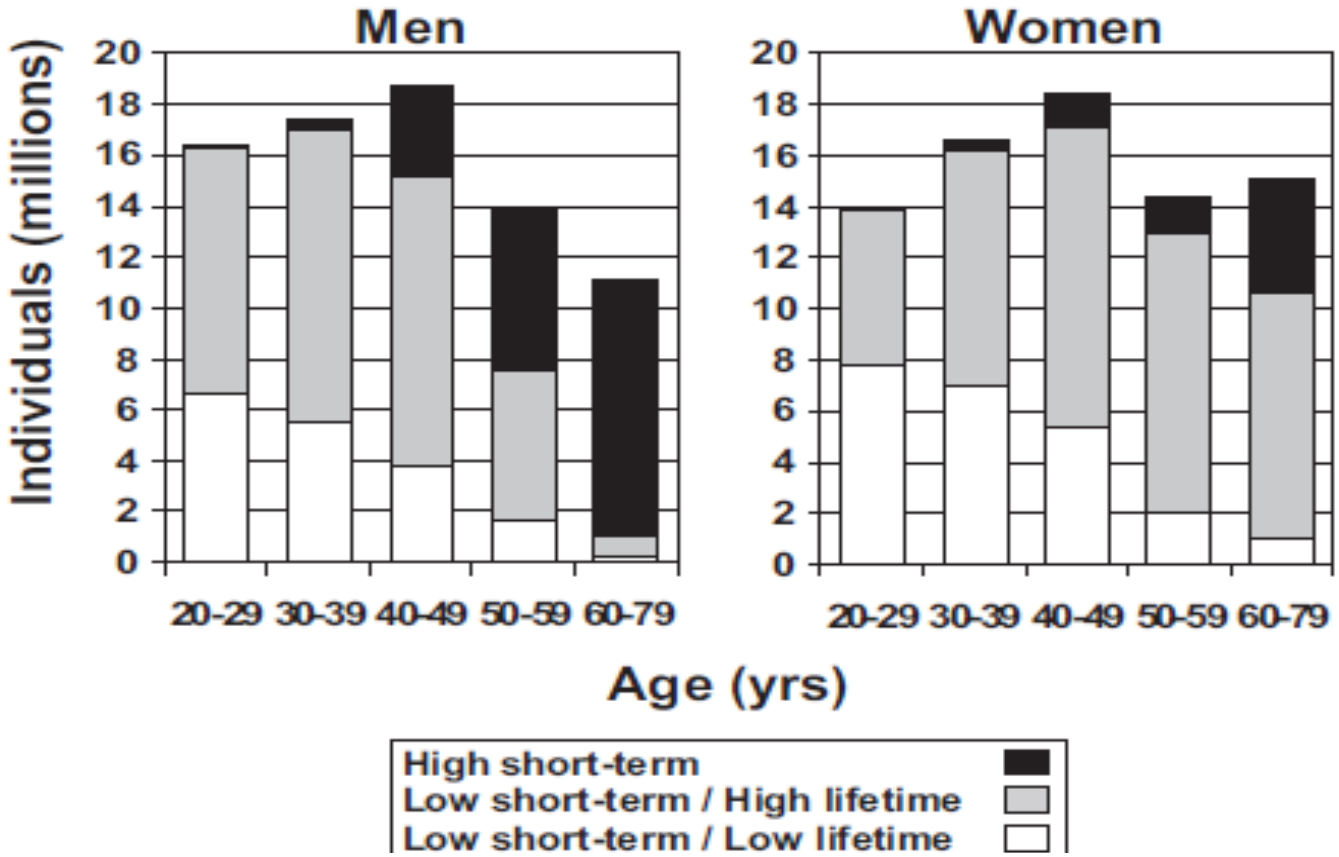
Low Short-term but High Lifetime Risk



Marma AK et al. Circulation: Cardiovascular Quality and Outcomes. 2010;3:8–14

What to do?

- A large proportion of younger patients have low short-term BUT high lifetime risk

- What to do?
  - Counselling
  - Focus on lifestyle change
    - Target optimal risk factors
  - Identify patients with risk modifiers
  - Consider EARLY preventative treatment?

3. What additional testing may be helpful to help manage this patient CV risk?

a) Coronary angiography
b) Lipoprotein(a) level
c) Exercise stress test
d) NT-pro-BNP
e) None of the above

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Pearson GL et al Canadian Journal of Cardiology 37 (2021) 1129–1150

4. Sara, the resident rotating in your clinic, is interested to understand more about your decision to measure Lp(a) in Mr. Risc. She wonders how Lp(a) would help in his management. What do you teach her?

a) Individuals with high Lp(a) > 50 mg/dL have an additional source of atherogenic lipoproteins and their risk may be underestimated by Framingham score
b) A low Lp(a) is very reassuring and indicates that lipid-lowering therapy is not needed
c) A high Lp(a) indicates the need for specialized therapies that lower Lp(a) as opposed to standard lipid-lowering therapies
d) A high Lp(a) renders the standard lipid profile uninterpretable
e) None of the above

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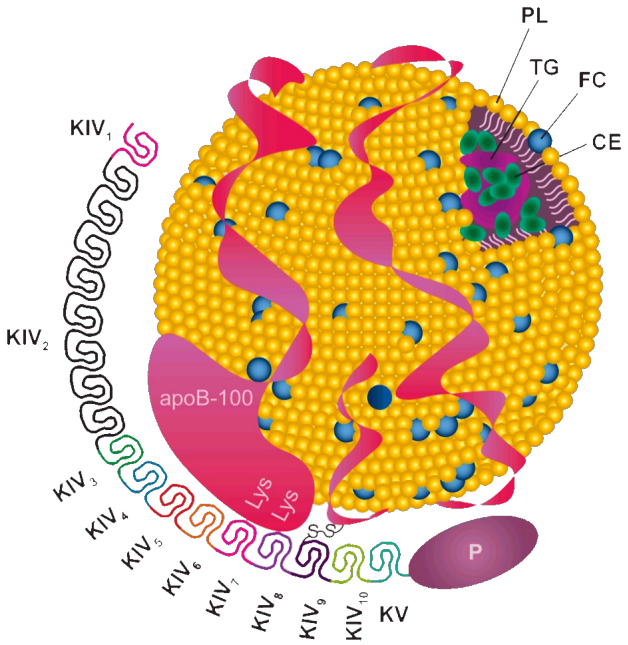
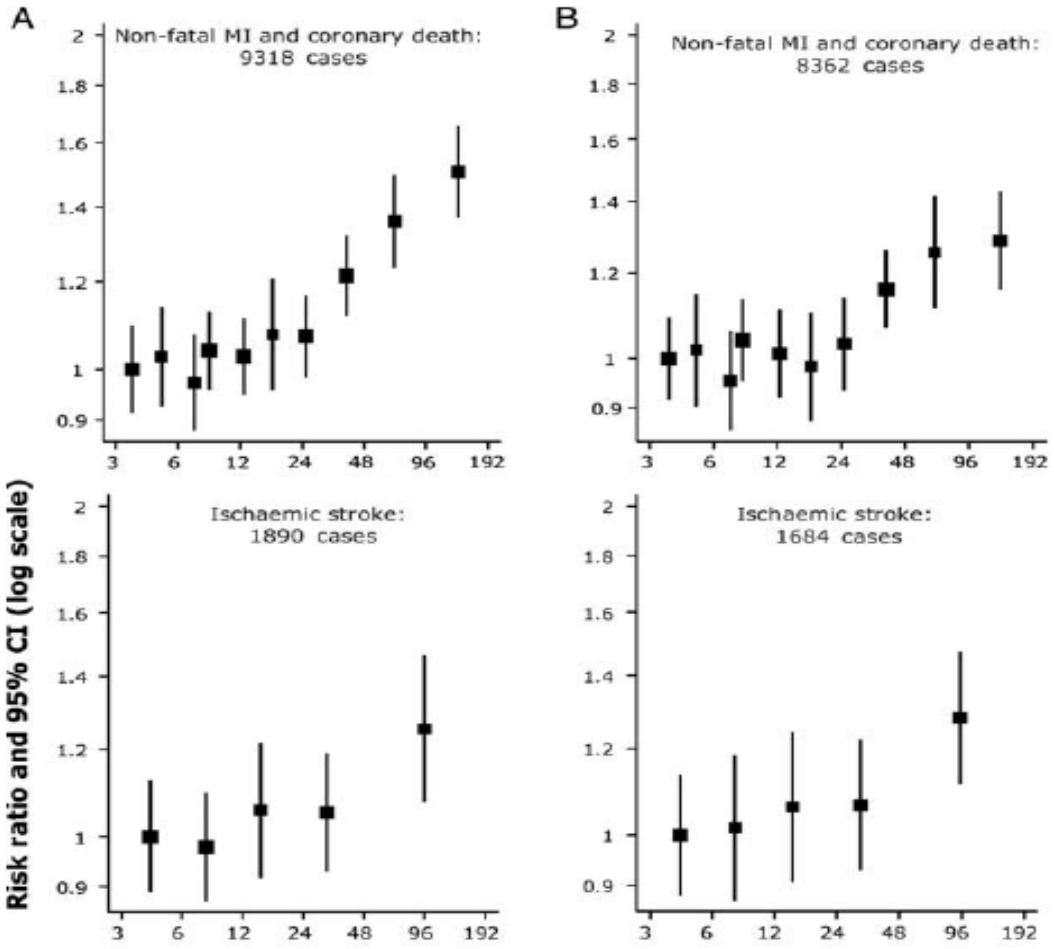
What is Lipoprotein(a)?



- LDL-like particle with a Apolipoprotein(a) covalently bound to Apolipoprotein-B
- Highly atherogenic, pro-calcific
- Lp(a) levels are explained by genetics
  - Not lowered by lifestyle, diet, exercise and statins
- Most common genetic dyslipidemia
  - 6 million Canadians have high Lp(a)

Lp(a) is atherogenic



Erqou et al *JAMA* 2009

Management

- Individuals with high Lp(a), consider:
  - Lifestyle change
  - Treat LDL-C (and all risk factors) much more aggressively
  - Consider ECASA (ONLY if CV risk is high and bleeding risk is low)
  - Consider PCSK9i (secondary prevention)

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BP 135/85 mm Hg

Non-smoker, no diabetes

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What's his risk?

9 pts = 8% risk of CV event in 10 years (low risk)

What is his vascular age? 51-52

Lp(a) 90 mg/dL

5. How would you manage this patient?

a) Since Mr Risc is a young, low-risk patient, therefore lifestyle measures only are appropriate

b) For a low-risk patient like Mr Risc, with moderately high LDL-C and high Lp(a), lifestyle measures in addition to statin therapy should be considered

c) Mr Risk is an intermediate risk patient with familial hypercholesterolemia, therefore consider lifestyle measures and add statin+ezetimibe

d) Mr Risk is a high risk patient solely based on his high Lp(a), I would consider starting a PCSK9 inhibitor

5. How would you manage this patient?

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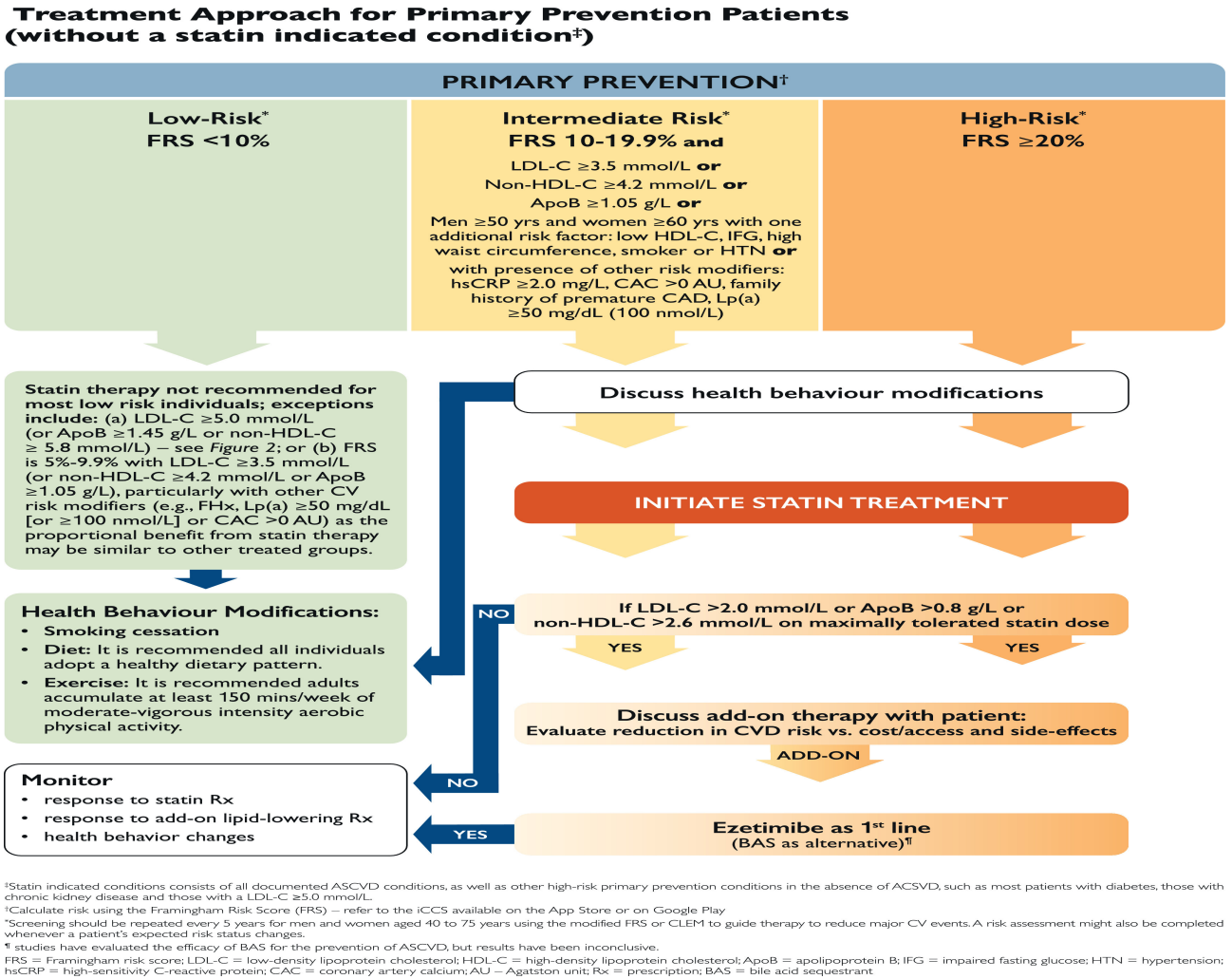
Overview of 2021 Guidelines



‡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.

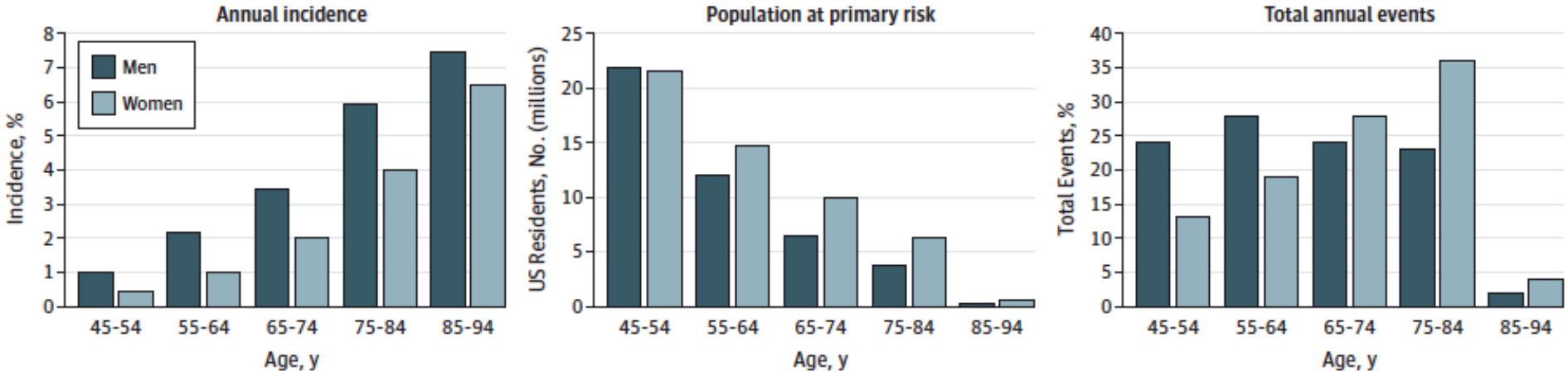
¶ studies have evaluated the efficacy of BAS for the prevention of ASCVD, but results have been inconclusive.

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

Pearson GL et al Canadian Journal of Cardiology 37 (2021) 1129–1150

Is Earlier treatment better?

Figure. Event Rates, Population at Risk, and Event Numbers by Sex and Age Groups

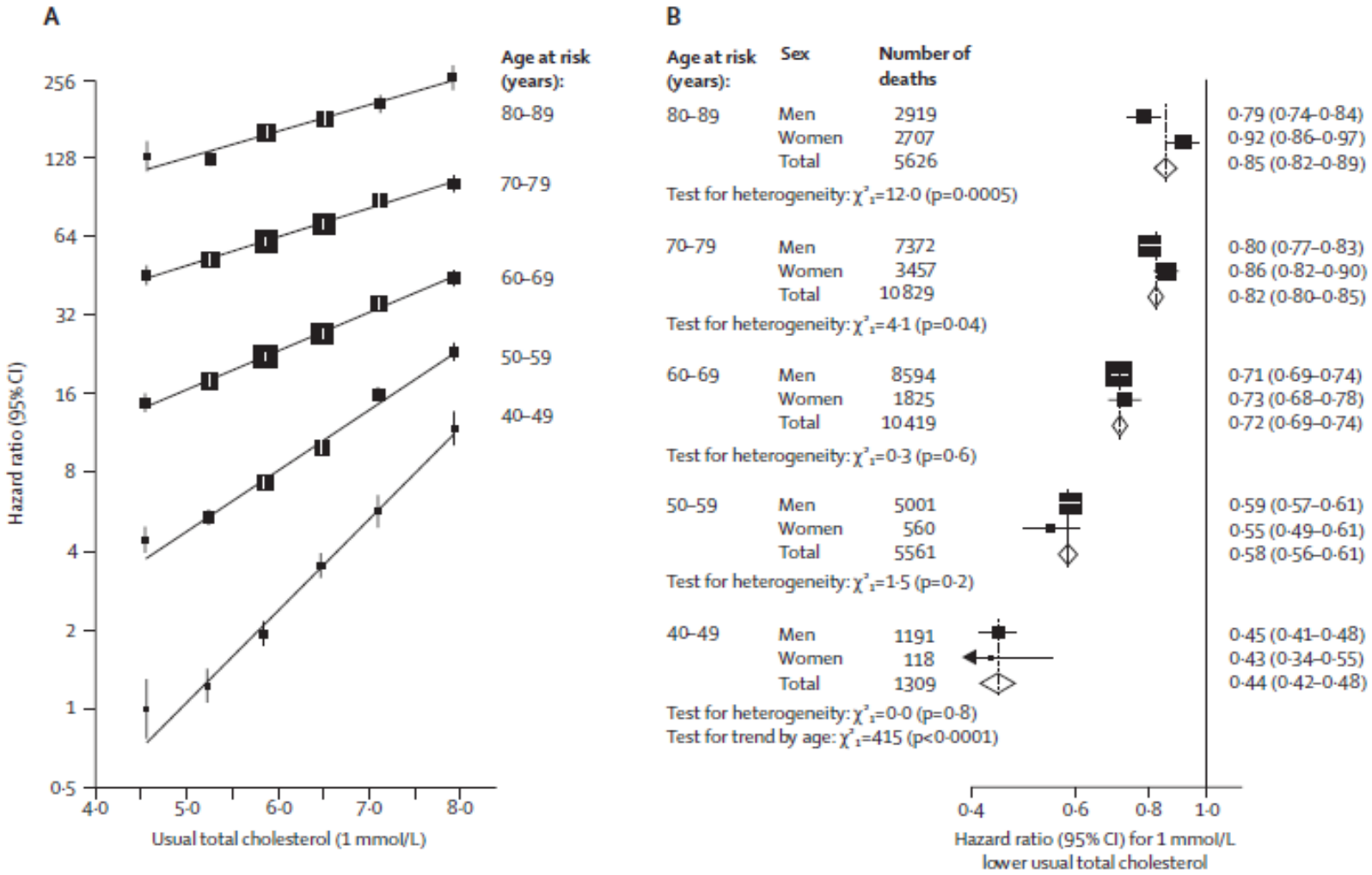


A, Average primary annual incidence rates of coronary heart disease, heart failure, stroke, or intermittent claudication. B, Numbers of US residents without clinical atherosclerotic cardiovascular disease represented in the 2005-2010 National Health and Nutrition Examination Survey. C, Percentage of the expected total of 930 621 annual primary events in men and 702 105 in women by age group.

50% of total events in men and almost 33% in women occur before age 65 years…

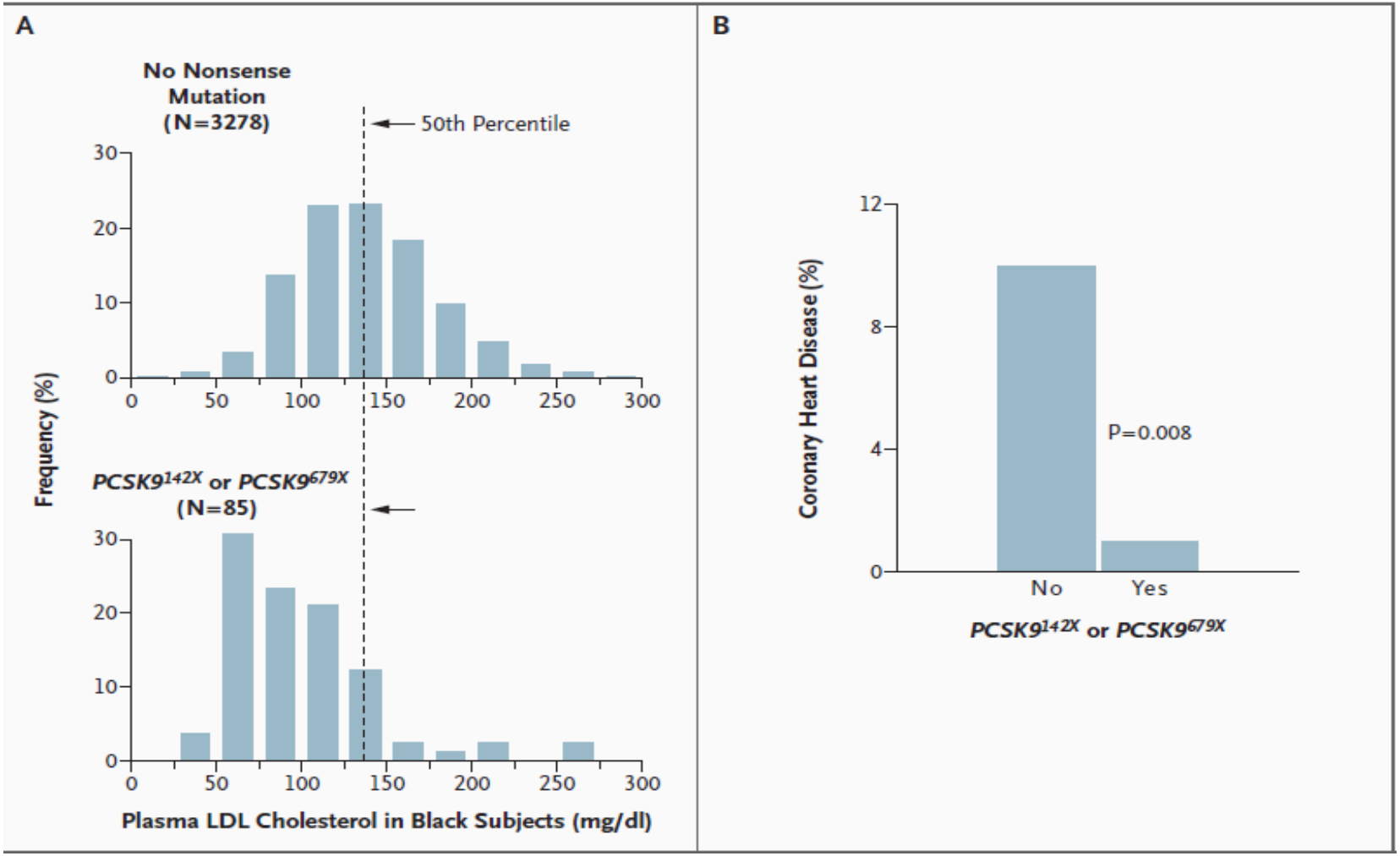
Sniderman et al JAMA-Cardiology 2017

LDL is worse when young



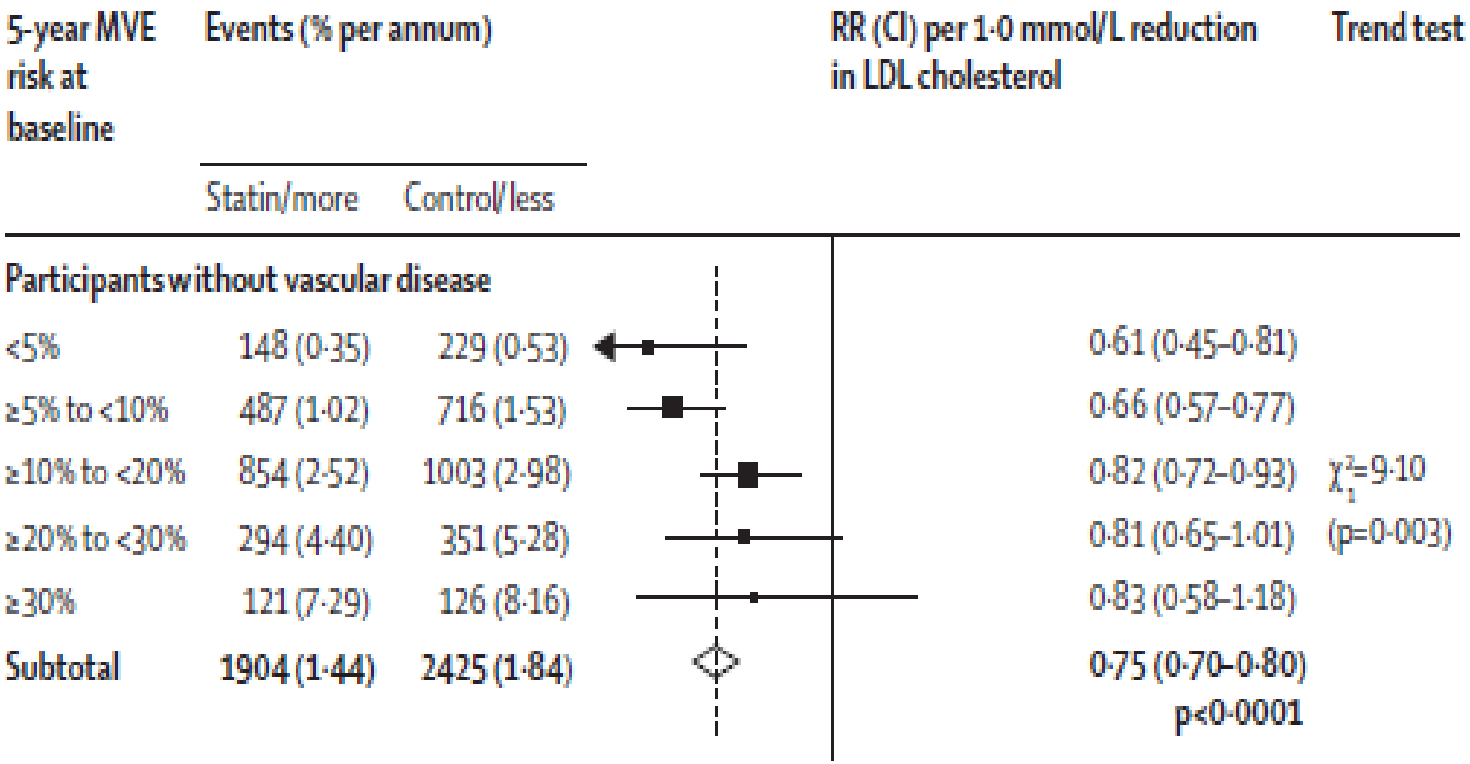
Prospective Studies Collaboration Lancet 2007

Life-long lipids and Risk of CHD



Cohen JC *et al*, NEJM 2008

Cholesterol Treatment Trialists



CTT collaboration *Lancet* 2010

How much benefit?

Research

JAMA Cardiology | Original Investigation

A Long-term Benefit Approach vs Standard Risk-Based Approaches for Statin Eligibility in Primary Prevention

George Thanassoulis, MD, MSc, FRCPC; Allan D. Sniderman, MD; Michael J. Pencina, PhD

CONCLUSIONS AND RELEVANCE A long-term benefit approach to statin eligibility identifies nearly 1 in 6 individuals as having a high degree of expected long-term benefit of statins, with a number needed to treat of less than 7. This approach identifies younger individuals with higher LDL-C levels who would not be currently recommended for treatment and may provide a more optimal approach for determining statin eligibility in primary prevention.

Thanassoulis G et al. JAMA Cardiol. 2018 Nov 1;3(11):1090-1095

Workshop
Secondary prevention

Case 2: Mr. Young

- 59M yrs old, non-smoker, 6 months post 2nd ACS, stented pLAD + pCIRC

- BMI = 27 kg/m^2
- BP 130/80
- No diabetes
- TC = 3.9 mmol/L
- HDL-C = 1.2 mmol/L
- TG = 2.5 mmol/L
- LDL-C = 1.6 mmol/L (on atorvastatin 80 mg + ezetimibe daily)

Case: Mr. Young

- 59 yrs old, non-smoker, 6 months post 2nd ACS, stented pLAD + mid RCA

- BMI = 27 kg/m^2
- BP 130/80
- No diabetes
- TC = 3.9 mmol/L
- HDL-C = 1.2 mmol/L
- TG = 2.5 mmol/L
- LDL-C = 1.6 mmol/L (on atorvastatin 80 mg + ezetimibe daily)

- apoB = 0.85 g/L
- Non-HDL-C = 2.7
- Lp(a) 100 mg/dL

6. Based on Mr. Young's lipid/lipoprotein profile, what is your interpretation and recommendation for management?

a) triglycerides are ≥1.5 mmol in plasma, this indicates that there are fewer cholesterol depleted particles and therefore no treatment is needed

b) triglycerides are ≥1.5 mmol/L in plasma, apoB (or non-HDL-C) should be used to accurately estimate CV risk prior to recommending therapy

c) triglycerides are ≥1.5 mmol/L in plasma, therefore a fibrate is recommended to reduce CV risk

d) triglycerides are ≥1.5 mmol/L in plasma and therefore the lipid panel is uninterpretable. No decision regarding treatment can be made.

e) None of the above

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e) None of the above

6. Since his TG ≥ 1.5 mmol/L, you add an apoB to his laboratory requisition. Your colleague notices your requisition and asks how the apoB would help in the management of this patient. How do you respond?

a) ApoB provides an assessment of the total concentration of all atherogenic particles in plasma since each particle contains 1 apoB molecule

b) apoB is a better marker of cardiovascular risk than LDL-C

c) benefit of therapy will also be best predicted by change in apoB, so it can be useful to monitor if treatment is initiated

d) All of the above

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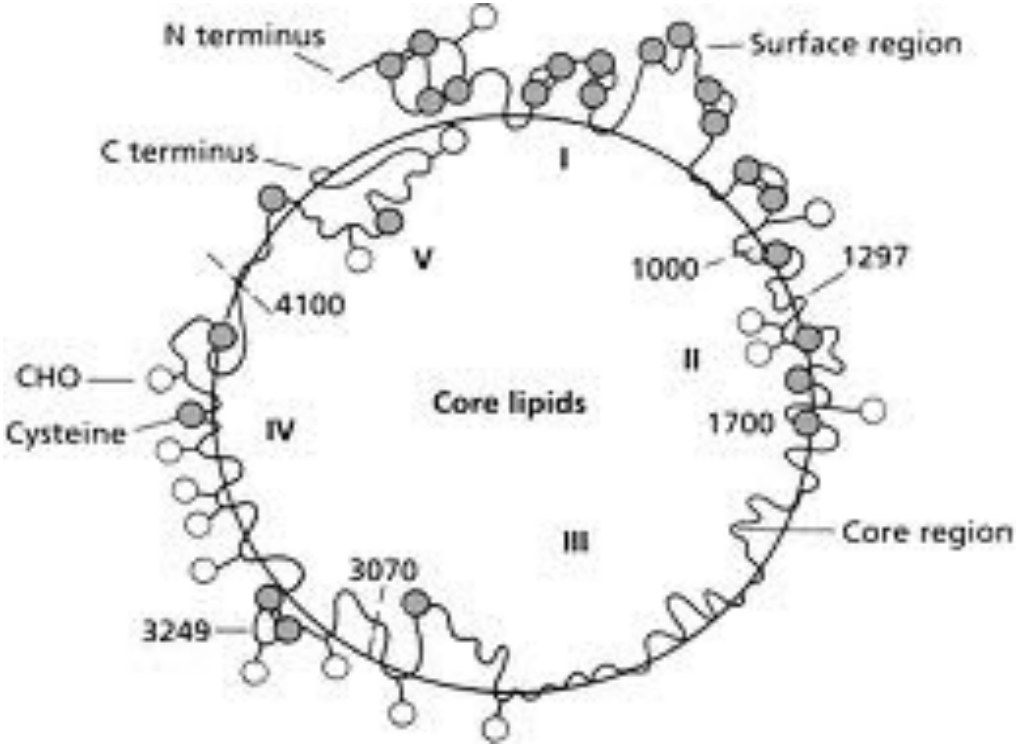
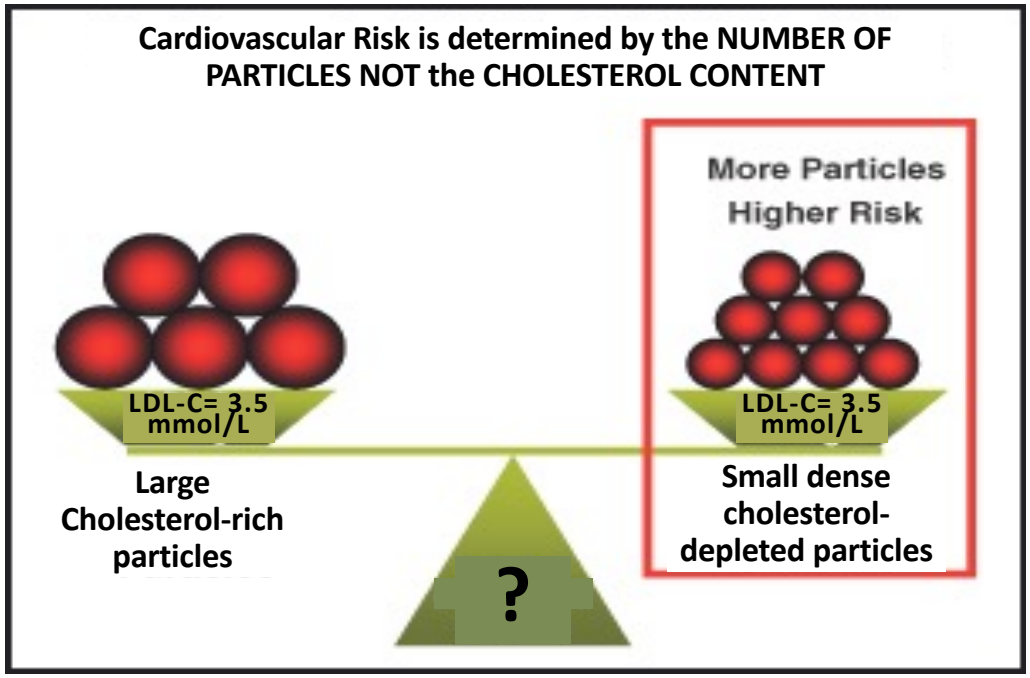
Apolipoprotein B

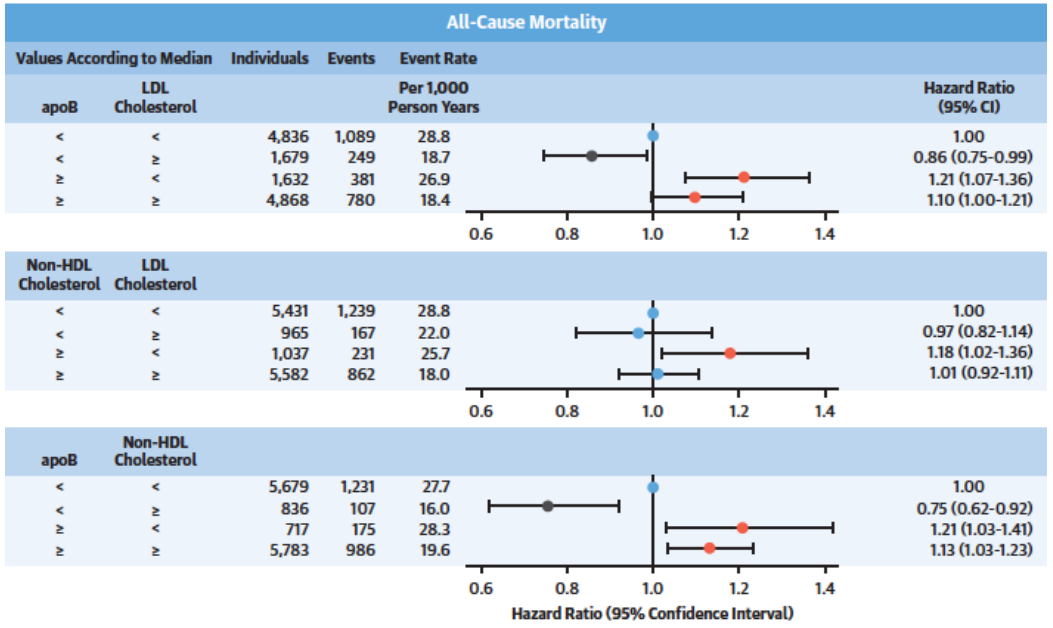


High apoB = danger



ApoB and recurrent events

- Best lipoprotein marker for determining the risk of mortality and recurrent events
- Can determine adequacy of treatment
- More accurate measurement when LDL-C is low
- ApoB > non-HDL-C > LDL-C



Johanssen et al. JACC. 2021 Mar 23;77(11):1439-1450

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).

Pearson GL et al Canadian Journal of Cardiology 37 (2021) 1129–1150

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- Lp(a) 100 mg/dL

7.How would you manage this patient?

a) Cardiac rehabilitation for improvement in lifestyle and exercise
b) Switch atorvastatin 80 mg to pravastatin 40 mg
c) Add niacin
d) Add fibrate
e) Add SGLT2 inhibitor

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Lifestyle, diet and exercise

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

Mediteranean diet	↓ 28-30 % CVE (ARR 0,6-1 % [NNT = 100-167)	
Portfolio diet	↓ 11 % CVE	Ideal efficacy ↓ LDL-C by 21-29 % (comparable to lovastatine 20 mg) Real-world efficacy : ↓ LDL-C 8-14 %
DASH diet (*Dietary Approaches to Stop Hypertension*)[97,98]	↓ 20 % CVE	↓ LDL-C by 3 %

Cardiac Rehabilitiation is important!!!

Weight loss and reduction in abdominal obesity 5-10 % reduction in BMI	↓ CVE by 6 % for a ~5 unit change in BMI ↓ CVE by 9% for a 12,6 cm reduction in WC	↓ LDL-C by 11 % ↑ HDL-C by 3-12 % ↓ TG by 32 %
Physical exercise 30-60 min/d moderate to high intensity	↓ CVE 20-30 %	↑ HDL-C by 5-10 %
Smoking cessation	↓ CVE by 52 %	↑ HDL-C by 7-12 %
Combined lifestyle changes	↓ **CVE (and mortality) by 75 %**	

8. What additional changes would you consider to his lipid-lowering therapy?

a) Switch atorvastatin 80 mg to rosuvastatin 40 mg
b) Add PCSK9i and consider IPE
c) Add IPE only
d) Add fish oil OTC supplements
e) None of the above

8. What additional changes would you consider to his lipid-lowering therapy?

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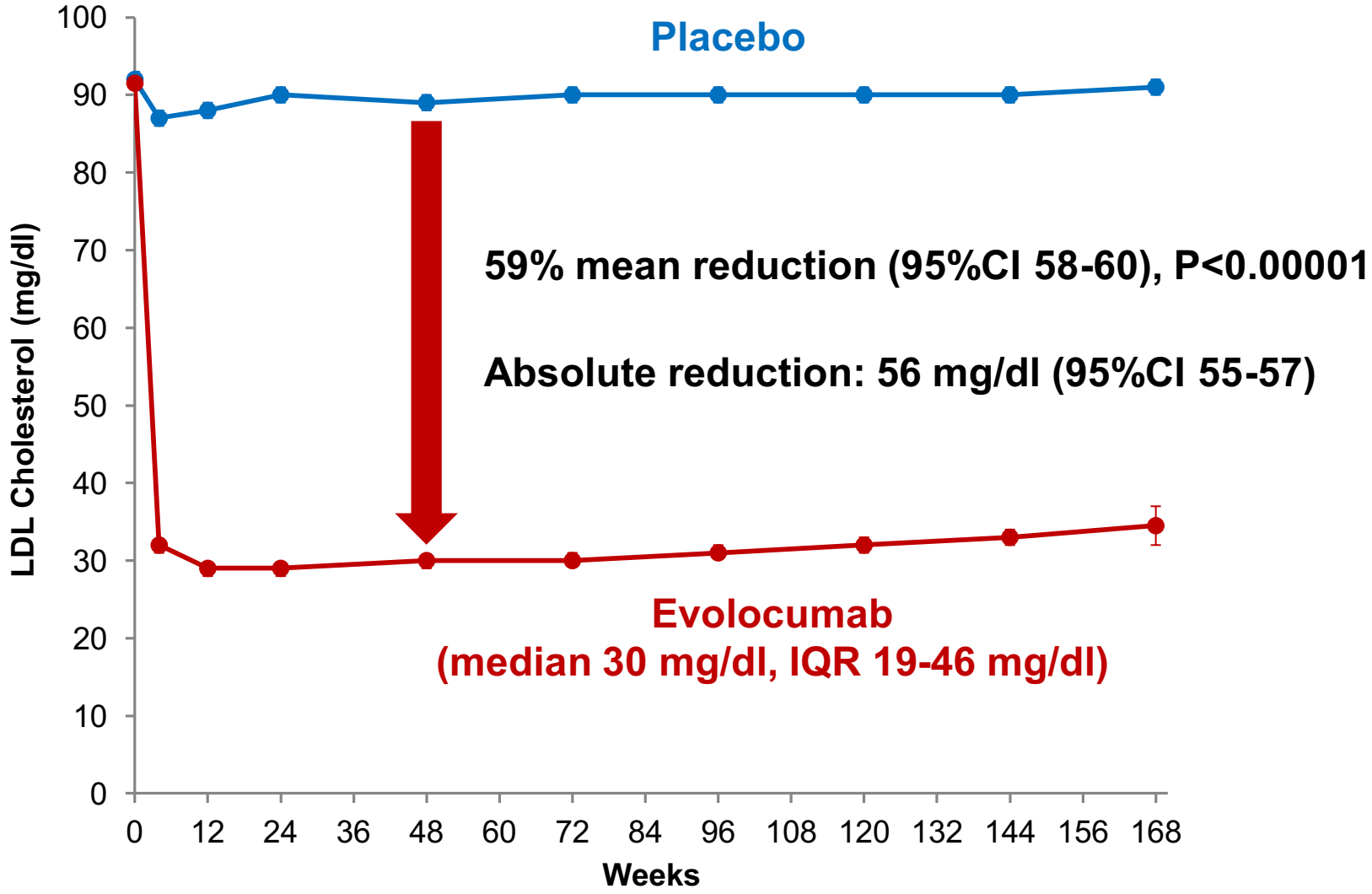
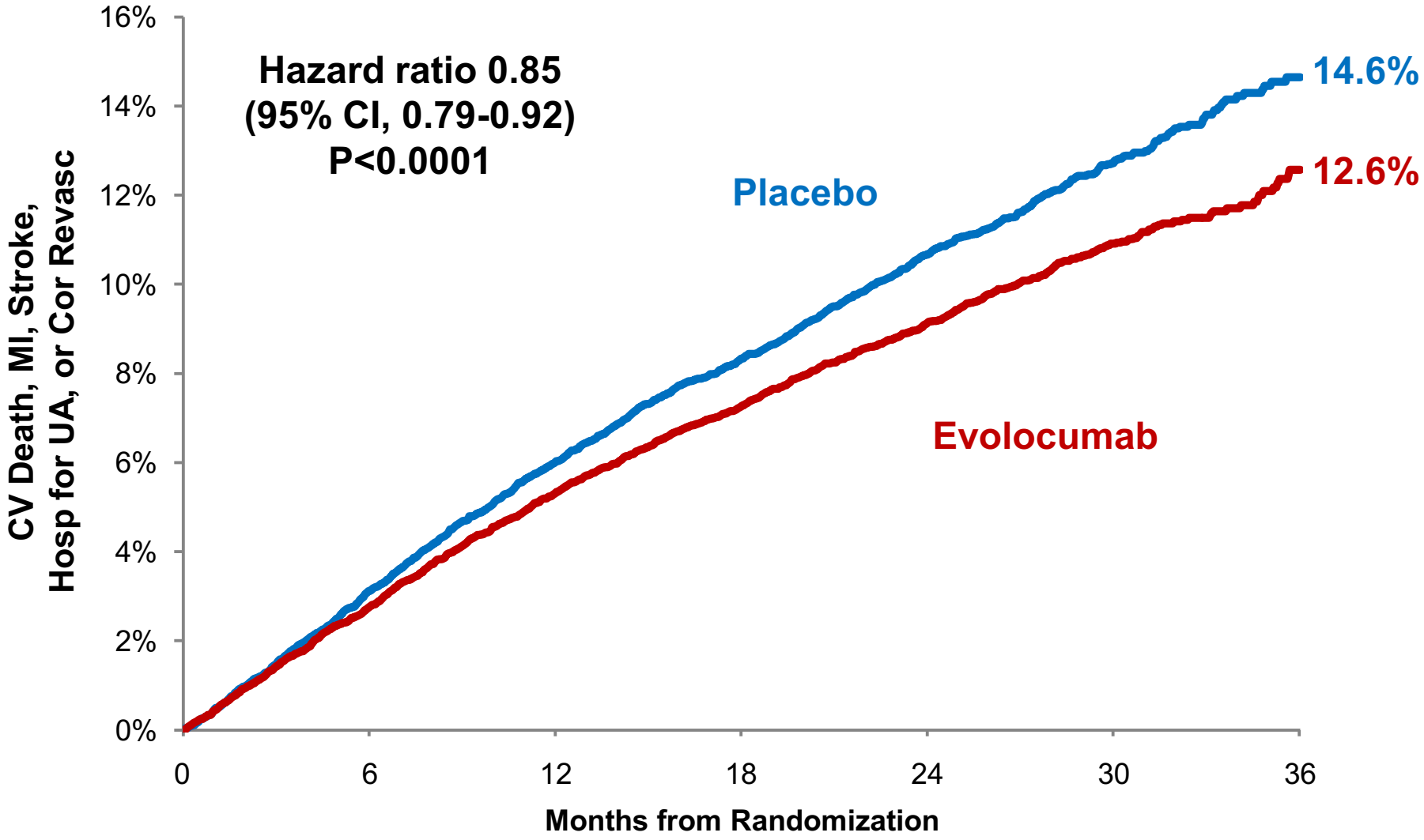
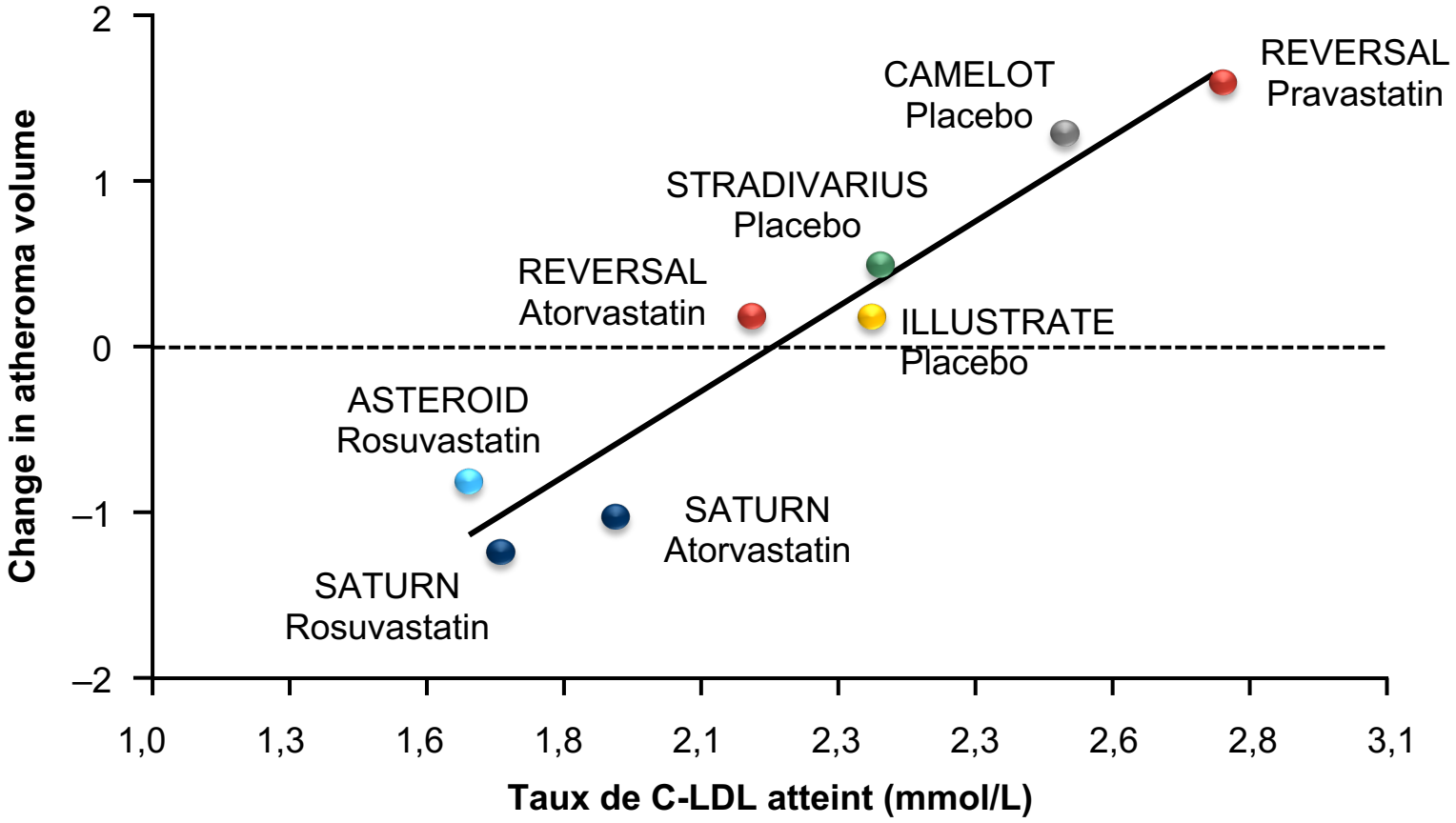
LDL Cholesterol



Primary Endpoint



Very low LDL-C: Is there a benefit?

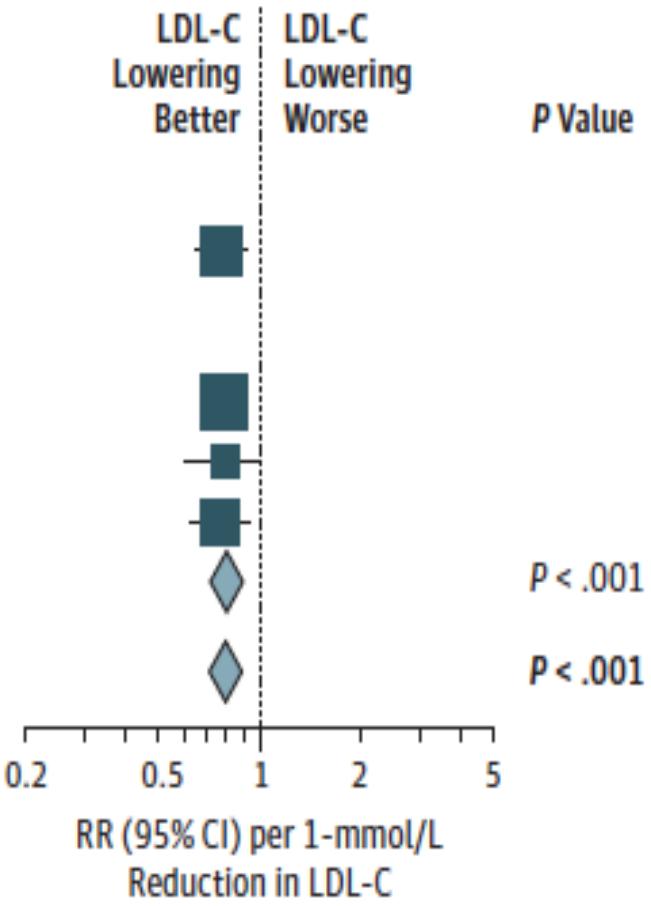


Puri et al. European Heart Journal (2013) 34, 1818–1825

Very low LDL-C: Is there a benefit?

A Meta-analysis of effect of 1-mmol/L LDL-C lowering on the risk of major vascular events

Trial	Events, % per annum: Experimental Arm	Events, % per annum: Control Arm	RR (95% CI)	P Value
Statins				
CTTC <2 mmol/L subgroup	910 (4.1)	1012 (4.6)	0.78 (0.65-0.94)	
Nonstatin LDL-C lowering				
IMPROVE-IT	2455 (4.5)	2649 (4.9)	0.79 (0.67-0.93)	
FOURIER <1.8 mmol/L subgroup	81 (3.7)	103 (4.9)	0.80 (0.61-1.04)	
REVEAL	2068 (3.3)	2214 (3.5)	0.77 (0.63-0.96)	
Summary	4604	4966	0.79 (0.70-0.88)	P < .001
Overall summary	**5514**	**5978**	**0.79 (0.71-0.87)**	**P < .001**



Sabatine ML et al. JAMA Cardiol. 2018;3(9):823-828.

Very low LDL-C: Is there a benefit?

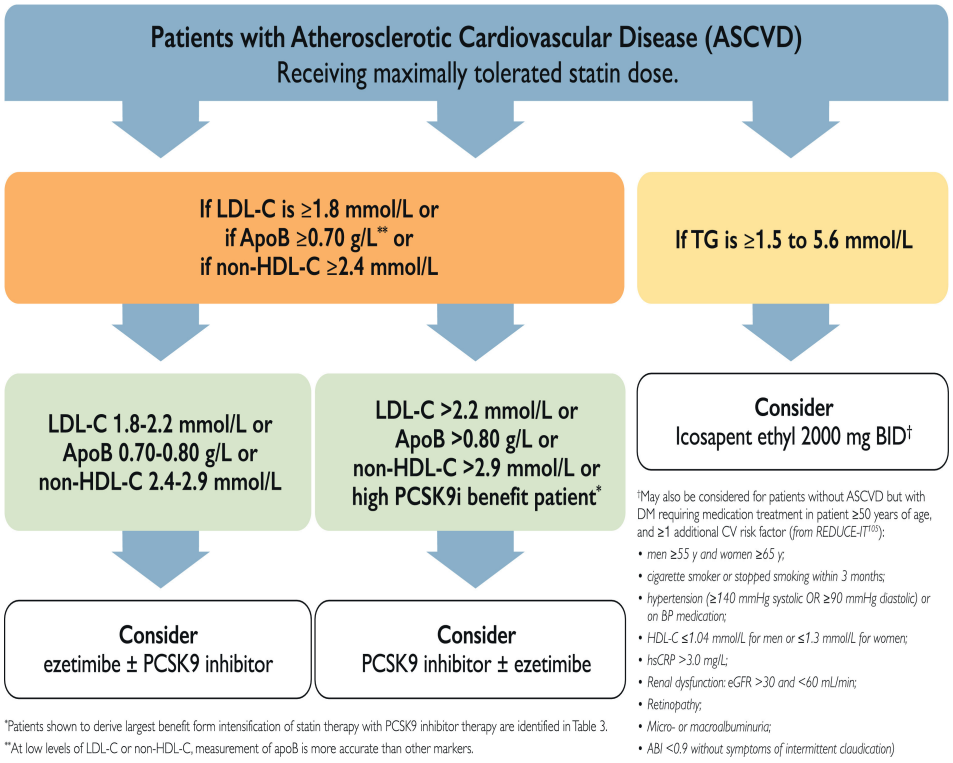
Table 3: Secondary prevention patients shown to derive the largest benefit from intensification of statin therapy with the addition of a PCSK9 inhibitor

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

Pearson GL et al Canadian Journal of Cardiology 37 (2021) 1129–1150

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)*

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9. After starting PCSK9i, his TGs remain at 2 mmol/L. Mr. Young inquires about a new “fish oil” pill that he heard from his brother in Florida that might be beneficial. He asks you whether it might be appropriate for him. What do you respond?

a) IPE is a highly purified chemically modified form of omega-3 fatty acid that increases plasma EPA and DHA levels. You would recommend IPE.

b) The IPE effect is due almost entirely to lowering elevated triglycerides. His TGs are not sufficiently elevated to warrant therapy. You would not recommend IPE.

c) The addition of IPE to maximally tolerated statins in individuals with prior ASCVD and TGs $\geq$ 1.5 mmol/L, led to a 25% RRR in a large randomized trial. You would recommend IPE.

d) IPE is not beneficial for patients who are taking statins. You would not recommend IPE.

e) The expected benefit of IPE for this patient are very similar to that seen with OTC omega-3 supplements. You would recommend an OTC formulation.

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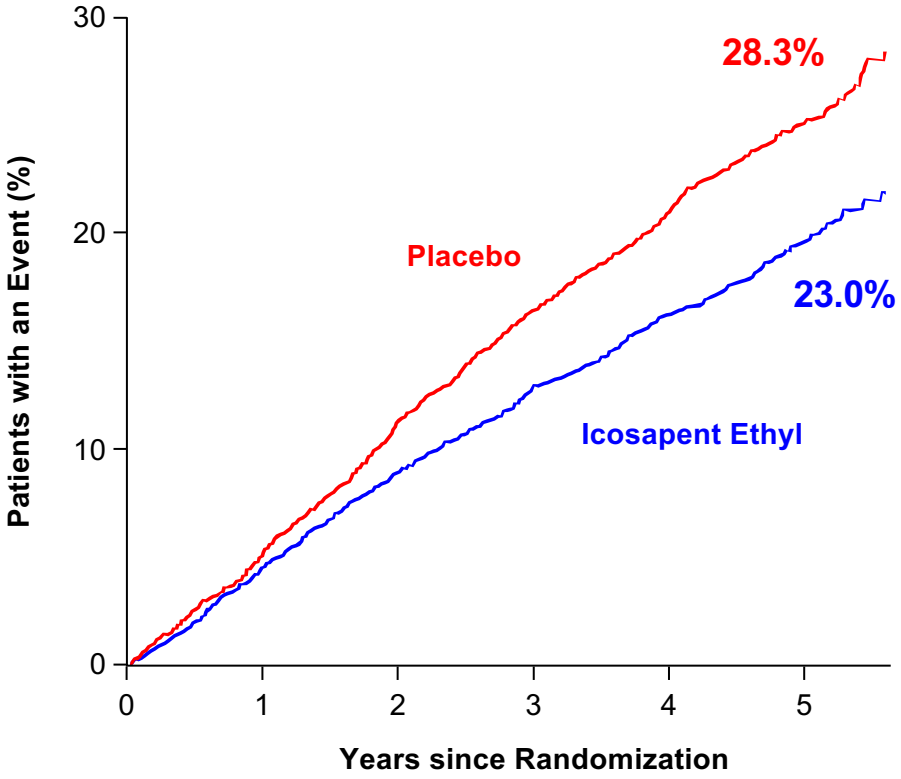
REDUCE-IT trial

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

Summary

1. In primary prevention, first determine whether a patient has a statin-indicated condition and if not calculate CV risk
   - Statins are recommended in all high-risk patients and any intermediate risk patients with LDL-C ≥ 3.5 mmol/L (or other risk modifiers)

2. In secondary prevention, the threshold for treatment intensification is 1.8 mmol/L for LDL-C, 0.7 g/L for apoB ans 2.4 mmol/L for non-HDL-C
   - Identify patients who have high benefit from PCSK9i and intensify therapy promptly
   - Identify patients who may benefit from IPE (TG ≥ 1.5 mmol/L)

1. Focus on atherogenic lipoprotein concentration as this is the best parameter for need for treatment intensification
   - apoB >> non-HDL-C >>> LDL-C

2. Measure Lp(a) in all patients once and consider this additional source of atherogenic lipoproteins
   - More aggressive control of all risk factors and consider PCSK9i