Practical approach to lipid lowering – which guideline to follow, what to measure, and how to treat?

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Learning Objectives

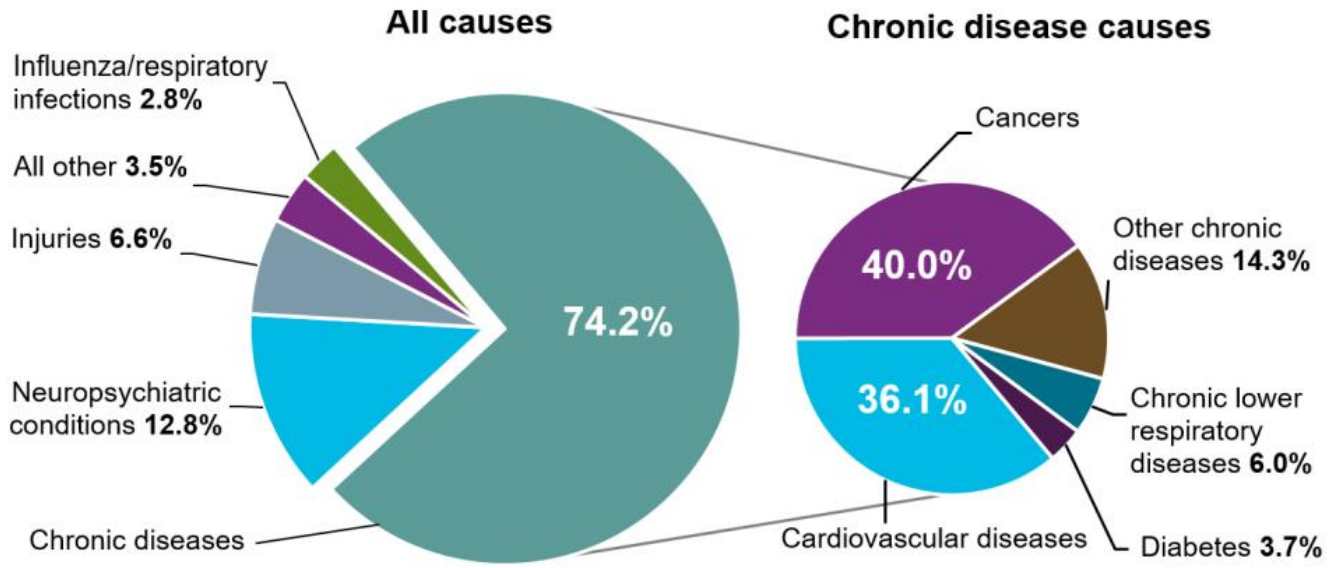
- To understand the rationale and data behind lipid lowering guidelines
- To review recent Canadian Lipid Guidelines
- To provide a practical framework for treatment of high risk primary prevention and secondary prevention

Beth L. Abramson MD Disclosure

Relationships with financial sponsors:

- **Grants/Research Support:** Amgen, Bayer, Boehringer Ingelheim, Jansen, HLS Therapeutics, Novartis, Novo Nordisk
- **Speakers Bureau/Honoraria:** Abbott, Amgen, Bayer, Biosyent, Boehringer Ingelheim, CHRC, HLS Therapeutics, Novartis, Novo Nordisk, BMS- Pfizer, Servier, Sanofi
- **Consulting Fees:** Amgen, Bayer, HLS Therapeutics, Novartis, Novo Nordisk, Sanofi
- **Patents:** N/A
- **Other:** Author: Heart Health for Canadians

CVD causes 36% of the total number of deaths in Ontario[1]



Causes of death, all causes and chronic disease causes, Ontario, 2015[1]

Source: Death (Vital Statistics – Death), Ontario Ministry of Health and Long-Term Care, IntelliHEALTH ONTARIO, Extracted March 5, 2019.
Prepared by: Public Health Ontario, Health Promotion, Chronic Disease, and Injury Prevention; Cancer Care Ontario, Prevention and Cancer Control (Population Health and Prevention).
Notes: Cause of death based on primary cause, Ontario residents only.

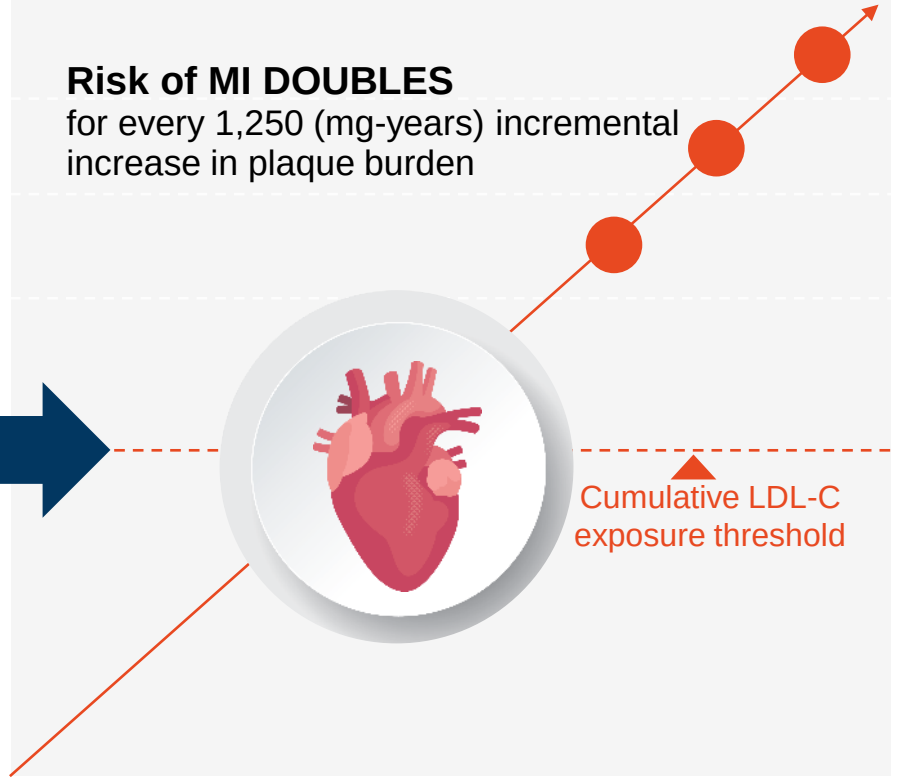
- Nearly 1 in 11 Ontarians have heart disease[1]
- There are over 50,000 heart attacks and strokes per year[1]
  - Many could be prevented with a robust prevention strategy[3]
- increasing prevalence and high incidence of new diagnoses of Heart Disease in Ontario over time (2012-2018)[2]
- Lack of routine preventive care during COVID means the situation will likely get worse[4]

1. CCO and Ontario Agency for Health Protection and Promotion (Public Health Ontario). The burden of chronic diseases in Ontario: key estimates to support efforts in prevention. Toronto: Queen's Printer for Ontario; 2019.
2. Mackinnon ES, Goeree R, Goodman SG, et al. CJC Open. 2021;4(2):206-213. doi:10.1016/j.cjco.2021.10.003
3. Value-for-Money Audit: Cardiac Disease and Stroke Treatment, Office of the Auditor General of Ontario, December 2021
4. Lau D, McAlister FA. Can J Cardiol. 2021;37(5):722-732. doi:10.1016/j.cjca.2020.11.001

1. Public Health Ontario, July 2019. The Burden of Chronic Diseases in Ontario (publichealthontario.ca). Accessed August 31, 2022

Both magnitude and duration of LDL-C exposure impact risk

Plaque burden can be calculated from LDL-C levels and duration of exposure



Reducing plaque burden—at any age—positively impacts lifetime risk

Ference BA, et al. *J Am Coll Cardiol.* 2018;72:1141-1156.

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

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

Canadian Journal of Cardiology 10.1016/j.cjca.2021.03.016

Glen J. Pearson PharmD, George Thanassoulis MD, Todd J. Anderson MD, Arden R. Barry PharmD, Patrick Couture MD, PhD, Natalie Dayan MD, Gordon A. Francis MD, Jacques Genest MD, Jean Grégoire MD, Steven A. Grover MD, Milan Gupta MD, Robert A. Hegele MD, David Lau MD, PhD, Lawrence A. Leiter MD, Alexander A. Leung MD, Eva Lonn MD, G. B. John Mancini MD, Priya Manjoo MD, Ruth McPherson MD, PhD, Daniel Ngui MD, Marie-Eve Piché MD, PhD, Paul Poirier MD, PhD, John Sievenpiper MD, PhD, James Stone MD, PhD, Rick Ward MD, Wendy Wray RN, MScN

Secondary Testing

Coronary Artery Calcium (CAC) Measurement - Recommendations

- We suggest that CAC screening using computed tomography imaging might be appropriate for asymptomatic, middle-aged adults (FRS 10-20%) for whom treatment decisions are uncertain *(Conditional Recommendation, Moderate Quality Evidence)*.
- We suggest that CAC screening using computed tomography imaging might not be undertaken for a) high risk individuals b) patients receving statin treatment or c) most asymptomatic, low-risk adults *(Strong Recommendation, Moderate Quality Evidence)*.
- We suggest that CAC screening might be considered for a subset of low-risk middle-aged individuals with a family history of premature CHD (men <55 years; women <65 years) *(Conditional Recommendation, Low Quality Evidence)*.
- We suggest that in patients who warrant risk factor management on the basis of usual criteria, CAC scoring not be undertaken. Moreover, CAC scoring (seeking a result with a value of zero) should not be used as a rationale for withholding otherwise indicated, preventive therapies *(Strong recommendation, Low Quality Evidence)*.

Lipoprotein (a) Measurement - Recommendation

- We suggest that Lp(a) might aid risk assessment in subjects at intermediate Framingham risk or with a family history of premature coronary artery disease *(Conditional Recommendation, Moderate Quality Evidence)*.

Values and preferences - Lp(a) is a marker of CVD risk. Particular attention should be given to individuals with Lp(a) levels above 30mg/dL for whom CVD risk is increased by approximately twofold. Although no randomized clinical trials are available to support basing treatment decisions solely on an elevated LP(a) level, identification of high levels of Lp(a) might be particularly useful for mutual decision-making in intermediate-risk subjects. Moreover, in younger patients who have a very strong family history of premature CVD suspected to be related to atherogenic dyslipidemia but who by virtue of young age, do not meet usual risk criteria for treatment, detection of high Lp(a) might help inform mutual decision making regarding treatment. Lp(a) is not considered a treatment target and repeat measures are not indicated.

- RISK ENHANCERS…..
- Lpa, covered in Ont, Once in a lifetime
- CAC scores – regional variation, not widely accessible in Ont., available in B.C.-

2021 CCS Recommendations for Lp(a) as a Biomarker for Improving Risk Stratification and Dyslipidemia Management

Measuring Lp(a) level **ONCE** in a person's lifetime as a part of the initial lipid screening is recommended

(Strong Recommendation; High Quality Evidence)

For all patients in the setting of **primary prevention** with an **Lp(a) ≥50 mg/dL (or ≥100 nmol/L)**, earlier and more intensive health behaviour modification counselling and management of other ASCVD risk factors is recommended

(Strong recommendation; Expert consensus)

https://www.lpaclinicalguidance.com/

ASCVD, atherosclerotic cardiovascular disease; Lp(a), lipoprotein a.

Pearson GJ et al. *Can J Cardiol*. 2021 Mar 26;S0828-282X(21)00165-3. doi: 10.1016/j.cjca.2021.03.016.

Treatment Approach for Primary Prevention Patients (Without a Statin Indicated Condition)‡

Primary Prevention†

Low-Risk*
FRS <10%

Statin therapy not recommended for most low risk individuals; exceptions include:
(a) LDL-C ≥5.0 mmol/L (or ApoB ≥1.45 g/L or non-HDL-C ≥5.8 mmol/L) – *see Figure 2*; or (b) FRS is 5%-9.9% with LDL-C ≥3.5 mmol/L (or non-HDL-C ≥4.2 mmol/L or ApoB ≥1.05 g/L), particularly with other CV risk modifiers (e.g., FHx, Lp(a) ≥50 mg/dL [or ≥100 nmol/L] or CAC >0 AU) as the proportional benefit from statin therapy may be similar to other treated groups

Health Behavior Modifications:
- Smoking cessation
- Diet: it is recommended all individuals adopt a healthy dietary pattern
- Exercise: it is recommended adults accumulate at least 150 mins/week of moderate-vigorous intensity aerobic physical activity

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 years and women ≥60 years 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)

High-Risk*
FRS ≥20%

Discuss Health Behavior Modifications

Initiate Statin Treatment

If LDL >2.0 mmol/L or ApoB >0.8 g/L or non-HDL-C >2.6 mmol/L on maximally tolerated statin dose

YES

NO

YES

Discuss add-on therapy with patient:
Evaluate reduction in CVD risk vs. cost/access and side-effects

Add-on ezetimibe 1st line
(BAS as alternative)¶

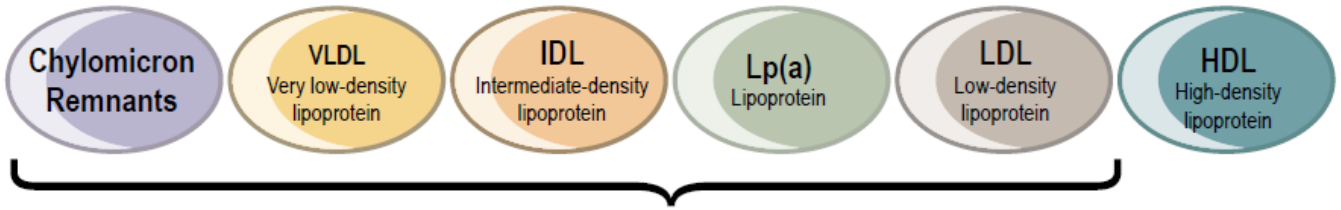
YES

MONITOR: response to statin Rx, response to add-on lipid-lowering Rx, health behavior modifications

‡Statin indicated conditions consists of all documented ASCVD conditions, as well as other high-risk primary prevention conditions in the absence of ASCVD, such as most patients with diabetes, those with chronic kidney disease and those with 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. From: https://doi.org/10.1016/j.cjca.2021.03.016, Pearson et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular

Primary and Secondary Lipoprotein Determinants

LDL-C: Calculated from standard Lipid Profile
Apo B: Measured separately



Non-HDL-C = Total Cholesterol-HDL-C

Atherogenic
Apo B-containing
Lipoproteins

RECOMMENDATION

- We recommend that non-HDL-C and apo B should continue to be considered alternate targets to LDL-C to evaluate risk in adults *(Strong Recommendation, High Quality Evidence)*.

Values and preferences - As clinicians are most familiar with LDL-C we continue to recommend its use as the primary target, but recognize the advantages of non-HDL-C or apo B.

8

Risk Assessment

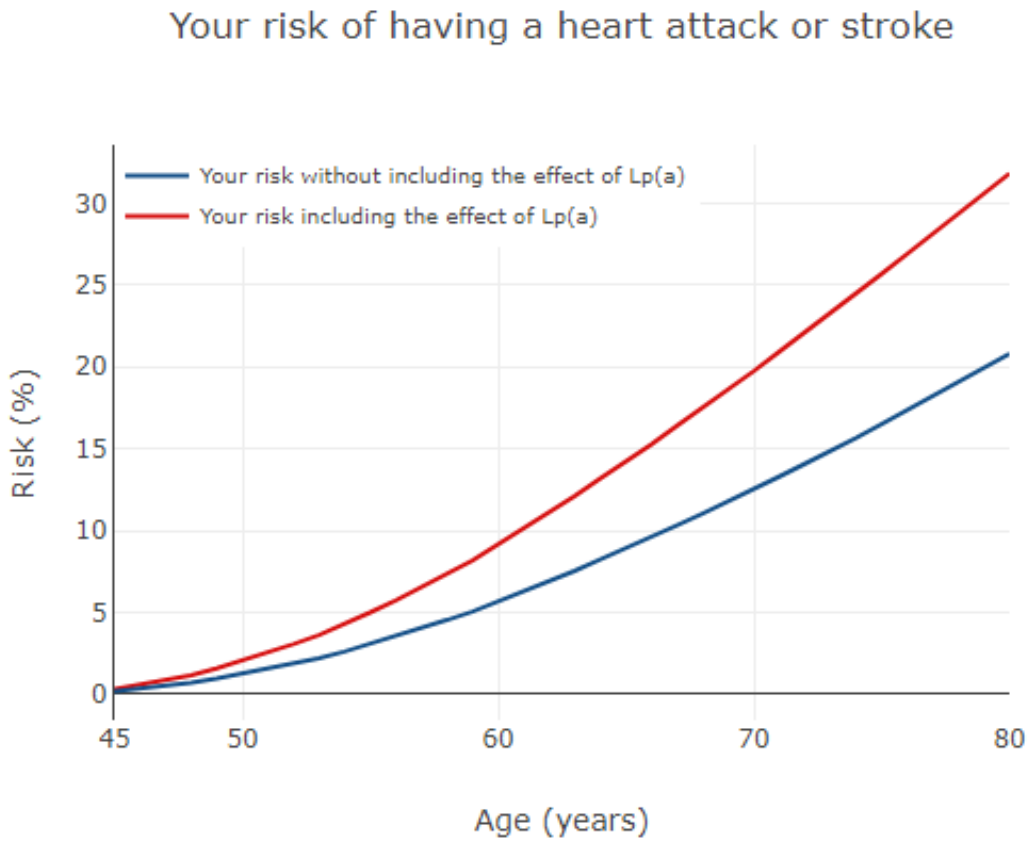
- Most Non HDL is LDL
- Apo B is atherogenic, but may not add a lot if Non HDL is considered
- Lpa useful

Lpa increases risk over a lifetime. Risk is linear.

Lp(a) nmol/L	Δ Lp(a) compare median	Lp(a) percentile	Increased lifetime risk of major cardiac event from high Lp(a)	Intensification of LDL reduction needed to minimize the added risk of high Lp(a)			
				Begin age 30 y	Begin age 40 y	Begin age 50 y	Begin age 60 y
320	300	99		1.2 mmol/L	1.4 mmol/L		2.3 mmol/L
270	250	97.5	x2.19	1.0 mmol/L	1.2 mmol/L	1.5 mmol/L	1.9 mmol/L
220	200	93.5	x1.87	0.8 mmol/L	0.9 mmol/L	1.2 mmol/L	1.5 mmol/L
170	150	90	x1.60	0.6 mmol/L	0.7 mmol/L	0.9 mmol/L	1.1 mmol/L
120	100	82.5	x1.37	0.4 mmol/L	0.5 mmol/L	0.6 mmol/L	0.8 mmol/L
70	50	75	x1.17	0.2 mmol/L	0.2 mmol/L	0.3 mmol/L	0.4 mmol/L
20	ref.	50	ref.	ref.	ref.	ref.	ref.

Modified from Kronenberg, F., Mora, S., Stroes, E.S., Ference, B.A., Arsenault, B.J., Berglund, L., Dweck, M.R., Koschinsky, M., Lambert, G., Mach, F. and McNeal, C.J., 2022. Lipoprotein (a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. European heart journal, 43(39), pp.3925-3946.

https://www.lpaclinicalguidance.com/



Your risk of having a heart attack or stroke up to age 80 is: **20.8%**

With an Lp(a) level of 180 nmol/L, your estimated risk of having a heart attack or stroke up to age 80 changes from 20.8% to: **31.8%**

https://cardiometabolicprevent.ca

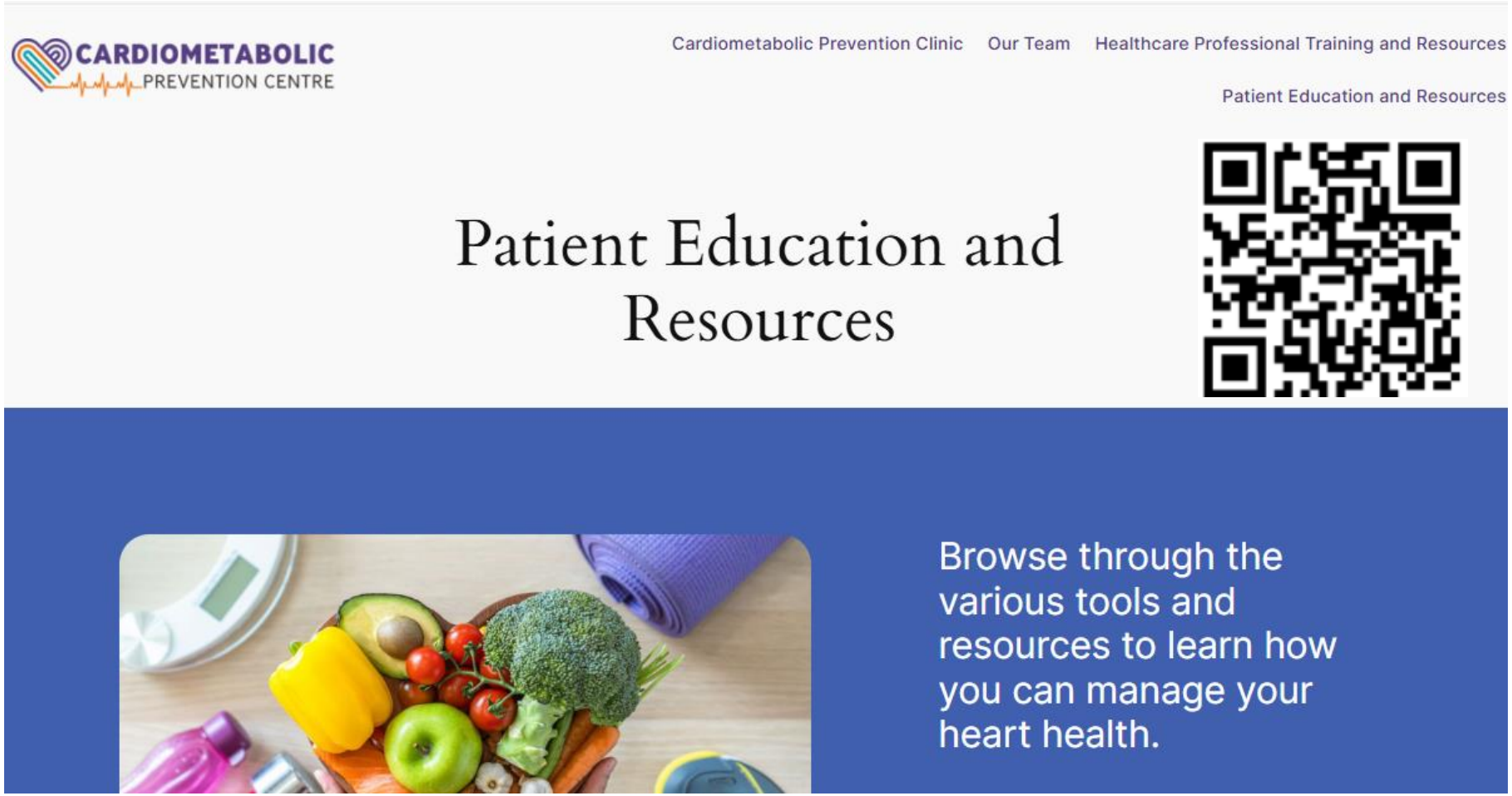
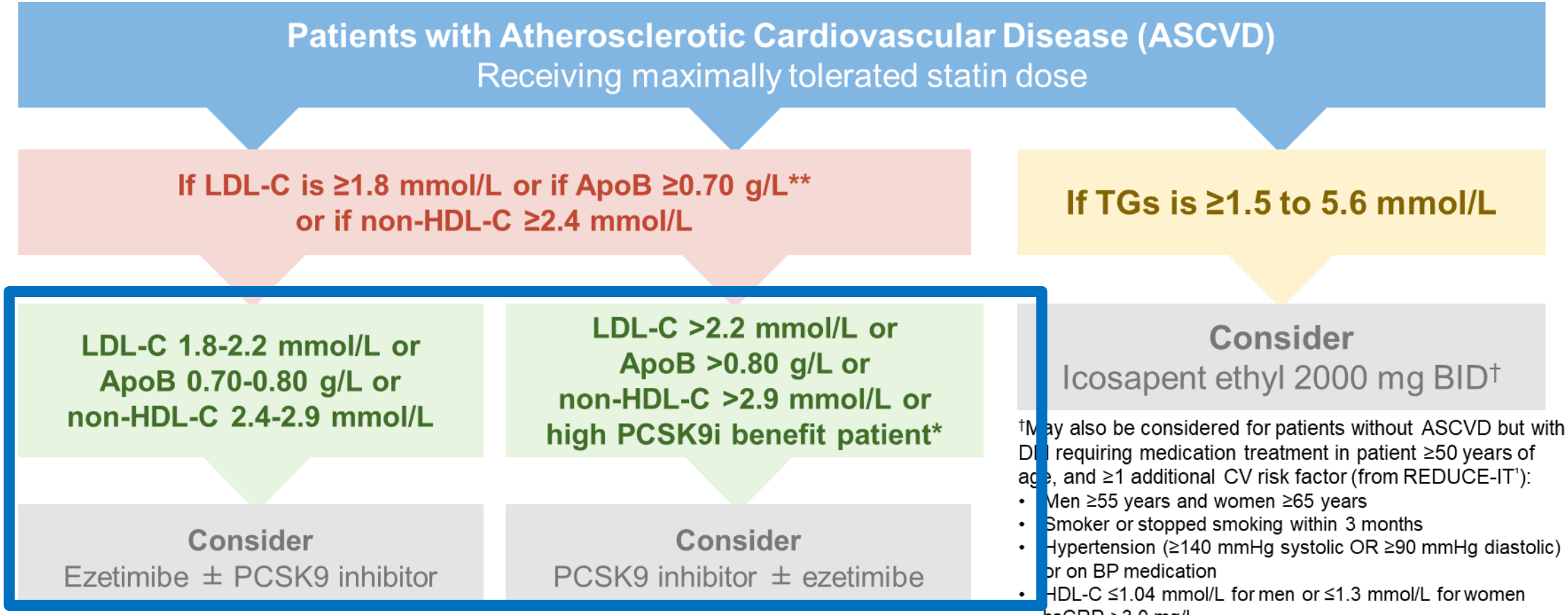


Figure 3: Treatment Intensification Approach for Patients with Atherosclerotic Cardiovascular Disease (ASCVD)



†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[1]):

- Men ≥55 years and women ≥65 years
- 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

*Patients shown to derive largest benefit from 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.

1. Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, Pedersen TR, LaRosa JC, Waters DD, DeMicco DA, Simes RJ, Keech AC, Colquhoun D, Hitman GA, Betteridge DJ, Clearfield MB, Downs JR, Colhoun HM, Gotto AM Jr, Ridker PM, Grundy SM, Kastelein JJ. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol 2014; 64:485-494. ABI, ankle-brachial index; ApoB, apolipoprotein B; BID, twice daily; BP, blood pressure; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TGs, triglycerides.

CCS guidelines for secondary CV prevention: LDL-C targets lowered over 20 years

Date	LDL target for patients with ASCVD
2003	<2.5 mmol/L
2006	<2.0 mmol/L
2009	
2013	<2.0 mmol/L (<1.8 mmol/L in highest risk)
2016	
2021	**Additional Rx if LDL >1.8 mmol/L despite high-dose statin**

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol, Rx, prescription.

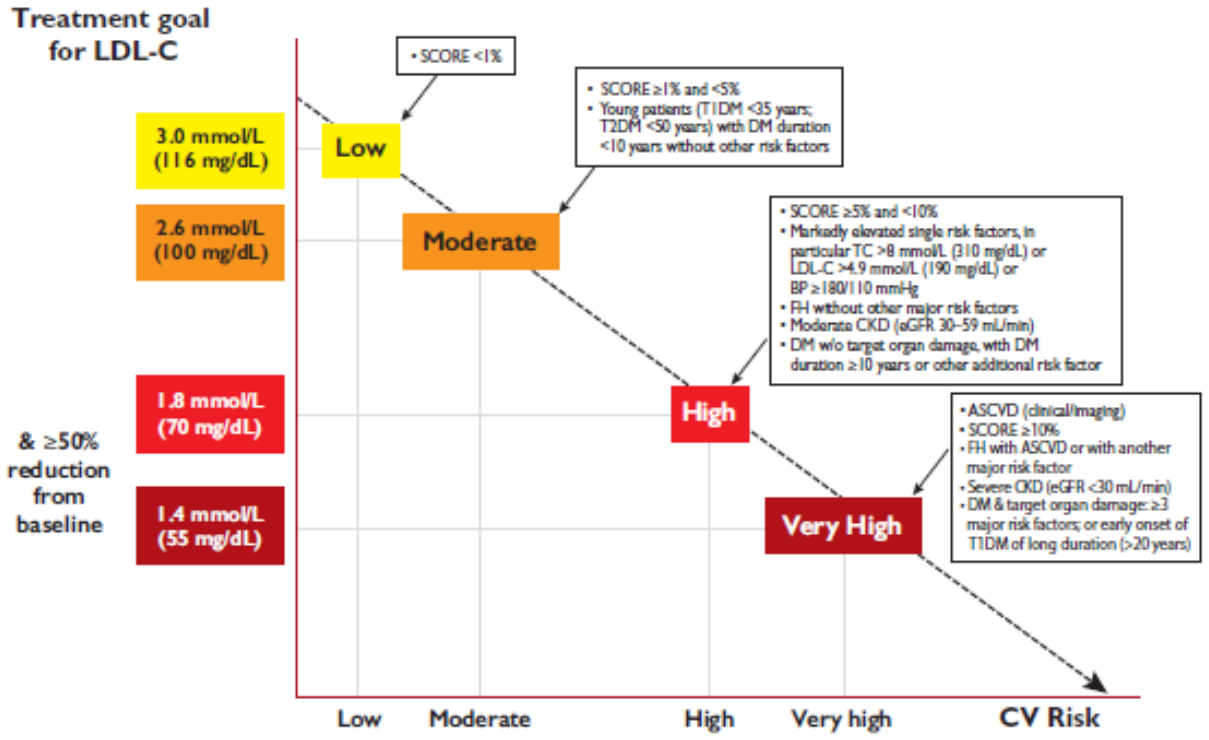
Cannon C et al. N Engl J Med. 2004;350(15):1495-504

European Goal 1.4 in those with ASCVD!

ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–78
doi:10.1093/eurheartj/ehz455

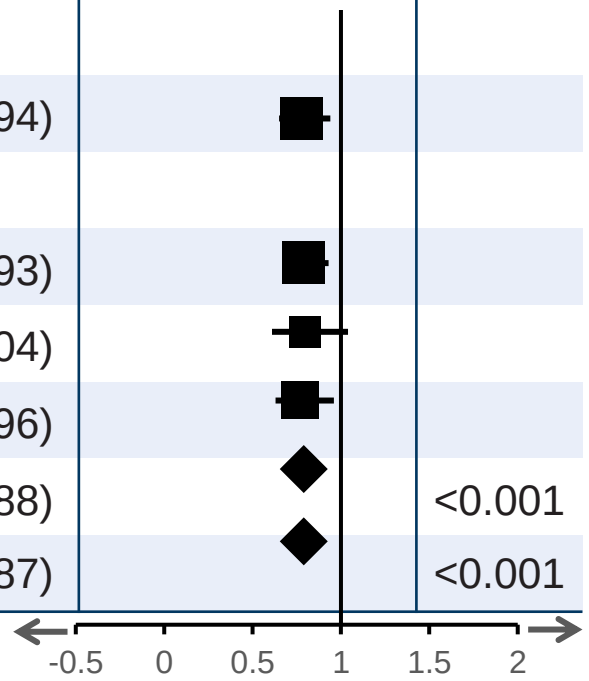
ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce*



Consistent Risk Reduction in Major Vascular Events in Patients with Average Baseline LDL-C 1.8 < mmol/L

Trial	Events (% per annum)		RR (95% CI) per 1 mmol/L reduction in LDL-C	P value
	Experimental Arm	Control Arm		
Statins				
CTTC <2 mmol/L subgroup	910 (4.1)	1012 (4.6)	0.78 (0.65, 0.94)	
Non-statin 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)	<0.001
Overall summary	5514	5978	0.79 (0.71, 0.87)	<0.001



LOWER IS BETTER!!!

CTTC, Cholesterol Treatment Trialists' Collaboration.
Adapted from Sabatine MS et al. JAMA Cardiol. 2018;3:823-828.

Lipid managent over the decades has changed....

Reducing The Risk of Major CV Events With IPE (Vascepa)

REDUCE-IT Trial

MACE-5P
RRR=25%
ARR=4.8%
NNT=21

HR=0.75 [0.68–0.83]
P=0.00000001

CV Death
RRR=20%

HR=0.80 [0.66–0.98]
P=0.03

Population: 8,179 patients with established CVD or with diabetes and ≥1 CV risk factors who have elevated TG levels despite receiving statin therapy

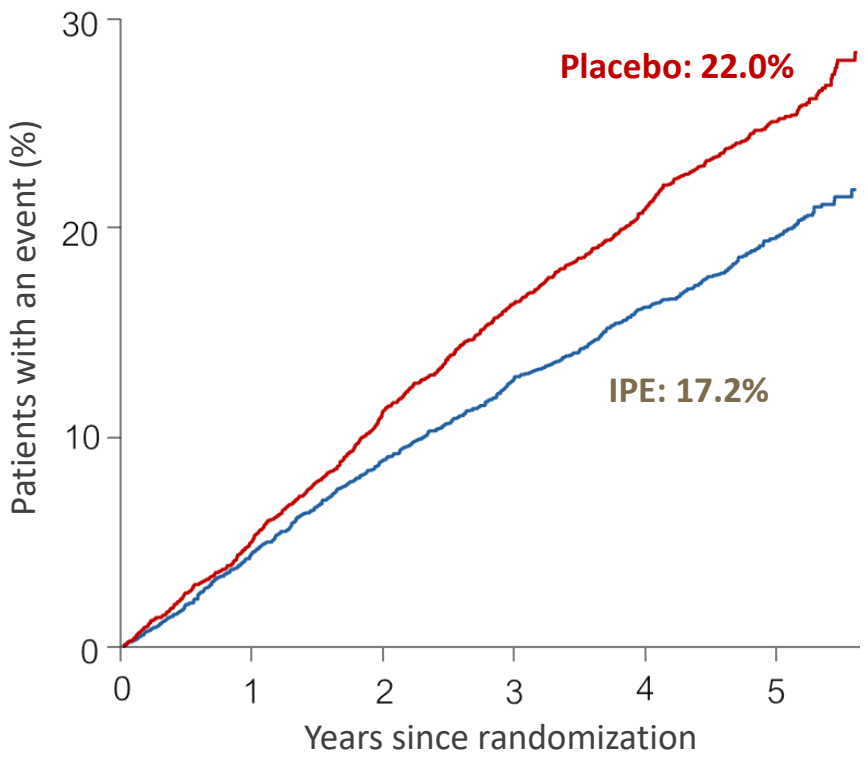
Intervention: IPE 2 g BID

Primary Endpoint: MACE-5P

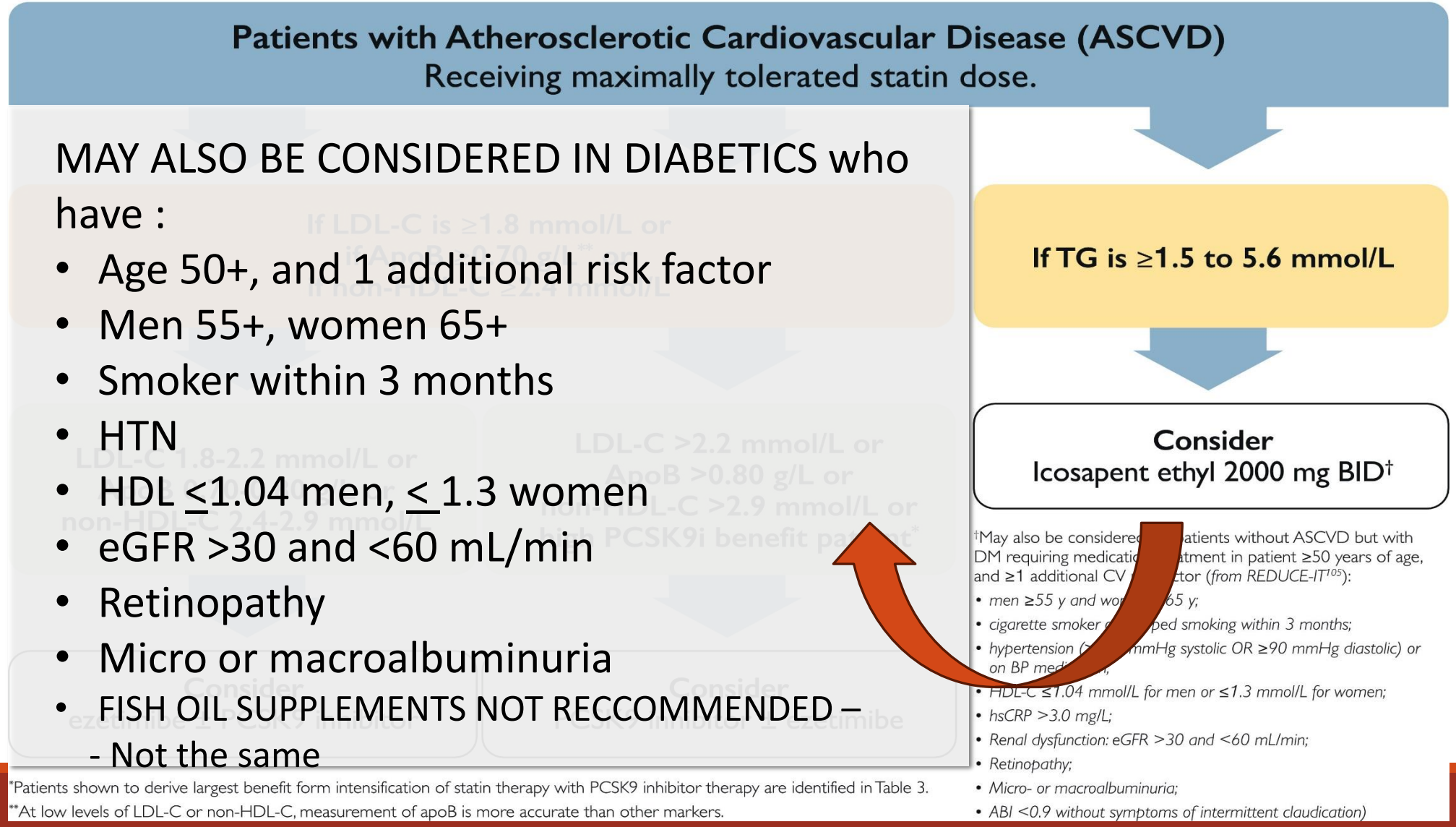
Lipid Threshold for Initiation: TG=1.5–5.6 mmol/L

Median follow up: 4.9 years

Primary Endpoint



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



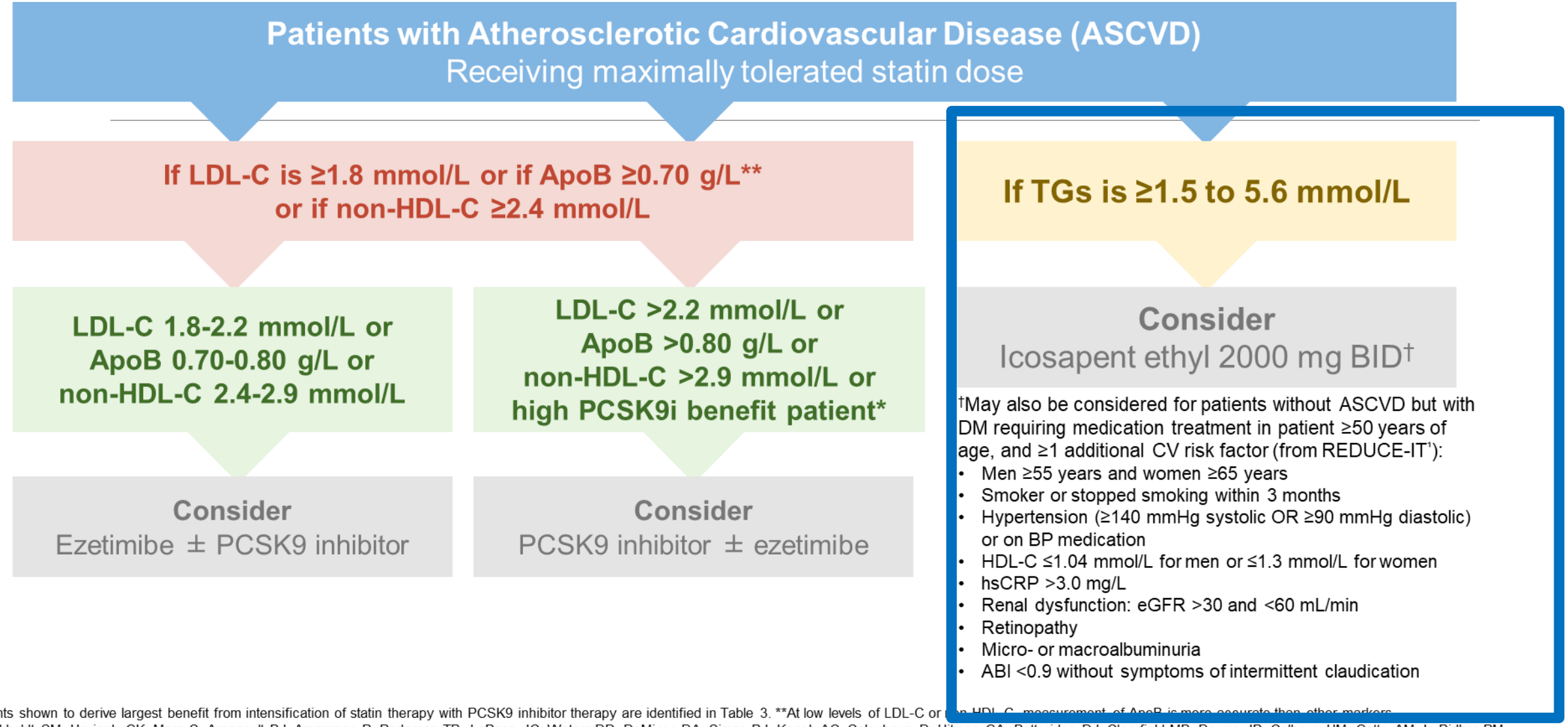
MAY ALSO BE CONSIDERED IN DIABETICS who have :

- Age 50+, and 1 additional risk factor
- Men 55+, women 65+
- Smoker within 3 months
- HTN
- HDL ≤1.04 men, ≤ 1.3 women
- eGFR >30 and <60 mL/min
- Retinopathy
- Micro or macroalbuminuria
- FISH OIL SUPPLEMENTS NOT RECCOMMENDED – - Not the same

IPE = Vascepa

Adapted from Pearson GJ et al. Canadian Journal of Cardiology DOI: (10.1016/j.cjca.2021.03.016)

Figure 3: Treatment Intensification Approach for Patients with Atherosclerotic Cardiovascular Disease (ASCVD)



*Patients shown to derive largest benefit from intensification of statin therapy with PCSK9 inhibitor therapy are identified in Table 3. **At low levels of LDL-C or [illegible] measurement of ApoB is more accurate than other markers.

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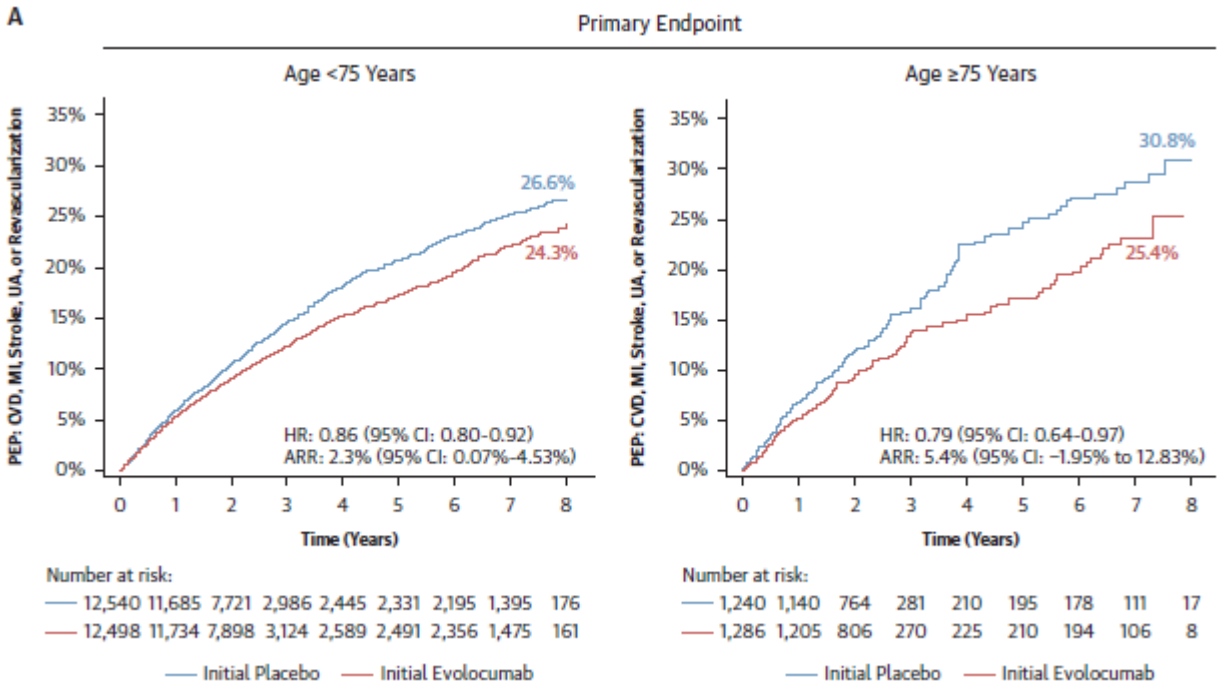
New Guidelines Address Lowering LDL with “intensification therapy”

- No data that very low LDL is harmful
- Consider if LDL > 1.8 as a threshold to intensify
- No lower limit

TREAT THE ELDERLY!

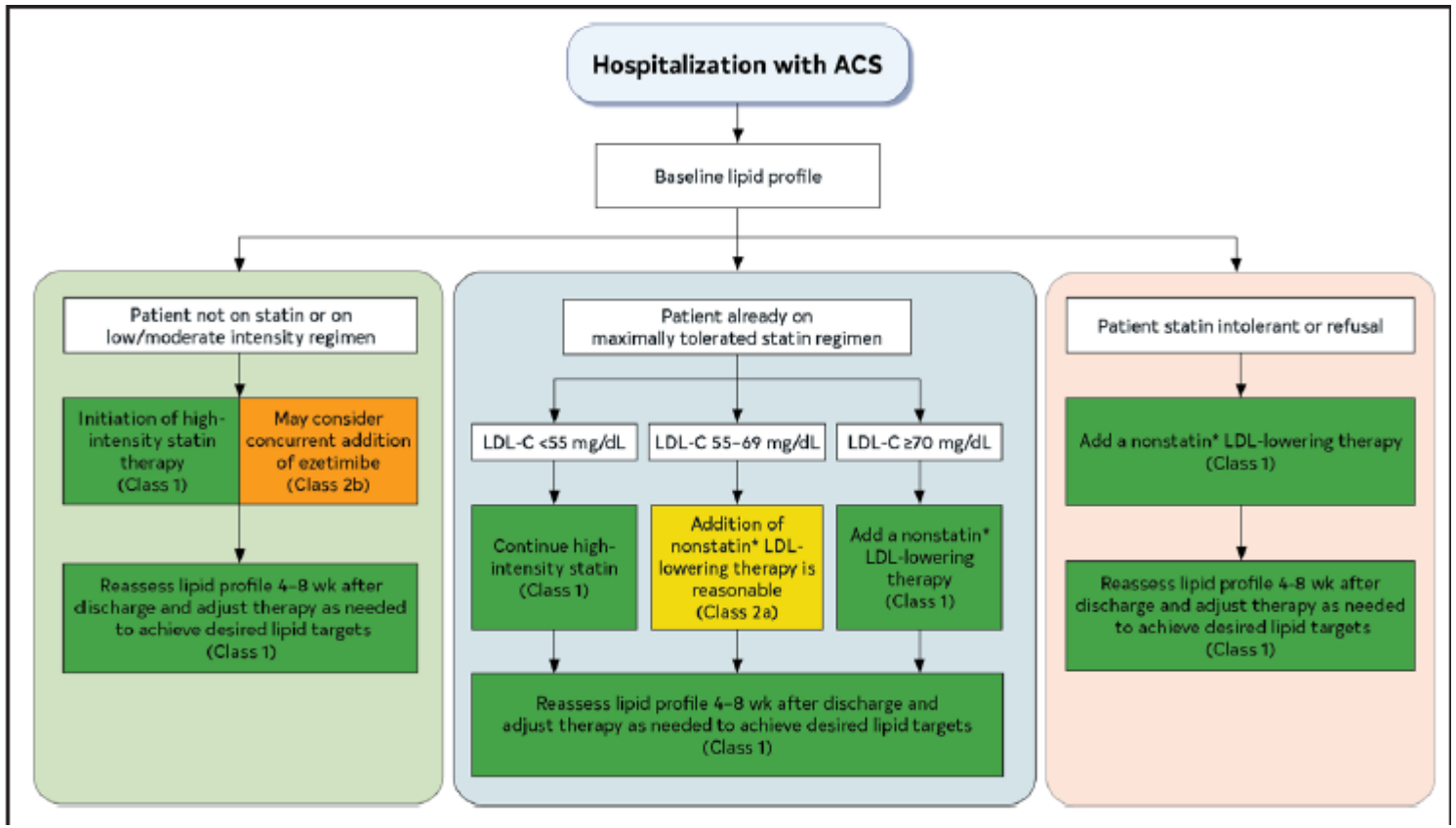
Long-Term Lipid Lowering With Evolocumab in Older Individuals

Samer Al Said, MD, MSc,[a] Michelle L. O'Donoghue, MD, MPH,[a] Xinhui Ran, MS,[a] Sabina A. Murphy, MPH,[a]



(JACC. 2025;85:504–512)

2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines



Circulation. 2025;151:e00–e00. DOI: 10.1161/CIR.0000000000001309

PEER simplified lipid guideline 2023 update

Prevention and management of cardiovascular disease in primary care

Michael R. Kolber MD MSc CCFP Scott Klarenbach MD MSc FRCPC Michel Cauchon MD CCFP FCFP Mike Cotterill MD CCFP

Guidelines are based on Evidence…..THIS ONE IS NOT!

Don’t measure lpa

Don’t follow lipid levels for adherence and intensification

Don’t treat high TGs

Don’t treat all CAD patients with Statins…

Don’t take the time to care for your patient with an Evidence Based Approach!!!

ELSEVIER

CJC Open 6 (2024) 1189–1198

Quality Improvement

Prevention and Management of Cardiovascular Disease in Primary Care: A Comment on the PEER Simplified Lipid Guideline

G.B. John Mancini, MD,[a] Glen J. Pearson, PharmD, FCSHP, FCCS,[b] Arden R. Barry, PharmD,[c]

- Discordance is greatest with respect to :
- Interpretation of lipid profile
- Implications of elevated TG
- Utility of Apo B and Non HDL –C
- The role of non statin medications
- The importance of adherence and F/U
- lpa

Canadian Journal of Cardiology 40 (2024) S1–S3

Editorial

The Challenges of Contemporary Atherosclerotic Cardiovascular Disease Management

Beth L. Abramson, MD, MSc, FRCPC, FACC,[a] and
Jean Grégoire, MD, FRCPC, FCCS, FACC, FACP[b]

[a] *Division of Cardiology, University of Toronto, St Michael's Hospital, Toronto, Ontario, Canada*

[b] *Institute de Cardiologie de Montréal, Université de Montréal, Montréal, Quebec, Canada*

- These impediments are exacerbated by recent publications, that, in an attempt to simplify care,ultimately distort evidence and will unintentionally increase gaps in care

Lpa on the horizon...

Beyond the ocean...

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease

Michelle L. O'Donoghue, M.D., M.P.H., Robert S. Rosenson, M.D., Baris Gencer, M.D., J. Antonio G. López, M.D., Norman E. Lepor, M.D., Seth J. Baum, M.D., Elmer Stout, M.D., Daniel Gaudet, M.D., Ph.D., Beat Knusel, Ph.D., Julia F. Kuder, M.A., Xinhui Ran, M.S., Sabina A. Murphy, M.P.H., Huei Wang, Ph.D., You Wu, Ph.D., Helina Kassahun, M.D., and Marc S. Sabatine, M.D., M.P.H., for the OCEAN(a)-DOSE Trial Investigators*

Lipoprotein (a) Lowering With **Pelacarsen** on Major CV Events in Patients With CVD (Lp(a) HORIZON)

- 8323 participants
- TQJ230 80 mg sc monthly vs placebo
- Study Start Date :Dec 2019
- Estimated Primary Completion Date : May 29, 2025
- Estimated Study Completion Date :May 30, 2025

Olpasiran Trials of Cardiovascular Events and Lipoprotein(a) Reduction (OCEAN(a)) - Outcomes Trial

- 7297 participants
- Study Start Date Dec. 2022
- Estimated Primary Completion Date :Dec, 2026
- Estimated Study Completion Date : Dec, 2026

You Don’t see What you are Preventing!

Tips from Lipid Guidelines Around The World…

- Treat the elderly (USA) –good evidence to reduce risk
- Secondary prevention- don't be afraid to prescribe:

  Use statins + Ezetimibe + PCKS-9I
- aim for LDL 1.4 (Europe)
- Check lipids within a month post MI – time matters!
- Pay attention to Triglycerides:
- If high TG & CVD or DM – Rx. IPE (vascepa) to reduce events
- Consider other markers in primary prevention – lpa
- Ask about previous HT/DM in pregnancy when assessing risk (Canada Eh!) – increases Risk 2-8 fold!

"Good news.
Your cholesterol has stayed the same,
but the research findings have changed."